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Pregnancy for female surgeons: an eternal challenge

Andréa Povedano[1,2*], Luciana Ribeiro[2,3]

Brazilian College of Surgeons

Medical career in Brazil has experienced the phenomenon of feminization. However, surgical specialties have not proportionally accompanied this growth. Among the factors supposedly responsible for the preference of young doctors for clinical specialties in detriment to surgical ones are the concern about having children, starting a family, and the need to reconcile the responsibilities and professional obligations imposed by the practice of surgery. This article brings an analysis of the problems involving pregnancy and the professional career of female surgeons, including their main occupational risks.

Female participation in surgical practice dates back to ancient history when the art of healing was closely linked to divine powers. Archeological records suggest practices equivalent to medicine practiced by Egyptian queens and Greek deities. In the Middle Ages, under strong religious influence, the practice of medicine by women, and in particular the surgical practice, was strongly discouraged and even prohibited, being viable only in exceptional cases, for example, when the profession was inherited from a deceased spouse. Women practicing acts of "healing" were at risk of being accused of witchcraft and sentenced to death[1].

With the arrival of the modern era, women still had less social participation. Perhaps, the first woman to practice surgery on the European continent was Margareth Bulkley. Records suggest that Bulkley was forced to assume a male identity (Sir James Barry, British army surgeon) as a way to graduate in medicine in 1809 in Scotland and to work in surgery without discrimination. Her true identity was discovered only after her death in 1865[1]. The title of first woman graduate in medical school in the world is credited to Elizabeth Blackwell, and it was in 1849 in the USA[2].

In Brazil, women were allowed only to attend regular university careers after the enactment of the Leôncio de Carvalho law in 1879. Before this date, wealthier families with avant-garde thoughts in relation to their daughters needed to send them abroad, as they did with Maria Augusta Generoso Estrela and Josefa Águeda de Oliveira. They were considered the first Brazilian female medical doctors, both having graduated from medical school in the USA in 1881 and 1882, respectively. The first doctor formally graduated as a medical doctor in Brazil was Rita Lobato Lopes in 1887. The first female surgeon to join the Brazilian College of Surgeons, the biggest and oldest association of surgeons in the country, was Mariza Garrido in 1959, only 30 years after its foundation[3].

Fortunately, the current scenario is very different from the past. Currently, in the United States of America, 37.1% of physicians registered at the American Medical Association are women[4]. In the United Kingdom, the percentage of women in medicine is even higher, which is 47.5% of the total number of registered professionals. However, when analyzing the percentage of medical specialists by gender, only 37% are women[5]. In the East, the number of women in medicine also continues to rise, but in a more discreet way. In the 2020 Japanese medical statistics, 23% of the country's medical force was represented by women[6].

Following the trend of developed countries, the medical career in Brazil has already experienced feminization. According to the data from the last Brazilian medical statistics, the female presence in medicine has increased by 50% in the last 20 years. Today, women represent 46.6% of the Brazilian medical force, which is mainly due to the younger generations, represented mostly by medical doctors under 34 years old[7].

Despite the increase of female representation in the medical field, surgical specialties have not been attractive to women. According to the data from the Brazilian Medical Association, only 23.4% of medical doctors registered as general surgeons are women[4]. Regarding the members of the Brazilian College of Surgeons, women correspond only to 17.5% of the total amount. However, most young female surgeons will be able to evoke in their memory some female exponent that inspired or encouraged their surgical career, from Brazilian female surgeons with international recognition to excellent anonymous professionals pulverized in remote hospitals in Brazil.

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Some factors have been pointed out as reasons for the female choice of clinical specialties to the detriment of surgical ones, and some of these involve the values and social characteristics of the new generations. The younger generations are endowed with independence and individualism, and value not only the financial return and personal satisfaction but also the quality of life in their professional choices.

The concern about having children, making a family, and the need to reconcile the reality of adult life with the professional responsibilities and obligations required by the surgical practice makes many female physicians opt for specialties with "more manageable daily lives" and without major "surprises"[8]. Perhaps, this explains the great female demand for clinical specialties such as dermatology (79.7% of women), pediatrics (75.6% of women), and endocrinology (72.1% of women), to the detriment of surgical specialties, such as urology (only 2.9% of women), orthopedics and traumatology (7.4% of women), and neurosurgery (9.4% of women)[9].

While female surgeons of the Baby Bommer generation (born between 1945 and 1964) were compelled to choose between motherhood and dedication to their professional careers, younger generations such as Generation Y (born between 1981 and 2000) and Z (born from 2000 to the present day) struggle with difficulties in balancing between professional life and motherhood.

In Brazil, when we analyze the general panorama of professional women, pregnant women have already achieved paid maternity leave for 120 days, which counts from the date of delivery and is extendable for another 60 days, guaranteed by the Consolidation of Labor Laws (Law nº 12514 October 28, 2011). Public employees are also supported by a similar law, guaranteeing 180 calendar days of paid leave. Since the 1980s, all pregnant women have the stability in their jobs, from the moment the pregnancy is confirmed until 5 months after delivery. They have also got the right to be relocated from the previous function, in case of activities that put risks to the health of the pregnant woman and her child (Law nº 6932 July 07, 1981).

Despite the support guaranteed by the Brazilian legislation, the medical activity in our country is based on the multiplicity and accumulation of employment relationships, in addition to the need for freelancer jobs. All those factors end up imposing difficulties on mothers who are also surgeons[7]. In some countries, such as the USA and the UK, the medical work tends to be in a single place, with well-defined working hours and the possibility of using daycares, facilitating motherhood among female surgeons.

A phenomenon often observed in new generations of surgeons has been late motherhood. Even though the medical faculty is the graduation with the highest number of hours and the longest duration in Brazil, the surgeon's long learning curve (about 3 years longer than that of clinical specialties) and the extensive workload have led female surgeons to postpone motherhood beyond the training period or even after consolidating their professional careers. According to the data from the National Center for Health Statistics, American female surgeons have their first child 7 years later than the general population, i.e., at an average age of 33 years[10].

Late pregnancy, work profile, and hostile environment lead female surgeons to have higher rates of assisted reproduction and pregnancy complications, such as miscarriages, premature labor, placental abruption, high blood pressure, and also complications for the child, such as growth restriction and low birth weight[11]. The surgeon's physical demands, such as night work, long working hours, and the need to stand during the surgery for many hours, were related to a higher risk of these complications. A survey carried out in the USA with 1021 female surgeons of the most different specialties found a complication rate during pregnancy of 35.3%, being 14.5% the percentage of complications during pregnancy in the general population[12]. In a recent study, it was shown that surgeons who operate more than 12 h a week during the last trimester of pregnancy are at greater risk of gestational complications compared to those who operate less than 12 h a week.

Surgeons are exposed daily to chemical, physical, and biological agents, which can endanger their pregnancy. In 2000, the Occupational Health and Safety Administration (OHSA) recognized the association between an increased risk of abortion and congenital anomalies related to the presence of volatile anesthetic gases in suspension in the surgical environment, such as nitrous oxide and halogenated agents. Currently, there are safety recommendations regarding the limit of exposure to residual gases in the operating rooms. Although the recommended levels vary internationally, a systematic review showed no adverse effects on pregnancy when any of the guidelines were followed and pressure ventilation systems were used in addition to laminar flow air conditioning[12].

Another risk associated with gestational complications is surgical smoke, which is the product generated by energy sources during surgery, as well as other toxins in suspension, such as benzene, 1,2-dichloroethane, and formaldehyde. All these risk factors can be minimized with the use of N95 masks[12]. Most guidelines also suggest that pregnant women be excluded from procedures where intraoperative hyperthermochemotherapy is performed due to the risk of miscarriage and congenital anomalies[13].

Advances in minimally invasive surgery have increased the use of intraoperative radiology. The development of hybrid operating rooms equipped with C-arm X-ray machines or CT scanners is a reality in many hospitals. The volume of endovascular procedures and angiography has increased by 400%

in the past decade[14]. Excessive exposure to radiation is related to the risk of miscarriage and fetal complications, with the first 2 weeks of pregnancy being the most critical. From the second to the eighth week of pregnancy, there is an increased risk of congenital anomalies and fetal growth restriction, and from the eighth week onward, excess radiation is associated with cognitive deficits and microcephaly. Intrauterine exposure to radiation is also related to late complications such as an increase in the incidence of childhood cancer[15]. In Brazil, the Basic Radioprotection Guideline (CNEN NN3.01), regulated by the Ministry of Labor (ordinance MTB 1084/2018), follows the recommendation of the International Commission for Radiological Protection and determines that pregnant women should not receive an effective dose greater than 1 mSV. The use of glasses and lead aprons that cover from the neck to the knee as individual equipment and the use of specific dosimeters that control radiation exposure are also recommended[16].

Although studies related to the health preservation of the pregnant woman and the fetus in the surgical environment are increasingly frequent, it is necessary that structural changes in the social and labor organization also occur. Stipulated measures that support surgeons of childbearing age to become pregnant without the stigma associated with pregnancy, especially during medical residency, are important and cathartic for the new generations. This long road of changes has already begun when we observe a reorganization of social values with greater participation of men in daily domestic activities, technological facilities of modern life (programmable appliances with remote control), and advances in science (egg freezing, fertilization-assisted clinics, gamete bank, etc). All these tools have been important to harmonize the life expectations and desires of female surgeons.

By analyzing the past, many improvements were achieved. By projecting the future, new challenges will arise. However, one thing is certain, i.e., there are no limits to the aspirations and fulfillments of the strong women who chose to pursue a surgical career in this country.

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Women health: holistic view

José Maria Soares Júnior[1,2*], Renato Delásio Lopes[2], Isabel Cristina Espósito Sorpreso[1], Edmund Chada Baracat[1]

The term women's health involves psychobiological health and gender issues, and women's sexual and reproductive rights. In this context, educational guidance by health professionals is essential for adequate health promotion[1]. Traditionally, this concept adds values of quality of life and longevity, respecting the cultural and environmental aspects in which women live[1]. In addition, the women participate in this process as a user, but they can also promote and disseminate self-care, which strengthens female health in society.

Women's health education involves a multidisciplinary team, which begins with care from prenatal care (mother and fetus), through childhood and adolescence, reaching the reproductive and climacteric period, ending in senescence[2].

Estrogen, produced by the ovaries after stimulation by gonadotropins, defines the characteristics of the sexual organs. It also influences the central nervous, cardiovascular, and musculoskeletal systems. The woman is born with a finite number of oocytes that undergo, during her reproductive life, the process of ovulation or atresia, in a natural and continuous process, until menopause (last menstruation). After this period, a state of hypoestrogenism appears, which is marked by vasomotor symptoms and repercussions on the genitourinary, endocrine, cardiovascular, nervous, tegumentary, and bone systems. There are also reflections on the optical, auditory, and gastrointestinal systems[1-4]. Therefore, women's health must be viewed holistically.

In childhood, disorders of growth and pubertal development bring about several social and economic issues, but the most prevalent is genital discharge due to vulvoginitis resulting from the accidental introduction of a foreign body or inadequate clothing and hygiene habits. At puberty, the immaturity of the cortical-hypothalamic-pituitary axis draws attention because it can be confused with polycystic ovary syndrome, which can lead to psychological esteem for the rest of the woman's life[5].

During childhood, the identification of abnormalities of the female genital organs (malformations or disorders of sexual development) of the girl that can be noticed from birth, but the partial forms can bring psychological disorders, requires a well-trained multidisciplinary team for the proper correction and minimizes the repercussions on the woman's life[6]. In some cases, there may be absence of menstruation due to obstruction of the drainage pathway or absence of internal genitalia or gonadal dysgenesis, as well as alteration of the cortical-hypothalamic-pituitary-ovarian axis, resulting in primary amenorrhea, as well as having an impact on sexual development and in growth, such as bone metabolism and the psychological aspect of children and adolescents[6].

The reproductive period begins with the first menstruation and the cycles can be irregular and after 2 years on average, they can become regular most of the time. During this period, the woman acquires her full reproductive capacity. Therefore, special attention should be given to reproductive health; since in Brazil, teenage pregnancy rates are still very high, which brings socio-economic and emotional consequences for women and also for their offspring. Therefore, the concepts of family planning, involving contraception, as well as the prevention of sexually transmitted diseases, should be applied to adult women, but reinforced in adolescence[5-7]. In this context, long-term methods, which do not depend on the memory of use, can be good options for contraceptive guidance in adolescence[7].

Another phenomenon that occurs in part of the population is the postponement of pregnancy for economic, social, and professional reasons and even for misconceptions, such as the reproductive period is extending, as life expectancy increases[8]. Therefore, all health professionals should warn about the role of age as a factor of infertility, even before the age of 30 years, for correct family planning[8].

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In puberty and adulthood, polycystic ovary syndrome is the most frequent cause of menstrual and reproductive dysfunction, with tegumentary (acne, hirsutism and androgenic alopecia), cardiovascular (obesity and endothelial dysfunction), and endocrine (carbohydrate and lipid disorders) repercussions. Therefore, the complexity of this syndrome requires multidisciplinary follow-up and lifestyle changes. Menstrual dysfunction commonly leads the patient to seek medical assistance because of its repercussions on quality of life and also on general health, increasing the risk of anemia[9].

We should also point out other conditions that frequently cause menstrual disorders, pelvic pain, and changes in quality of life, also having an impact on women's fertility, such as uterine leiomyoma, endometrial polyp, adenomyosis, endometriosis, pelvic inflammatory disease, and uterine malformations. These affections are related to the organic structure, and may affect other tissues or organs, as is the case of endometriosis and pelvic inflammatory disease[10]. Therefore, the knowledge of these conditions should not be restricted to the gynecologist, but in other specialties in which these diseases can affect, such as the gastrointestinal and peripheral neurological systems.

The climacteric is a period of transition in a woman's life, which goes from the end of the reproductive phase to senectude, with important physical and emotional changes. Menopause is just the date of the last menstruation, which is recognized after 12 months of amenorrhea. In Brazil, it occurs between 48 and 50 years. The climacteric is divided into two phases: transition to menopause and postmenopause[3-4]. In the first phase, menstrual disorders are frequent and impact quality of life. At the end of this period, when the menstrual cycle becomes longer, with absence for two more cycles, vasomotor symptoms may appear, which will be more frequent and intense in the postmenopause. In this phase, the state of hypoestrogenism is more consolidated, leading to hot flashes, sweating, insomnia, and other correlated symptoms that can determine an important impact on the woman's life. This period is also an opportunity to screen for neoplasms, such as cervical cancer and breast cancer, and also provide guidance on healthy lifestyle practices and even initiate therapies to correct carbohydrate disorders and dyslipidemia, which can promote cardiovascular diseases[4,5,11-13]. It should be noted that women often gain weight and may develop endothelial dysfunction that would result in systemic arterial hypertension or other cardiovascular diseases. In the study by Fonseca et al.[12], 70% of the women were overweight or obese at the first gynecological consultation during the climacteric. Therefore, there is a need for a multidisciplinary team to face and treat the repercussions of weight gain and the risk of cardiovascular disease, which can have a silent evolution in this period and manifest abruptly with acute myocardial infarction or stroke.

The repercussions of hypoestrogenism are related to the genitourinary syndrome and loss of bone mass, which can result in osteoporosis and fracture, compromising the well-being of women at the end of the climacteric and senectude. In this context, hormone therapy with estrogens is the most effective tool to mitigate changes in hypoestrogenism, but it must be individualized and well evaluated to reduce risks[2].

Multiprofessional programs in the transition to menopause and postmenopause should address factors such as changes in lifestyle, knowledge about menopause, attitudes and clarification about symptoms, encouragement of smoking cessation and alcoholism, combating sedentary lifestyle, and adequate food intake have influence on symptoms and quality of life. At the same time, regular physical exercise should be encouraged, as at least 150 min of moderate-intensity aerobic exercise per week reduces the incidence of cardiovascular disease and improves cognition, muscle strength, and quality of life. This aspect is important for women to reach senectude in a healthier way[11,12].

Another important aspect of women's health, regardless of age, is active immunization through vaccination. The women's vaccination schedule comprises a basic scheme divided into age groups: 10-19 years, 20-59 years, and over 60 years, in addition to pregnancy and the puerperium. In this regard, the vaccines recommended for non-pregnant women include viral triple, hepatitis A and B, HPV, chickenpox, influenza, double or triple bacterial, meningococcal C, and conjugate, pneumococcal. Yellow fever is indicated for those who live in risk areas according to the World Health Organization[14,15].

Every health professional who assists women must contextualize their stage of life and determine the best strategy for diagnosing conditions, planning treatment, and adopting preventive measures. Care should be given respecting women's sexual and reproductive rights, without prejudice and being aware that these women play different roles throughout their lives.

AUTHORS' CONTRIBUTIONS

JMSJ: Conceptualization, Writing – original draft, Writing – review & editing. **RDL:** Conceptualization. **ICES:** Conceptualization. **ECB:** Conceptualization, Writing – original draft, Writing – review & editing.

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The role of women as critical care physicians

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The word "medicine" was derived from the Latin term *mederi*, which means knowing the best way of treating or healing. The Latin term *medicus* (doctor) is related to an individual dealing with people's health. Currently, the doctor is an individual who studied at and graduated from a medical school. As a healthcare professional, this individual is authorized by the state to practice medicine; to deal with human health by preventing, diagnosing, treating, and curing diseases, which requires detailed knowledge on certain disciplines, such as anatomy, physiology, and pathophysiology, broad understanding of different diseases and their treatments, as well as knowledge on pharmacology and psychology and also on their related applied practices. This assumption determines that if the individuals who studied and received a medical degree from an authorized Faculty of Medicine and possess the necessary skills, they are able to practice medicine regardless of their gender, race, and economic, political, or social situation. However, the Faculty of Medicine as well as other faculties since their inception were essentially strongholds of white men who formed an elite of knowledge and power with very few female colleagues sitting on the benches of these institutions, and it was very rare to practice the profession with distinction or evolving in the academic career with doctorate, positions of associate or full professors or heads of department or even public positions of distinction. In fact, this reality comes from a broader social structure that encompasses educational, socioeconomic, political, and cultural factors that have established predetermined roles for human beings, disrespecting individual needs and differences and hindering education, technical improvement, and practical application of acquired knowledge independent of their gender or sexual orientation[1-6]. The technical capacity to be a doctor should be developed, improved, and applied to improve the health and quality of life of humans. Working conditions should be observed and always improved with managers and administrators providing training, access to clinical evaluation, tests indicated after clinical evaluation, and appropriate treatment for all types of physical and psychological diseases that should be prevented, diagnosed, and treated. Intensive care medicine, since its implementation, has always been a male stronghold due to its complexity, intense work, prolonged shifts, and stressful situations with risk of life, requiring quick and assertive decision-making. Few medical women, even willing to specialize and work with intensive care medicine, could have access to this work environment that was reserved for medical men. Over time and over the years, we have seen more women attending medical school benches. Although the number of female students and medical trainees has reached an increasingly significant number, unfortunately we still observe few medical colleagues standing out in academic life, in public positions, or even in the professional evolution of their careers[7-17]. Menstrual cycles, pregnancy, motherhood, and responsibilities with the family, especially children, should be respected and solved and not characterized as weaknesses in the workplace.

Evaluating, observing, talking, and experiencing the banks of a medical school since 1978, progressing in my medical profession and academic career (I am currently an associate professor in pulmonology at FMUSP) with guidance and defense of more than 20 doctoral theses, and current scientific director of the Brazilian Association of Intensive Care Medicine (AMIB), I could conclude, without any conflict of interest regarding this topic, that several factors have to be observed and modified to allow the improvement of human beings regardless of gender or sexual orientation, age, race, political, or socio-economic level in the medical profession as well as in all professions to be able to evolve in their technical and human knowledge and exercise their profession with dignity and respect in order to help humanity prevent, understand, and treat the physical and mental diseases that can affect human beings. This requires in-depth study, knowledge evolution, technical training, physical and psychic training, as

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well as adequate structure and opportunities for the application of medical science to improve the health of the world's human population. We need to become aware and mature in the sense of perceiving and building protective mechanisms that allow people to develop in their fullness and be able to exercise their profession with respect, without jokes, calls, or unpleasant words, avoiding unequal opportunities. The power structures must be directed toward managing and providing conditions of individual development, equal opportunities, and conditions of study, professional development, and work that allow health professionals to diagnose and treat various physical and mental diseases. In intensive care units, with the humanization process, we have observed recently the progressive increase of medical women working in the treatment of critically ill patients, but still few in coordination and management positions. Women medical professionals should study, graduate, and exercise their profession in an equal way to men medical professionals with the same opportunities for professional development and their differentiated work skills respecting their individual and cultural characteristics and facilitating their improvement, growth, and practical application of medicine for the benefit of patients and the medical science[18-25].

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POINT OF VIEW

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Osteoporosis and fracture risk assessment: improving outcomes in postmenopausal women

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Osteoporosis is a skeletal disease characterized by impaired bone density, bone mineral density (BMD), and bone strength, resulting in bone fragility and an increased risk of fractures[1]. A fracture is the worst outcome for patients with osteoporosis, as it increases morbidity and mortality in addition to increasing the risk of new subsequent fractures. The main cause of osteoporosis in women is estrogen deficiency secondary to menopause[2,3]. Osteoporosis has a high prevalence and a social and financial impact. The prevalence of the diagnosis of osteopenia in postmenopausal women was present in 30–56.5% of the population, and osteoporosis enters the range of 14.7–43.4%[4]. Osteoporosis can lead to a major impact on public health, such as hospitalizations, surgeries with prostheses, temporary or permanent loss of mobility, and death[2,3].

Although BMD is a strong predictor of fracture risk, there are patients who may fracture even without presenting osteoporosis in the bone densitometry exam, making it necessary to evaluate risk factors other than bone density. In this context, the FRAX (Fracture Risk Assessment Tool) tool brings together other risk factors for fracture prediction independent of BMD, such as the presence of previous fragility fracture, hip fragility fracture in the parents, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and use of three or more units of alcoholic beverage per day[1-4].

Interestingly, FRAX is an algorithm that analyzes all clinical risk factors together and finally calculates the absolute risk of fracture in 10 years. Patients diagnosed with osteoporosis or those at high risk of fracture by FRAX deserve drug treatment targeting bone mass gain and fracture prevention. Among the drug strategies are anti-resorptive drugs (bisphosphonates and denosumab) and anabolic agents (teriparatide and romosozumab), which must be associated with other measures, such as physical activity, calcium intake, preferably in the diet, and supplementation of vitamin D[2].

The prevalence of osteoporosis increases with age, with a consequent increase in the number of fractures, either due to worsening of the bone structure, with thinning of the cortical bone, reduction of the trabeculae, and alteration of the bone microarchitecture, or due to the increased risk of falls, reduced lean mass, impairment of proprioception, and decreased visual acuity, among other factors. Osteoporotic fractures are those due to fragility, that is, low impact. Fragility fractures may be asymptomatic, mostly when occurred in the vertebral bodies with wedging, leading to height loss and dorsal hyperkyphosis[5].

Annually, almost 9 million fractures occur worldwide due to osteoporosis, which corresponds to an osteoporosis-related fracture every 3 s, and of these fractures, 1.6 million are hip fractures. The world estimate is that there are about 500 million people with osteoporosis, predominantly women, with an estimated fracture resulting from osteoporosis occurring in one in three women over 50 years and one in five men in the same age group[5].

BMD is directly related to fracture risk. The loss of 10% of BMD in the spine is associated with twice the risk of fracture, and the same loss of BMD in the hip leads to an increase in the risk of fracture by two and a half times. A previous fracture increases the risk of a new fracture by 86%, mainly in the subsequent 2 years. Despite the financial cost, morbidity, and mortality associated with osteoporosis, evidence shows that up to 80% of women with fragility fractures are not diagnosed or treated for osteoporosis[5].

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Assessing risk factors is a wise way to optimize resources for the best possible screening scheme. When the issue is fracture and refracture, the concept of the patient at imminent risk of fracture comes into play, a well-established situation whose intervention will be of great importance in the short term. In this concept, we have bone-related factors (mainly osteoporosis) and factors associated with falls, including risks during fracture rehabilitation. Patients at imminent risk of fracture are postmenopausal women who have had a previous fracture in the last 2 years, patients who already have a diagnosis of osteoporosis and start using glucocorticoids, and frail elderly people with a history of frequent falls, including those with neurological diseases or using psychoactive medications[5,6].

In Brazil, the estimated cost of fractures related to osteoporosis in 2018 was 310 million dollars, with 61% of this cost attributed to lost productivity and 19% to hospitalization (Figure 1). In a study involving four countries in Latin America, including Brazil, it was estimated that only 24% of patients with osteoporosis-related fractures received some type of drug treatment[7,8].

To improve people's health by reducing economic and social costs, multidisciplinary management, prevention of osteoporosis, as well as its active search, population screening with various diagnostic tools and its secondary prevention are urgent in global public health[5].

The first tool to assess fracture risk due to bone fragility is the clinical history. A good anamnesis makes it possible to identify classic risk factors as well as to suspect secondary causes that may contribute to a future fracture. BMD, usually performed by dual-energy X-ray absorptiometry (DXA), known as bone densitometry, is just one of several tools to stratify fracture risk[9]. It is not uncommon to observe in clinical practice patients with fractures outside the osteoporosis range. An important epidemiological study[10] demonstrated that most fractures occur in individuals whose T-score does not meet the conventional definition of osteoporosis (≤-2.5 SD) and therefore has low sensitivity when used alone for screening[10]. Glucocorticoid users, rheumatoid arthritis patients, diabetics, and long-term smokers are examples of patients whose risk of fracture is underestimated by DXA, since they present impairment of bone microarchitecture in addition to reduction of bone density[11].

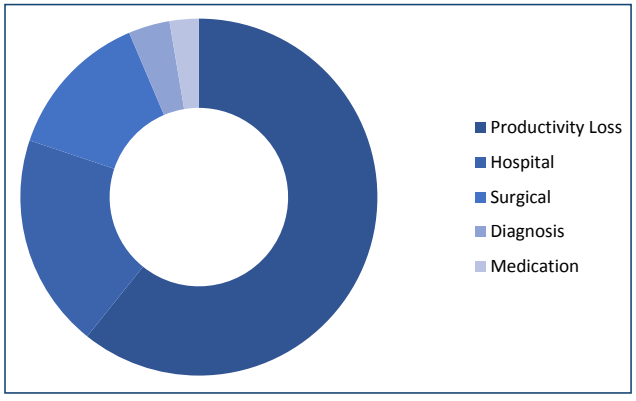

Figure 1. Osteoporosis in Brazil, financial cost. Adapted from Aziziyeh et al.[6].

Considering that not all patients will have easy access to DXA, the FRAX was implemented as a mathematical algorithm that brings together risk factors such as gender, age, use of glucocorticoids, presence of rheumatoid arthritis, current smoking, and history of parents with hip fracture, alone or in association with DXA of the femoral neck region. The FRAX is validated for women and men, 40–90 years old, and estimates in 10 years the absolute risk of hip fracture and major fractures (hip, proximal humerus, forearm, and spine)[9].

FRAX has some limitations; among them, it does not include the presence of diabetes mellitus and it does not distinguish between smoking history or glucocorticoid dose. Thus, in Brazil, it is recommended to adjust the FRAX with the NOGG/UK (National Osteoporosis Guidelines Group) strategy, accessed through the ABRASSO (Brazilian Association of Bone Evaluation and Osteometabolism) website (http://abrasso.org.br/calculadora/calculadora)[9].

In more than 10 years of use, it was observed that the current FRAX also has important limitations because it does not reliably contemplate some patient profiles[12]. In fact, FRAX does not consider diabetic patients, fracture time, or glucocorticoid dose. A patient who has had a recent fracture does not have the same risk as another who fractured more than 5 years ago[13]. A patient who uses glucocorticoids at a dose equivalent to prednisone 5 mg/day does not have the same risk as another who uses doses greater than 15 mg/day[12].

There are also other factors known to increase the risk of fractures, such as chronic falls, chronic kidney disease, or the use of drugs with a negative impact on bone metabolism[14,15]. Interestingly, it is possible to adjust FRAX for certain populations and even for patients who underwent TBS (Trabecular Bone Score), an image method that evaluates the bone microarchitecture of lumbar spine region. Some studies have already shown that the association of DXA and FRAX adjusted by TBS increases the number of individuals at high risk for osteoporotic fractures by up to 30% when compared to DXA alone[11,16].

Therefore, it is essential to consider tools to carry out fracture risk stratification more reliably, as well as evaluating the patient as a whole, considering genetic background, clinical,

and laboratory profiles. Attention should also be given to other environmental factors such as risk of falls, ability to perform physical activity, and nutritional support, as well as socioeconomic context and access to osteoporosis drugs. Figure 2 shows the fracture risk stratification criteria (low, moderate, high, and very high risk) and the main drug strategies for each group[17].

AUTHORS' CONTRIBUTIONS

MOP: Conceptualization, Writing – original draft, Writing – review & editing. **PPAP:** Conceptualization, Writing – original draft, Writing – review & editing. **AML:** Conceptualization, Writing – original draft, Writing – review & editing. **FMFG:** Conceptualization, Writing – original draft, Writing – review & editing. **MAARL:** Writing – review & editing.

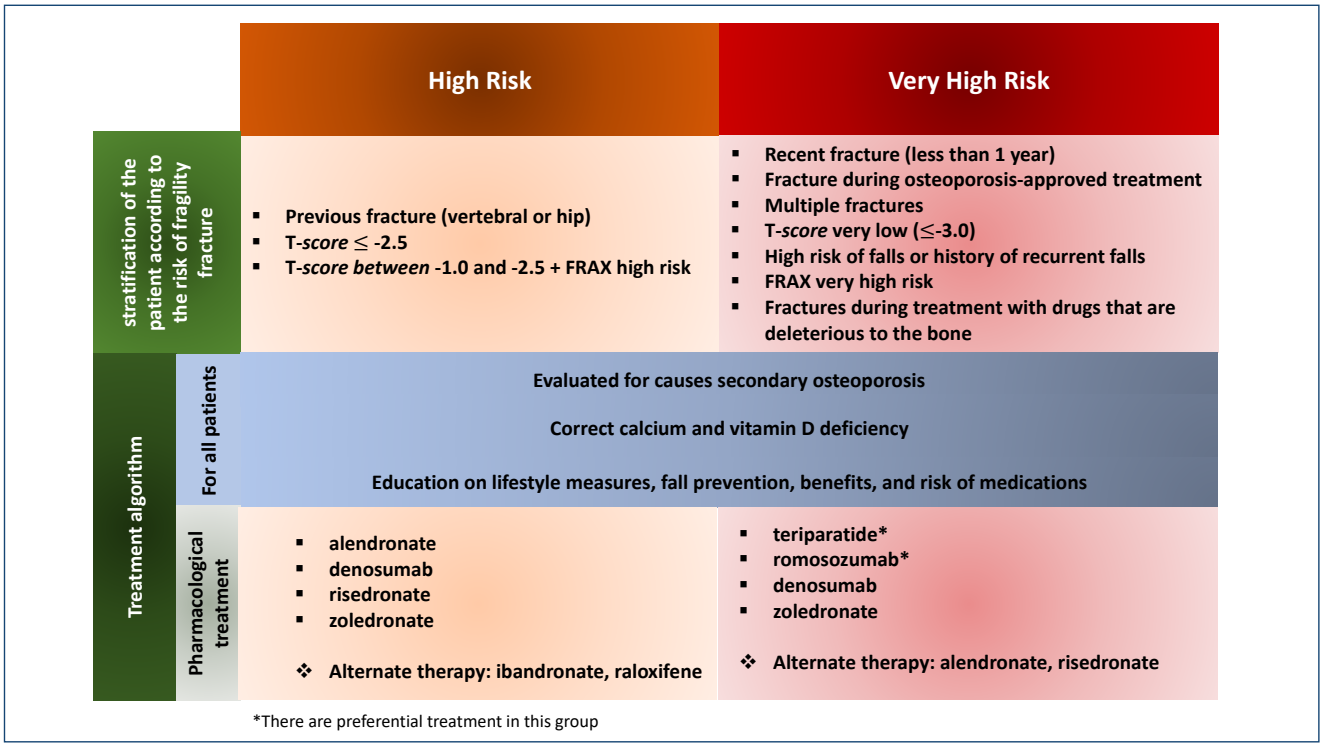

Figure 2. Stratification of the patient according to the risk of fragility fracture and their treatment algorithm in postmenopausal osteoporosis[17].

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SHORT COMMUNICATION

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Venous thromboembolism in women

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INTRODUCTION

Pregnant women have all the following three etiopathogenic components of Virchow's triad: (a) venous stasis, caused by compression of the inferior vena cava and left common iliac vein by the gravid uterus and by reduced venous tone because of the myorelaxant action of progesterone; (b) hypercoagulability, secondary to induction of hepatic synthesis of coagulation factors VII, VIII, and X by placental estriol, increased levels of fibrinogen and plasminogen activator inhibitor types I and II, and reduced synthesis of protein S; and (c) endothelial injury, which occurs during nidation, endovascular remodeling of the uterine spiral arteries, and expulsion of the placenta[1,2].

During pregnancy, the risk of venous thromboembolism (VTE) increases by 5–10 times and can be 35 times higher during puerperium when compared with the rate among non-pregnant women of the same age. After delivery, the frequency reduces rapidly, but there is a residual risk for up to 12 weeks. Approximately two-thirds of deep venous thrombosis (DVT) occurs during the gestational period, equally distributed across the three trimesters. However, 43–60% of pulmonary embolism episodes occur during the first 6 weeks of the puerperium[1,2].

Among pregnant women, when compared with non-pregnant women, DVTs in the left lower limb (90 vs. 55%) and the iliofemoral segment (72 vs. 9%) are even more predominant. This is because of the accentuated compression of the left common iliac vein against the fifth lumbar vertebra by the right common iliac artery, caused by the gravid uterus[1,2].

The main risk factors for VTE during pregnancy are overweight, obesity, age of 35 years or more, inherit or acquired thrombophilias, long-distance travel, immobility, hospital admission during pregnancy, certain comorbidities (inflammatory intestinal disease, urinary tract infection, systemic lupus erythematosus, pregnancy-induced systemic arterial hypertension or pre-eclampsia, and non-obstetric antenatal surgery), obstetric hemorrhage, and hyperemesis.

Prevention of VTE in pregnancy by means of application of guidelines and implementation of mechanical and/or pharmacological prophylaxis is still the best strategy for reducing the rate of these events[1,2].

PECULIARITIES OF ANTICOAGULANT TREATMENT DURING GESTATION AND PUERPERIUM

Administration of warfarin between the 6th and 12th weeks of gestation can induce fetal embryopathy (nasal hypoplasia and/or stippling of the epiphyses), abnormalities of the central nervous system (dysplasia of the dorsal midline with agenesis of the corpus callosum, atrophy of the cerebellar midline, dysplasia of the ventral midline with optical atrophy, and amaurosis and hemorrhage), and fetal bleeding. However, warfarin is safe while breastfeeding[3].

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Despite the existing direct oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban), they are contraindicated in pregnancy because they cross the placental barrier and in breastfeeding because they pass into breast milk[3].

Therefore, the treatment of VTE in these periods should preferably be done with heparins, preferably low molecular weight heparins (LMWH) or fondaparinux, when there are restrictions on their use[3].

CHOICE OF DELIVERY IN ANTICOAGULATION WOMEN

The choice of delivery route is obstetric, and there is no contraindication against artificial cervical ripening or induction of labor. Delivery of an anticoagulated pregnant woman should be scheduled for 37–40 weeks. LMWH should be withdrawn 12 h before delivery if given at prophylactic dosages or 24 h before if administered at intermediate or full dosages, enabling safe administration of spinal or epidural anesthesia. The patient should continue wearing antiembolism stockings throughout the procedure, regardless of the mode of delivery chosen[4,5].

Although the risk of VTE associated with caesarean in isolation is low, the rate of VTE occurrence becomes significant when other risk factors exist, and so thromboprophylaxis should be prescribed, based on risk stratification with a risk assessment model[4,5].

RISK STRATIFICATION

Stratification of VTE risk in pregnancy should be performed for all women who intend to become pregnant or as soon as they become pregnant and should be repeated throughout the prenatal period, since new risk factors could emerge. The patient's preferences and views should be taken into account when choosing thromboprophylaxis, even though the treatment options are restricted in this situation[4].

The most relevant guidelines on the subject of diagnosis, prophylaxis, and treatment of VTE in pregnancy are those published by the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, the Royal College of Obstetricians and Gynaecologists, and the American College of Chest Physicians[1-5].

VENOUS THROMBOEMBOLISM AND CONTRACEPTION

In Brazil, one in every five women uses oral contraceptives (OCs), which offers benefits that go beyond contraception, such as reduction of menstrual bleeding, dysmenorrhea, premenstrual syndrome, migraine, acne, and hirsutism. The long-term benefits of OCs include reduced rates of endometrial, ovarian, and colorectal cancer[4].

OCs increase the risk of VTE from a baseline rate of 5/10,000 woman-years among non-users to 9 to 10/10,000 woman-years among users[3,4]. To keep this risk in perspective, it is important to remember that the risk of VTE is 29/10,000 during pregnancy and 300–400/10,000 in puerperium[4].

The thromboembolic risk of OCs depends on the estrogen dosage and the type of progestogen combined with it. Old OCs with high estrogen levels (>50 µg of ethinylestradiol [EE]) are linked with a greater risk of VTE than modern OCs (<50 µg of EE). Notwithstanding, no reduction of risk was confirmed with OCs containing 20 µg of EE compared with pills containing 30 µg of EE[4].

The type of progestogen also influences the risk of VTE, and second-generation progestogens (levonorgestrel [LNG] and norethisterone) are safer than third- and fourth-generation ones[4].

The risk of VTE associated with OCs increases with body weight and age and with reintroduction or change of OC after a withdrawal exceeding 4 weeks[4].

Among users of OCs, those with hereditary thrombophilia are at higher risk of VTE. However, because of the low prevalence of hereditary thrombophilias and the high cost of screening for them, routine testing is not recommended[4] and the presence of a personal or family history of VTE is a stronger and more common risk factor for OC-linked VTE[4].

Non-oral contraceptives, including patches and vaginal rings, are also associated with an increased risk of VTE, raising the risk of VTE by 7.9 and 6.5 times, respectively[4].

Coagulation does not exhibit significant changes with progesterone-only OCs, implants containing LNG, LNG intrauterine system, or medroxyprogesterone injection in depot form; therefore, the use of these is safe in this situation[4].

VENOUS THROMBOEMBOLISM AND ASSISTED FERTILIZATION

In vitro fertilization (IVF) is the most widely used technique for human reproduction in infertile couples, and VTE is a rare complication of this technique, occurring in 0.1–2.4% in each fertilization cycle[4].

The risk of VTE is two times higher during the prenatal period after IVF, when compared with the baseline risk of other pregnant women, due to a 5–10 times increase in the risk during the first trimester of gestations after IVF, partly secondary to ovarian hyperstimulation syndrome (OHS),

which is an iatrogenic and potentially fatal complication that occurs in 33% of all cycles generated by IVF[5]. Women who have OHS are at 100 times greater risk of VTE, and, in severe OHS, thromboprophylaxis with LMWH reduces VTE without significant increase in bleeding[4].

VTE associated with IVF has a propensity to sites in the upper extremities and the cervical region rather than in the left lower limb[4].

IVF also increases the risk of arterial thrombosis, which occurs earlier, on average on the 10th day after the transfer of the embryo[4].

VENOUS THROMBOEMBOLISM AND HORMONE REPLACEMENT THERAPY

Although recent data show that the risks could outweigh the benefits for women who take hormone replacement therapy (HRT), many are still prescribed estrogens to minimize symptoms of climacteric, which can be an additional risk factor for VTE, particularly during the first year[4].

Observational studies, systematic reviews, and meta-analyses consistently report a 2–3 times greater risk of VTE among postmenopausal women on HRT[4].

There is evidence that the risk of VTE among users is dependent on the route of estrogen administration. Oral route estrogen provokes procoagulant changes, such as increased resistance to active C protein, by reducing serum concentration of protein S, probably because of the passage of estrogen through the liver and reduction of fibrinolytic activity; these changes are not observed with the transdermal route[4].

To prevent VTE in women who request HRT, it is important to identify susceptible subsets. Hereditary thrombophilias are well-established risk factors for VTE, increasing the risk by three times in postmenopausal women. The combination of these mutations with estrogen taken orally increases the risk of VTE compared to the risk among women without these mutations and not taking estrogen[4].

Women with a personal and family history of VTE are considered high-risk and, therefore, are not candidates for HRT with oral route estrogen[4].

HRT is the most effective treatment for climacteric symptoms associated with falling estrogen levels after menopause[6], and after evaluation of the risks and benefits, HRT should be prescribed with the lowest transdermal estrogen dose alone or combined with micronized progestins and the shortest duration possible[4].

VENOUS THROMBOEMBOLISM IN TRANSGENDER WOMEN

The terms transgender and gender nonconformity describe a situation in which a person's gender identity differs from the external sexual anatomy they were born with. The objectives of gender affirmation in transgender women are to suppress male characteristics and induce female characteristics to the extent possible. Gender affirmation can encompass hormone therapy (HT) and affirmation surgery[7].

Provision of physician-guided gender affirmation HT has shown improved quality of life, and it reduces the disorders observed in this population, including VTE[7].

Several different studies have demonstrated an increased risk of VTE in transgender women who are on HT, which is related to the type and dosage of the hormones employed and, primarily, to the route of administration[1]. This can be a determinant factor in the choice of HT, making transdermal administration the preferred route for transgender women with a personal or family history of VTE or those who have thrombophilia[7].

Oral administration induces the hepatic first-pass effect with increased pro-thrombotic factors, whereas non-oral routes and transdermal administration in particular do not appear to induce increased VTE[7].

This can be a determinant factor in the choice of HT, making transdermal administration the preferred route for transgender women with a personal or family history of VTE or those who have thrombophilia[7].

It should be emphasized that HT is not an elective treatment in this population but an absolute necessity to achieve the desired phenotype. In many places, these women are at the margins of society and cannot access professionals who are able to prescribe HT. As a consequence, estrogens are very often obtained illegally and taken on the person's own initiative, without professional guidance on the safest composition, dosage, and route of administration. Another point to be considered is that non-oral HT presentations are normally more expensive than oral preparations and thus inaccessible to the majority of people. One feasible strategy to attenuate the risk of VTE in groups at risk is to initiate prophylactic anticoagulation simultaneously with HT, especially for the first 6–12 months of treatment[7].

VENOUS THROMBOEMBOLISM IN WOMEN WITH CANCER

Breast and cervical cancer are prominent causes of female morbidity and mortality worldwide. Excluding non-melanoma skin cancers, breast cancer is the most common among

women, accounting for 2.1 million new cases and approximately 600,000 deaths in 2018[6,8]. In Brazil, it is the most common cancer in females in all regions of the country[8]. Cervical cancer is the second most frequent cancer among women in the North, Northeast, and Midwest regions, while it ranks fourth and fifth in the South and Southeast regions, respectively[8].

Cancer is widely known to increase the risk of thromboembolic complications. This risk is related to the characteristics of the patient, their comorbidities, and their clinical conditions, in addition to several factors related to the tumor and the phase of treatment. Appropriate prophylaxis for DVT should be based on risk groups and individual patient conditions. In many cases, multiple factors are present, and the risks are cumulative[8]. The risk must be well defined using risk assessment models so that the application of prophylactic recommendations is adequate and effective. In general, the duration of prophylaxis in cancer patients is longer and should always be considered, always remembering the risk stratification, especially in the perioperative and chemotherapy periods[8].

CONCLUSIONS

VTE is a current challenge in obstetric practice, particularly after the reductions in hemorrhagic complications and infectious diseases observed in more developed settings. Preventative interventions of a mechanical and pharmacological nature based on guidelines and protocols reduce its occurrence and its short- and long-term complications.

Irrespective, adequate attention to contraception and HRT also demands maturity and knowledge. Simply prohibiting the use of OCs and HRT without carefully assessing risk factors and family and personal history does not decisively combat the occurrence of VTE and unnecessarily exposes women to a risk of reduced quality of life.

It is important to emphasize that transgender women exhibit peculiarities inherent to the use of HT and difficulties with access to medical services, which, in the final analysis, expose this population to higher incidences of underdiagnosed complications. The occurrence of VTE in the transgender population is one of the many facets that modern medicine must deal with.

AUTHORS' CONTRIBUTIONS

MAM: Conceptualization, Data curation, Formal Analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **JCPO:** Conceptualization, Investigation, Visualization, Writing – original draft. **EEJ:** Conceptualization, Investigation, Visualization, Writing – review & editing. **ALMLO:** Conceptualization, Investigation, Methodology, Visualization. **AJAR:** Conceptualization, Investigation, Visualization, Writing – review & editing. **MLS:** Conceptualization, Investigation, Validation, Visualization. **WJBA:** Conceptualization, Investigation, Supervision, Visualization. **RKAF:** Conceptualization, Formal Analysis, Investigation, Visualization. **BG:** Conceptualization, Investigation, Project administration, Visualization. **APRMP:** Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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Impact of breast augmentation on female sexuality

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SUMMARY

INTRODUCTION: The breasts are symbols of femininity, sexuality, and maternity. Breast augmentation is among the most sought-after procedures for women and has a positive impact on quality of life. Sexuality is one of the items that contribute to increased quality of life. Surgical outcomes can be evaluated from the patients' perspective using developed and validated questionnaires. For the assessment of sexuality, the most commonly used instruments are the Female Sexual Quotient and the Female Sexual Function Index, which estimate several domains of sexuality and can be used to evaluate the impact of surgery on it.

OBJECTIVE: The objective of this study was to evaluate the impact of breast augmentation on female sexuality.

METHODS: We selected 87 patients from the Plastic Surgery Outpatient Clinic of Hospital São Paulo (Federal University of São Paulo) who wished to undergo breast augmentation. The patients were classified into two groups: the Female Sexual Quotient questionnaire was applied to one group, and the Female Sexual Function Index questionnaire was applied to the other group to evaluate sexuality preoperatively as well as at 2 and 4 months postoperatively.

RESULTS: In both groups, there was a significant increase in the total score of the Female Sexual Quotient and Female Sexual Function Index questionnaires, and an individual increase in each domain assessed, with a significant increase in the domains of orgasm and sexual satisfaction, as well as foreplay and arousal, indicating an improvement in the patients' sexuality postoperatively.

CONCLUSION: Breast augmentation has a positive impact on female sexuality; furthermore, the Female Sexual Quotient and Female Sexual Function Index are sensitive in detecting this impact.

KEYWORDS: Mammaplasty. Self concept. Sexuality. Surveys and questionnaires. Quality of life.

INTRODUCTION

The breasts are an important symbol of femininity, sexuality, and maternity in women[1-4]. Breast distortions, changes in breast shape, variations in breast size, as well as breast surgery can have a great impact on women's quality of life[5].

Quality of life is related to several areas of personal life, including sexuality. Discontentment in relation to body contour may lead to sexual dysfunction and impair quality of life[6-9].

According to the International Society of Aesthetic Plastic Surgery, breast augmentation is the most commonly performed plastic surgery worldwide[10]. One of the most appropriate and valued ways to evaluate the results of plastic surgery is through a questionnaire answered by the patients, in which the impact of surgery on their daily activities, quality of life, satisfaction, and physical and sexual well-being, among others, is evaluated[11].

The Female Sexual Quotient (QS-F) is a questionnaire that was developed in Brazil to evaluate the overall quality of a woman's sexual performance and satisfaction. The assessment consists of 10 questions with answers ranging from 0 (never) to 5 (always) about the phases of the sexual response cycle and the following domains: sexual desire and interest, foreplay, personal arousal and attunement with partner, comfort, orgasm, and satisfaction. This method was developed for the Brazilian population and can be used to measure the change in women's sexuality after a surgical procedure[12].

The Female Sexual Function Index (FSFI) is a tool developed to evaluate women's sexual function with 19 questions on the domains of desire, arousal, lubrication, pain, orgasm, and satisfaction. The questionnaire can be used to assess changes in quality of life with regard to sexuality[13].

OBJECTIVE

The purpose of this study was to evaluate the impact of breast augmentation on female sexuality.

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METHODS

This is a clinical, secondary, interventional, longitudinal, prospective, and analytical study conducted at a single center. The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP).

We selected 87 patients from the Plastic Surgery Outpatient Clinic of Hospital São Paulo of UNIFESP, who had hypomastia and desired breast augmentation.

The inclusion criteria were as follows: women between 18 and 55 years of age; a minimum educational level of 5th grade of elementary school; and women with small breast size according to the Sacchini index (Sacchini<9.0 cm)[14].

The noninclusion criteria were pregnancy, delivery, or lactation within less than 1 year, systemic diseases or chronic use of medication, smoking, or chest deformities, and a previous breast surgery.

The exclusion criteria were pregnancy, failure to fill out the questionnaires properly, withdrawal from the ongoing study, presence of a complication that required a new surgical intervention, or nonattendance at postoperative follow-up visits.

The patients were classified into two groups, according to the sexuality questionnaire applied: patients in the first group (QS-F) were assessed using the QS-F questionnaire before and after surgery, while those in the other group (FSFI) were assessed using the FSFI questionnaire.

The surgeries were performed in the surgical center of Hospital São Paulo by the breast reconstruction group with the placement of subglandular silicone implants.

All patients received a first-generation cephalosporin as prophylactic antibiotic therapy during the induction of anesthesia; antisepsis was observed with the use of alcohol solution and placement of sterile drape. An incision measuring approximately 4 cm in the mammary fold and dissection of the skin, subcutaneous cellular tissue, and mammary gland were performed. A cavity was made, and the round, textured silicone gel implant was placed in the pre-pectoral position, followed by plane closure and dressing placement.

The patients completed the questionnaire during the preoperative visit and in the postoperative period at their 2- and 4-month follow-up visits. The QS-F was developed and validated in the Brazilian population and is composed of 10 questions on approximately 5 domains of female sexual function (desire and interest, foreplay, arousal and tuning, comfort, and orgasm and satisfaction) with a score ranging from 0 (never) to 5 (always) per question. The higher the score, the higher the sexual performance/satisfaction[12].

In the other group, the Brazilian version of the FSFI questionnaire was used; this version comprises 19 questions that evaluate the sexual function in the last 4 weeks in the following six domains of female sexuality: desire, arousal, lubrication, orgasm, satisfaction, and discomfort/pain. Each question is assigned a score from 0 to 5, with 0 indicating that the item was not experienced by the patient, 1 almost never or never, and 5 almost always or always. The higher the final score, the better the sexual function[13].

RESULTS

In the QS-F group, 45 patients completed the study and 2 patients were excluded, while 40 patients in the FSFI group completed the study. Both groups had a mean age of between 25 and 26 years and a mean body mass index of 21.4 kg/m^2.

Figures 1 and 2 illustrate the mean total scores of the QS-F and FSFI questionnaires, respectively, preoperatively as well as at 2 and 4 months postoperatively.

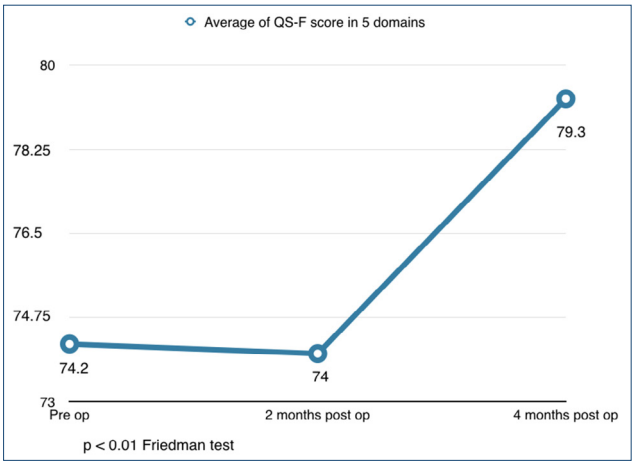

Figure 1. Average of Female Sexual Quotient total score, by time.

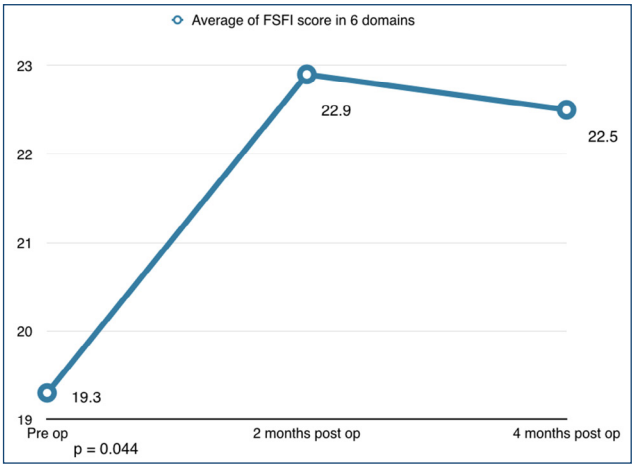

Figure 2. Average of Female Sexual Function Index total score, by time.

Figure 3 shows the correlation of the domains evaluated separately in each questionnaire and indicates whether there was a significant increase 4 months after surgery. The only domain that presented significant improvement in isolation in both groups was the domain of arousal and harmony with the partner.

In the QS-F group, the mean score in the arousal and harmony with the partner domain was 8.2 preoperatively, increased to 8.3 at 2 months postoperatively, and 8.9 at 4 months postoperatively. In the FSFI group, the mean score in the arousal domain was 2.8 preoperatively, increased to 3.6 at 2 months postoperatively, and 3.6 at 4 months postoperatively.

DISCUSSION

The breast is part of the female body and is closely related to self-image and contentment with oneself. Breast changes and deformities can cause physical and psychological disorders in women[2]. A breast surgery that proposes to change its shape and size can lead to improvements in several pillars of quality of life[15]. Self-confidence and personal satisfaction with one's own body affect how an individual relates to himself or herself, including his or her sexuality, which is related to sexual attraction and responsiveness[16-18].

To understand the changes breast augmentation causes in women's sexuality, two questionnaires validated as evaluation instruments, the FSFI and the QS-F, were applied preoperatively as well as at 2 and 4 months postoperatively.

In the group in which the QS-F questionnaire was applied, the mean score of the questionnaire covering the five domains in the preoperative period was 74.2, which decreased to 74 at 2 months postoperatively and increased to 79.3 at 4 months postoperatively. A slight reduction in the score was observed at 2 months postoperatively, which can be attributed to the recent postoperative period in which there is still pain and discomfort in the breasts and guidance to restrict sexual activity. However, a subsequent significant increase was seen 4 months postoperatively ($p<0.01$), demonstrating improvement in the sexuality of these patients.

QS-F	FSFI
Sexual desire and interest: increase p=0.204	**Desire:** increase p=0.014
Foreplay: increase p<0.01	**Arousal:** increase p=0.184
Personal arousal and attunement with partner: increase p<0.01	**Lubrication:** increase p=0.017
Comfort: increase p=0.997	**Pain:** increase and after decrease p=0.637
Orgasm and Satisfaction: increase p<0.01	**Satisfaction:** increase p=0.016 **Orgasm:** increase p=0.081

Figure 3. Comparison of results in each domain in both groups. Average of Female Sexual Function Index total score, by time.

In the group in which the FSFI was applied, the average score of the questionnaire covering the six domains preoperatively was 19.3, which increased to 22.9 at 2 months postoperatively, and was 22.5 at 4 months postoperatively, which indicated an improvement in the sexuality of these patients (p=0.044).

Sahebalzamani et al., developed a questionnaire on sexuality for both women and their partners, involving several items about the couple's sexual life with the objective of evaluating a change in sexual satisfaction of the woman and her partner after breast augmentation. Similar to the present study, the questionnaires were applied before the surgery and 2 months postoperatively.

A significant increase in sexual satisfaction was found in women who underwent breast augmentation, corroborating the results of this study; however, no significant change in their partners was observed[19]. Coriddi et al., also demonstrated an improvement in sexual well-being after breast augmentation using BREAST-Q as an assessment tool[20].

Both questionnaires address the same aspects of female sexuality; however, the QS-F organizes these aspects into five different domains, while the FSFI uses six different domains. There is some divergence in the nomenclature of the domains in each questionnaire; however, a comparison of both reveals that the domains are equivalent, as can be seen in Figure 3.

The QS-F group showed an increase both at 2 months postoperatively and a further increase in the patients' average score at 4 months postoperatively in all domains assessed. However, the increase was significant in the domains of arousal and attunement with one's partner, foreplay, and orgasm. Furthermore, although the FSFI group showed a higher score at 4 months than at the initial assessment in all domains, only the domain of desire and arousal had a significant increase.

The domain of desire and arousal is closely related to the psychological part of a woman, how she feels about herself, and her self-confidence in relation to her partner. A probable explanation for this significant increase in both groups is that patients who seek breast augmentation are somehow dissatisfied with their body image, which negatively affects their self-esteem, impacting their sexual desire and arousal. After breast augmentation, women have greater satisfaction with their body image, which leads to greater sexual desire and arousal[16].

In both groups, the domains of comfort, pain, orgasm, and satisfaction did not show a significant increase.

Although the questionnaires were developed in different countries—QS-F in Brazil and FSFI in the United States—both were sensitive in assessing sexual function with similar results in comparable groups and demonstrated improved sexuality after breast augmentation.

CONCLUSION

Breast augmentation has a positive impact on the sexual function of women with hypomastia. The QS-F and the FSFI questionnaires were sensitive tools for detecting this change in sexual function.

AUTHORS' CONTRIBUTIONS

PAMPG: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. **EMKA:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. **MLM:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. **MSN:** Supervision, Writing – review & editing. **LMF:** Supervision, Writing – review & editing

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ORIGINAL ARTICLE

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Cardiovascular diseases in women: a differentiated view and risk stratification

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Brazilian Society of Cardiology

SUMMARY

Cardiovascular diseases are the main cause of mortality in men and women worldwide, surpassing mortality from all associated neoplasms. In women, its prevalence and mortality increase at menopause, but complications of reproductive age, such as preeclampsia and eclampsia, lead to increased cardiovascular risk throughout their lives. Coronary ischemic disease is is the leading cause of death in Brazil and worldwide, with atherosclerotic disease being the principal pathophysiological mechanism. However, in women, other mechanisms are associated with myocardial ischemia, such as microcirculation disease and/or vasospasm, due to the anatomical and hormonal characteristics of women in different stages of their lives. Knowledge of the most prevalent cardiovascular diseases in women, as well as the specific risk factors, the traditional ones with the greatest impact, and the under-recognized ones, is of fundamental importance in their risk stratification, diagnosis, and management, fundamentally aiming at reducing mortality.

KEYWORDS: Cardiovascular diseases. Menopause. MINOCA. Heart disease risk factors.

INTRODUCTION

The most prevalent cardiovascular diseases (CVD) in women are ischemic heart disease (IHD), followed by cerebrovascular disease. IHD is the leading cause of death in Brazil, accounting for 12.03 and 12.2% of deaths in women and men, respectively; however, the percentage of deaths due to cerebrovascular accident (CVA) is higher in women than in men (10.39 and 8.41%, respectively)[1].

The main cause of IHD is coronary atherosclerotic disease (CAD) in men and women, but IHDs without obstructive lesions, such as microcirculation disease (CMD), vasospasm, coronary embolism/thrombosis, and spontaneous coronary artery dissection (SCAD), the latter more frequent during pregnancy, are more common in women and not infrequent in younger ones[2].

In the reproductive phase, hypertensive disorders of pregnancy (HDP) remain an important cause of complications and maternal-fetal mortality, being the second leading cause of mortality and disability-adjusted life years (DALYs)[1]. Complications such as preeclampsia (PE) and eclampsia (ECL), Hellp syndrome, gestational diabetes (GD), and acute kidney disease (AKD) increase a woman's cardiovascular risk (CVR) throughout her life cycle. Therefore, HDP, notably PE, ECL, and GD, are considered sex-specific cardiovascular risk factors (CVRFs)[3,4].

Heart failure with preserved ejection fraction (HFpEF), which is more prevalent in women, becomes more frequent with aging. Hormonal pathophysiological mechanisms, especially after menopause, lead to a higher prevalence of HFpEF, such as changes in the renin-angiotensin-aldosterone system, response to endothelial injury, left ventricular (LV) remodeling, and microcirculation dysfunction[5].

Other HF phenotypes in women are Takotsubo cardiomyopathy and peripartum cardiomyopathy (PPCM). In Takotsubo cardiomyopathy, there is acute, reversible, LV failure, usually secondary to stress-induced adrenergic discharge, and 95% of case are women who are affected mainly in the postmenopausal period. Most cases recover LV function within 3 months, with low recurrence (2–5%)[6]. PPCM is characterized by LV

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dysfunction at the end of pregnancy or in the first five postpartum months, especially in the first week, being a diagnosis of exclusion. The main risk factors (RFs) for PPCM are advanced age, PE, and multiple pregnancies. The prognosis is favorable, with the recovery of LV function within 6 months in more than 70% of cases[6]. Regarding mortality from HF, there are no differences in relation to men, although women are at greater risk (because they are older and have more comorbidities)[2].

CARDIOVASCULAR RISK FACTORS AND PECULIARITIES IN STRATIFICATION

Despite the importance of addressing CVRFs and their relationship with IHD in women, these are underrepresented in most clinical trials, and CVR stratification scores do not include RF inherent in women. The most current guidelines recommend that, in the evaluation of CVD, along with traditional and well-established RFs, gender-specific ones, such as polycystic ovary syndrome, use of hormonal contraceptives, HDP and its complications such as PE, ECL, and DG, menopausal hormone therapy, and the aggregate risks of inflammatory and autoimmune diseases, can be considered. It is important to remember that the traditional and most impacting RFs in women are diabetes mellitus (DM), systemic arterial hypertension (SAH), dyslipidemia, smoking, obesity, and sedentary lifestyle. No less important in women are the under-recognized RFs, such as depressive disorders and social determinants of health, which contribute as potentiating risk factors (PFs) for better risk stratification and cardiovascular prevention. It is well described that, in women, these RFs interact with each other promoting inflammation, endothelial dysfunction, atherosclerosis, and autonomic and immune dysfunction, with a consequent increase in risk[2] (Figure 1).

The use of the classic Global Risk Score (GRS) associated with knowledge about specific RF, under-recognized RF, and PF allows us to reclassify women in terms of their risk. A more comprehensive and effective stratification leads to the possibility of earlier interventions, such as lifestyle change guidelines and the use of statins, seeking to achieve established goals for the control of CVD. In women stratified by GRS at intermediate or low risk, in the presence of PF, the assessment of the coronary calcium score (CAC) should be considered. If the CAC is zero, the statin should not be started unless DM, a family history of premature CAD, or smoking is present. A CAC between 1 and 99 favors the use of statins, especially in women over 55 years old. If the CAC is greater than 100 or above the 75th percentile for age and sex, the use of statins is indicated[2] (Figure 2).

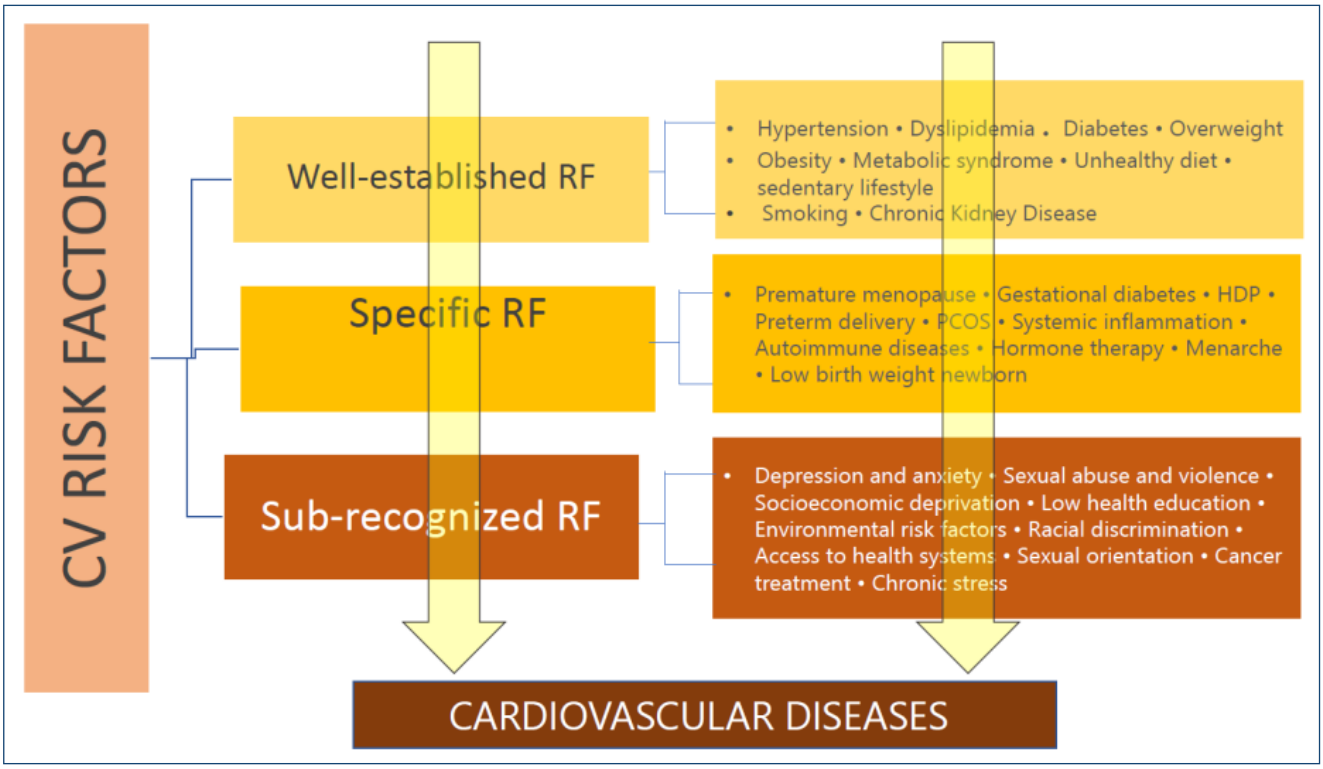

Figure 1. Cardiovascular risk factors in women (adapted from the Women's Cardiovascular Health Position 2022[2]). CV: cardiovascular; RF: risk factor; HPD: hypertensive disorders in pregnancy; PCOS: polycystic ovary syndrome.

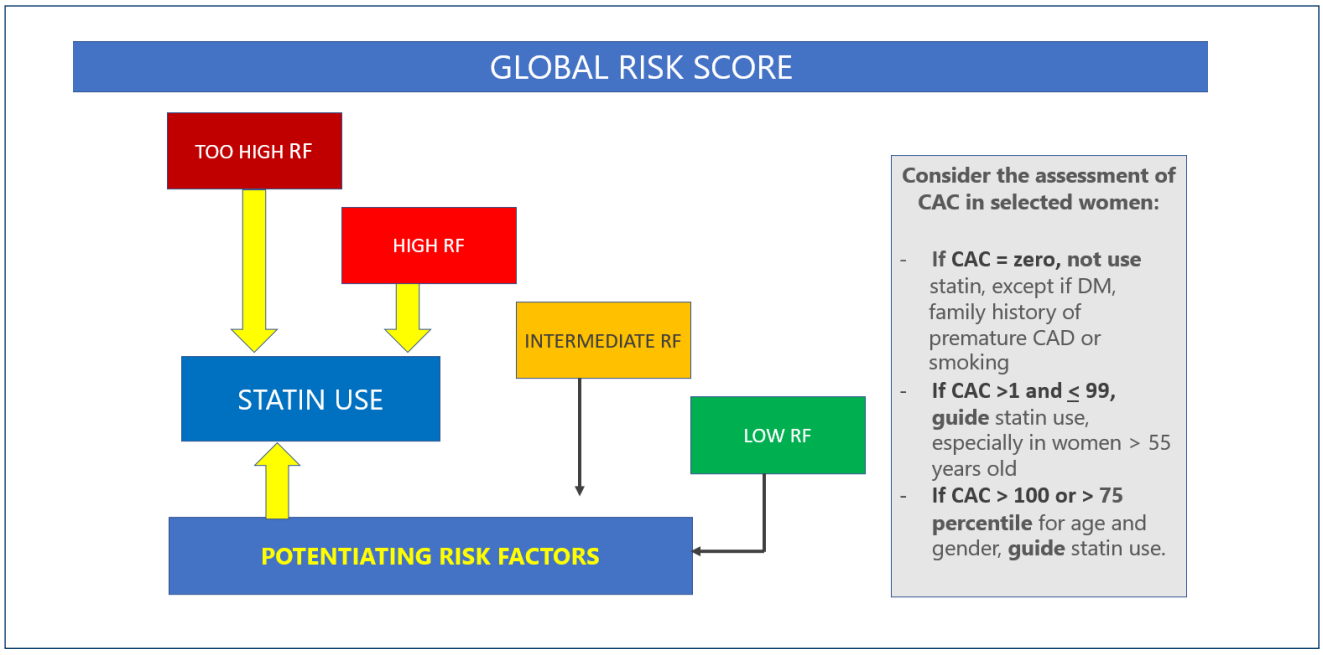

Figure 2. Stratification of cardiovascular risk in women (adapted from the Women's Cardiovascular Health Position 2022[2]). RF: risk fator; CAC: coronary calcium score; DM: diabetes mellitus; CAD: coronary artery disease.

CONSIDERATIONS ON DIAGNOSTIC METHODS IN DIC

Women with IHD behave differently from men due to the presence of peculiar pathophysiological characteristics, such as less caliber arteries and a higher prevalence of CMD. Coronary Ischemia without severe obstructive lesions (INOCA) and infarction without occlusive atherosclerotic lesions (MINOCA) are more frequent in women. Therefore, the sensitivity and specificity of the diagnostic tests are different, which deserves some consideration.

The baseline electrocardiogram (ECG) of women has its own characteristics such as a longer QT interval, changes in the ST-T segment, and flattening of the T wave. In addition, it can show changes that lead to misinterpretation, such as ST-T depression, T-wave inversion, and signs of LVH, which are described in up to 45% of women with breast implants[7].

Exercise stress testing (ET) has a sensitivity of 62% and specificity of 68% with a positive predictive value of only 47%, but a high negative predictive value. Factors that may contribute to the inaccuracy of the ST response as a predictive tool include a lower prevalence of obstructive CAD in women compared to men and ST changes due to estrogen, mitral valve prolapse, coronary vasospasm, and CMD, which are more prevalent in women than in men. The association of ET with stress myocardial scintigraphy is an excellent strategy to increase the accuracy of the method[8,9].

Coronary angiography can be normal or present less severe obstructive lesions, even in the presence of ischemic symptoms, which leads to its non-appreciation, delaying the diagnosis and treatment of IHD. It is important to remember that women are at greater risk of developing AKD due to the contrast, in addition to presenting vascular complications because of the anatomical characteristics of their vessels[10].

Coronary computed tomography angiography is important in the diagnosis of non-obstructive IHD. CAC is an important method in the therapeutic decision in women with low and intermediate risk stratification in the presence of PF (Figure 2). The presence of CAC greater than zero associated with mammary arterial calcification has a greater correlation with ischemic events in women than in men[11].

Cardiac magnetic resonance (CMR) provides data on perfusion and cell metabolism, with high sensitivity and specificity (89 and 80%) to detect IHD, and can be used in pregnant women, in addition to helping in the differential diagnosis of cardiomyopathies, and also in the analysis of cardiotoxicity in women undergoing treatment for breast cancer[12].

Measurement of carotid intima-media thickness by vascular ultrasound for risk reclassification is useful in women with at least two CVRFs. The presence of atheroma plaque in the carotid arteries is an aggravating factor for stratification in cases of intermediate risk[11].

FUTURE PERSPECTIVES

A clear understanding of disparities in morbimortality from CVD in women is essential for the development of measures to prevent and control these diseases, such as promoting a healthy lifestyle and controlling CVRFs deeply[2]. Reducing the burden of CVD in women by 2030 is an ambitious goal, but an imperative, especially as most CVRFs can be modified and mitigated[13]. It is important to understand which mechanisms contribute to the worsening of the profile of women with emerging and non-traditional, exclusive or more common RFs, contributing to a better understanding of their mechanisms of CVD.

Recent studies demonstrate that epigenetic modifications play an important role in the occurrence and development of CVD and are differently associated with cardiometabolic characteristics in type 2 DM, stroke, and myocardial infarction (MI) in men and women[14]. In the future, with greater knowledge about the molecular mechanisms of epigenetics in the regulation of CVD, more strategies for its prevention may be implemented, in addition to the design of new sex-specific drugs, increasing their efficiency.

During pregnancy, women with or without heart disease are more vulnerable to adverse cardiovascular events. Today, heart diseases are the main cause of maternal death[15], including HDP, more specifically PE, the main cause of maternal mortality and morbidity in Brazil and Latin America[16]. The Ministry of Health, despite having implemented several policies to strengthen and qualify actions in the care of pregnant women during prenatal care, childbirth, and the puerperium, did not reach the goal recommended by the WHO to reduce the maternal death rate, i.e., 35 maternal deaths for every 100,000 live births (2015)[17]. According to the data recorded in the Maternal Mortality Monitoring Panel in 2021, the country had an average of 107 deaths per 100,000 births[18]. Most cardiovascular complications that develop during pregnancy can be prevented and treated early. The development of combined cardio-obstetrics care should be implemented as a model of antenatal care to improve maternal and fetal outcome[19,20].

CONCLUSION

Several measures have been developed by the Brazilian Society of Cardiology (SBC) through the Women's Department of Cardiology, such as the publication of Positionings and Guidelines[2,3], and the availability of educational, multidisciplinary lives, directed to the public[21]. These and other ongoing actions have the main purpose of expanding knowledge about the specificities related to WOMEN. A task force connecting other SBC departments and related clinical societies, together with measures in public health and private medicine, can generate impactful actions in reducing morbidity and mortality from CVD in this population with low representation in relevant clinical trials.

Raising awareness of an extremely relevant topic such as CVD in women involves academic training in the area of women's health, creating integrative programs in base communities, training community leaders as educators on health and well-being in women, acting both in the identification of those exposed not only to traditional CVRFs but also to the "new" CVRFs, such as psychosocial illnesses and socioeconomic aspects, less addressed at different levels of health[22].

AUTHORS' CONTRIBUTIONS

MCCA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **MLC:** Data curation, Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **CMS:** Investigation, Methodology, Resources, Writing – original draft. **MENCC:** Investigation, Methodology, Resources, Writing – original draft. **RCMC:** Investigation, Methodology, Resources, Writing – original draft.

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ORIGINAL ARTICLE

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Abnormal uterine bleeding in reproductive age: a comparative analysis between the five Brazilian geographic regions

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FEBRASGO

SUMMARY

OBJECTIVE: This study aimed to comparatively evaluate the presence of abnormal uterine bleeding and associated factors among women from the five official Brazilian geographic regions.

METHODS: This is a cross-sectional, population-based, multicenter study of reproductive-age women from the five regions of Brazil. All participants answered questionnaires containing personal and socioeconomic data and information on uterine bleeding (self-perception and objective data).

RESULTS: A total of 1,761 Brazilian women were included, 724 from the Southeast, 408 from the Northeast, 221 from the South, 213 from the North, and 195 from the Central-West. Considering women's self-perception, the prevalence of abnormal uterine bleeding was 37.56% in the North region, 39.46% in the Northeast, 21.54% in the Central-West, 29.56% in the Southeast, and 25.34% in the South ($p<0.001$). Abnormal uterine bleeding was more prevalent in the North and Northeast, where women had lower purchasing power, became pregnant more often, and were the only ones financially responsible for supporting the family more often ($p<0.001$). The menstrual cycle lasted <24 days in less than 20% of the women in all regions (p=NS). Among these, approximately 8 out of 10 women had never undergone treatment in four out of the five regions evaluated. More than half of the evaluated women reported a worsening of their quality of life during bleeding.

CONCLUSION: The prevalence of abnormal uterine bleeding in Brazilian women was higher in the North and Northeast, followed by the Southeast, South, and Central-West regions. There was a worsening of quality of life during menstruation regardless of the woman's self-perception of abnormal uterine bleeding. Such results can direct the actions of health managers toward a better approach to abnormal bleeding.

KEYWORDS: Menorrhagia. Anemia. Menstruation disturbances. Public health. Metrorrhagia. Menstruation.

INTRODUCTION

The presence of abnormal uterine bleeding (AUB) is the first cause of gynecological care in the world[1]. AUB indicates the presence of menstrual changes in regularity, volume, frequency, or duration in the absence of pregnancy. It brings individual and collective impacts with worsening of quality of life, work absences, a drop in productivity, and increased costs to healthcare systems. Data from the United States show that more than 1 billion dollars are allocated to treatments for menstrual disorders every year, in addition to other expenses indirectly related[2]. However, in Brazil, these numbers are unknown so far.

Indicators from the Brazilian Institute of Geography and Statistics (IBGE)[3] demonstrate that more than half of the Brazilian population is female, which represents about 100 million women, of whom more than 73 million are of reproductive age. Brazil is divided into five geographic regions, considering particularities in relation to the territory covered and the criterion of grouping states with physical, human, cultural, and economic similarities[4]. According to IBGE, this division aims to contribute to and assist the federal government, states, and municipalities in the implementation and management of public policies and investments. The impact of this scenario of differences is recognized in the access to healthcare services, diagnosis, and treatment according to the region of operation. By taking this regionalization into consideration, understanding the prevalence of AUB and the health factors associated with it can indicate ways to improve the care offered.

Despite the scarcity of data in Brazil, a publication from the South region shows menstrual disorders in 46.4% of women[5], and another from the North region shows a prevalence of 22.1%[6]. Considering that both are regional studies, hence unable to reflect the reality of a country with continental dimensions, and that there are other references indicating the precarious access to healthcare services of 18.1% of the Brazilian population[7], the aim of this study was to comparatively evaluate the presence of AUB and some associated factors among Brazilian women of reproductive age in the five geographic regions of the country in order to understand how different realities can impact the care offered to this population.

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METHODS

This is a population-based, descriptive, multicenter, cross-sectional study of women of reproductive age from five official geographic regions of Brazil (Southeast, South, Central-West, Northeast, and North) randomly recruited in outpatient medical appointments. Pregnant women, lactating women, those with a history of hysterectomy, or those with cognitive difficulties that prevented understanding the questions asked were excluded.

All participants answered questionnaires containing data on the following: personal and socioeconomic status (following the criteria of the Brazilian Association of Research Companies [ABEP])[8], related to uterine bleeding, such as self-perception of increased bleeding (present or absent) and menstrual pattern (regularity, volume, frequency, or duration, with normal values defined by the International Federation of Gynecology and Obstetrics [FIGO])[9]; knowledge of AUB etiology; previous diagnosis of anemia and blood transfusion due to AUB; impact on quality of life; and difficulties of access to treatment (for the last two variables, the visual analog scale [VAS] was used, with 0 being no impact/no difficulty and 10 being the worst impact/extreme difficulty)[10].

Studies in the literature were used to calculate the sample size[11,12], considering the alpha significance level or type I error at 5% (alpha=0.05) (or 95% confidence interval) and the sample error at 3.0, 4.0, and 5.0%, obtaining a minimum sample of 1,761 participants.

The SAS System for Windows (Statistical Analysis System), version 9.4 (SAS Institute Inc., 2002–2012, Cary, NC, USA), was used in statistical analysis. Continuous variables were described as mean and standard deviation and evaluated using the Intercooled Stata 13.0 program. The chi-square or Fisher's exact test was used to compare categorical variables, and the nonparametric Mann-Whitney and Kruskal-Wallis tests were used to compare the values between the five groups representing the five regions.

All women signed the informed consent form. Approval was obtained from the Research Ethics Committee of the coordinating institution (CAAE 40654720.0.1001.5404) and from the ethics committee of each participating center in the five official regions. The study was developed with the support and funding of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO).

RESULTS

A total of 1,761 Brazilian women of reproductive age were included: 724 (41.1%) from the Southeast region, 408 (23.2%) from the Northeast, 221 (12.5%) from the South, 213 (12.1%) from the North, and 195 (11.1%) from the Central-West region. The mean age in the North region was 34.83±12.78 years, in the Northeast region 36.98±12.64, in the Central-West region 35.16±12.66, in the Southeast region 35.03±12.16, and in the South region 35.48±12.65, with no statistical difference across regions. Except for the South region, the mean body mass index (BMI) showed values above normal, that is, above 25 kg/m^2. Although there was no difference between regions in terms of women with normal BMI or overweight, in the North region there was a higher prevalence of grades 1 and 2 obesity (p<0.001). According to women's self-reports, in the North region, mixed-race ethnicity predominated (80.4% of participants). In the Northeast region, most women also declared themselves to be non-white. In the other regions, the white ethnicity predominated (Central-West: 75.4%; Southeast: 79.1%; and South: 93.2%). Among interviewees, women from the highest social stratum (classes A, B1, and B2) were from the Central-West and South regions, while in the North and Northeast regions, those from social classes with lower purchasing power predominated (C1, C2, and D-E), representing more than half of the participants. At the same time, in these regions of lower economic status, women became pregnant more often and declared themselves more frequently as the sole financial supporters of the family (p<0.001). In addition, women in the North and Northeast regions also had higher parity, with a greater number of natural deliveries and a lower history of cesarean sections compared to the other regions (p<0.001). Interestingly, although the mean age at menarche in all regions was around 12–13 years, in the North region, menarche occurred a little later than in the other regions (Table 1).

Considering women's self-perception of increased bleeding, the prevalence of AUB was significantly higher in the North and Northeast regions, distributed as follows: 37.56 and 39.46% in the North and Northeast regions, respectively; 21.54% in the Central-West region; 29.56% in the Southeast region; and 25.34% in the South region (p<0.001). Quantitatively, using the criteria defined by FIGO, the mean cycle duration and menstrual flow duration by region were significantly lower in the South region (Table 2) (p<0.001). The menstrual cycle lasted less than 24 days in less than 20% of women from all regions, with no statistical difference. Furthermore, less than 1 in every 10 women in each region had menstrual flow longer than 8 days, with no difference between regions. Women from the Northeast region had episodes of intermenstrual bleeding less frequently than those from other regions (p=0.017). No difference was observed between regions in relation to the prevalence of postcoital bleeding, which affected less than 10% of women in each region (Figure 1).

Table 1. Sociodemographic characteristics of the total sample of women of reproductive age divided by geographic region of Brazil (n=1,761).

Variable	North region (n=213)	Northeast region (n=408)	Central-West region (n=195)	Southeast region (n=724)	South region (n=221)	p-value
	Mean±SD or n (%)					
Age (years)	34.83±12.78	36.98±12.64	35.16±12.66	35.03±12.16	35.48±12.65	0.144
Ethnicity						
White	35 (16.44%)	169 (41.43%)	147 (75.38%)	572 (79.00%)	206 (93.21%)	N/A
Non-white	178 (83.56%)	239 (58.57%)	48 (24.62%)	152 (21.00%)	15 (6.79%)	
BMI (kg/m^2)	26.31±4.66	25.93±4.99	25.54±4.79	25.17±5.33	24.00±4.24	<0.001 1≠ (4,5); (2,3) ≠ 5
Complete years of study	10.44±4.98	13.99±4.79	16.75±4.31	14.60±5.56	15.64±5.49	<0.001 1≠(2,3,4,5); 3≠(2,4,5); 2≠5
Social Stratification-ABEP 2019						
Class A	10 (4.69%)	50 (12.25%)	81 (41.53%)	160 (22.10%)	101 (45.70%)	N/A
Class B1	14 (6.57%)	40 (9.80%)	52 (26.67%)	132 (18.23%)	54 (24.43%)	
Class B2	23 (10.82%)	57 (13.98%)	50 (25.64%)	213 (29.42%)	50 (22.62%)	
Class C1	42 (19.71%)	80 (19.62%)	6 (3.09%)	132 (18.24%)	012 (5.44%)	
Class C2	46 (21.60%)	85 (20.83%)	4 (2.05%)	64 (8.84%)	4 (1.81%)	
Class D/E	78 (36.61%)	96 (23.52%)	2 (1.02%)	23 (3.17%)	0	
Financial responsibility for family support						
Exclusively female	75 (35.21%)	133 (32.59%)	34 (17.43%)	136 (18.78%)	53 (23.98%)	N/A
Shared with partner	65 (30.51%)	128 (31.39%)	105 (53.85%)	373 (51.52%)	114 (51.58%)	
Others	73 (34.28%)	147 (36.02%)	56 (28.72%)	215 (29.70%)	54 (24.44%)	
Age at menarche (years)	13.04±1.78	12.69±1.66	12.42±1.50	12.11±1.35	12.41±1.40	<0.001 1≠(2,3,4,5); 2≠4
Pregnancies (number)	2.39±2.27	1.64±1.59	1.06±1.24	1.01±1.41	0.83±1.04	<0.001 1≠(2,3,4,5); 2≠(3,4,5)
Natural births (number)	1.64±2.20	0.70±1.23	0.22±0.63	0.34±0.86	0.20±0.57	<0.001 1≠(2,3,4,5); 2≠(3,4,5)
Cesarean sections (number)	0.52±0.82	0.67±0.91	0.69±0.92	0.45±0.82	0.49±0.78	<0.001 3≠(4,5); 2≠4
Forceps (number)	0.01±0.11	0.02±0.14	0.02±0.15	0.02±0.13	0.03±0.18	0.520
Miscarriage (number)	0.27±0.91	0.28±0.65	0.18±0.48	0.19±0.54	0.18±0.49	0.051

When analyzing women with quantitative alterations associated with AUB, among those with menstrual cycles lasting less than 24 days, about 8 out of 10 women in the North, Northeast, Central-West, and South regions had never undergone treatment (p<0.001). However, the complaint of bleeding duration of more than 8 days made women seek care more frequently. Most participants from the North, Southeast, and South regions with this complaint had sought treatment, but in the Northeast and Central-West regions, about 60% had not undergone any type of therapeutic intervention. The prevalence of anemia secondary to AUB and the need for hospitalization were significantly higher in the North region, and, among those who had anemia, the use of oral iron was the main treatment used (Table 2). More than 70% of participants who reported self-perception of AUB in the North, Northeast, and Central-West regions did not undergo any AUB treatment. In the Southeast and South regions, approximately half had performed some therapeutic approach (p<0.001).

Considering the socioeconomic characteristics of the participants, it is interesting to note that women who reported

Table 2. Comparative evaluation of uterine bleeding among women of reproductive age of the five geographic regions of Brazil (n=1,761).

Bleeding parameters	North region (n=213)	Northeast region (n=408)	Central-West region (n=195)	Southeast region (n=724)	South region (n=221)	p-value*
Interval between periods (days)	27.82±16.92	29.73±17.75	28.89±19.12	29.58±23.57	21.40±6.54	<0.001 5≠(1,2,3,4)
Duration of menstrual flow (days)	4.93±2.72	5.60±5.00	6.23±4.39	5.77±3.48	2.50±0.80	<0.001 5≠(1,2,3,4); 1≠3
Cycles <24 days (n %)	37 (17.37%)	78 (19.11%)	37 (18.97%)	139 (19.19%)	32 (14.47%)	0.099
Menstrual flow >8 days	15 (7.04%)	41 (10.12%)	15 (7.69%)	53 (7.32%)	17 (7.69%)	0.072
Selfperception of AUB (n %)						
Absent	133 (62.44%)	247 (60.54%)	153 (78.46%)	510 (70.44%)	165 (74.66%)	<0.001
Present	80 (37.56%)	161 (39.46%)	42 (21.54%)	214 (29.56%)	56 (25.34%)	
Intermenstrual bleeding (n %)	38 (17.84%)	45 (11.02%)	33 (16.92%)	136 (18.78%)	39 (17.64%)	0.017
Postcoital bleeding (n %)	20 (9.38%)	26 (6.37%)	16 (8.20%)	47 (6.49%)	15 (6.78%)	0.596
Need to use more than one type of absorbent (n %)	16 (7.51%)	47 (11.51%)	16 (8.20%)	223 (30.80%)	65 (29.41%)	<0.001
History of anemia (n %)	94 (44.13%)	120 (29.41%)	43 (28.28%)	338 (46.68%)	62 (28.05%)	<0.001
Hospital admission due to AUB (n %)	12 (5.63%)	13 (3.20%)	7 (3.58%)	11 (1.51%)	6 (2.71%)	0.023
Worsening quality of life (n %)						
Yes	133 (62.44%)	228 (59.29%)	134 (68.71%)	425 (58.70%)	124 (56.10%)	0.028
Worsening quality of life (VAS 0–10**, mean±SD)	4.49±3.66	5.28±3.11	5.64±2.65	5.33±3.15	5.14±2.78	0.013 1≠3
Difficulty in care service (VAS 0–10**, mean±SD)	6.24±2.08	6.36±3.41	4.07±3.40	2.81±2.56	2.74±3.38	<0.001 (1,2)≠(3,4,5); 3≠(4,5)

*Chi-square or Fisher's exact tests; non-parametric Mann-Whitney test; **VAS: visual analogue scale.

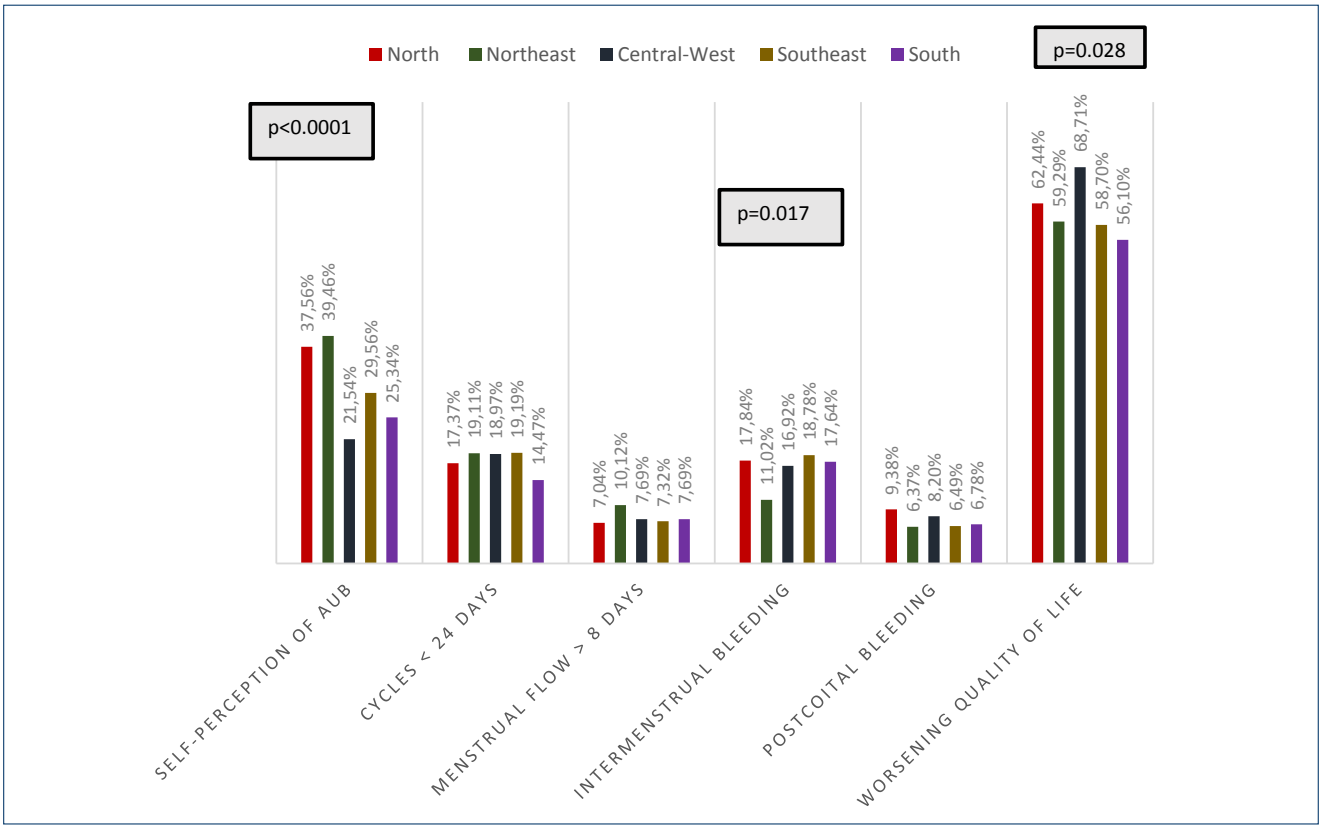

Figure 1. Comparative evaluation among women from the five geographic regions of Brazil for objective characteristics and self-perception of abnormal uterine bleeding, in addition to the relationship between menstrual bleeding and quality of life.

associating two types of absorbents during the menstrual period, less difficulty in medical care, and less impact of bleeding on the quality of life were from regions with greater economic power, the South and Southeast regions. Participants from the North and Northeast regions, considered to have less economic power, reported greater difficulty in accessing healthcare services (Table 2).

When asked whether the period of menstrual bleeding changed their lives, more than half of women in all regions reported a worsening of their quality of life, regardless of their self-perception of AUB, with significantly higher numbers in the North and Central-West regions (Figure 1). Considering the 0–10 scale, the highest, hence worst, score was obtained in the Central-West region (5.64±2.65) (Table 2).

DISCUSSION

Considering women's self-perception of having increased bleeding, this study demonstrated that the prevalence of AUB, anemia, and hospitalization due to bleeding is significantly higher in the North and Northeast regions, precisely where women have social stratification indicative of lower purchasing power. In addition, women from these regions had less frequent therapeutic interventions for AUB compared to regions with higher purchasing power (Southeast and South regions). Among the characteristics of bleeding, the main reason for seeking medical care was prolonged menstrual flow (more than 8 days), which occurred more frequently than cycles lasting less than 24 days. Even among women who did not report self-perception of AUB, there is a reported worsening of quality of life during the period of menstrual bleeding. Among all regions, the Central-West region concentrated the highest number of women reporting that menstruation worsened their quality of life (almost 7 out of 10), therefore with the highest and worst score. The North region had the second-highest number of women associating worsening quality of life and menstruation (62.4%), although it had the lowest score among all regions.

The literature shows AUB as the first cause of demand for gynecological care, and access to healthcare services is influenced by several factors, such as socioeconomic level, cultural aspects, and geographic characteristics that exert a direct impact on healthcare services[7]. In regions of lower socioeconomic power, that is, the North and Northeast regions, are concentrated the women who get pregnant the most, are most responsible for family support alone, and have a higher prevalence of AUB. However, they performed therapeutic interventions less frequently, probably given the greater difficulty in accessing care in these locations. In line with our results, data from the literature show that these regions of Brazil have the highest rates of inequity in access to medical consultations[13]. Furthermore, the North and Northeast regions still have more women on a "double shift" regime, i.e., adding formal work and household chores, followed by the Southeast, South, and Central-West regions. However, in these last three regions, the average monthly income is higher[3].

Similar aspects are found in studies on the prevalence of AUB in other underdeveloped and developing countries, with relevant disparities given the wide range of factors influencing access to healthcare services and the institution of adequate treatment and follow-up. Studies in South America, Africa, and India indicate prevalence of AUB ranging from 4 to 27%, intermenstrual bleeding between 1 and 17%, and menstrual irregularity in 8–83% of women, with the highest numbers in India and Turkey, countries where, like the North and Northeast regions of Brazil, are the lowest rates of treatment for AUB[14-16].

On the contrary, participants from regions with a higher socioeconomic stratum (Southeast and South) performed therapeutic interventions more frequently, reporting less difficulty in accessing healthcare. These regions have the largest centers with access to the best technologies in treatment for AUB, funding for research, and devices for surgical techniques with minimally invasive approaches. According to the literature, these represent the Brazilian locations with less inequality in access to consultations because of income[13].

Considering the current view of international medical societies, which recommend the characterization of AUB through objective parameters[9] in addition to increased volume according to the woman's self-perception, we observed that the duration of bleeding seems to be more uncomfortable than short intervals or increased volume, reinforcing the importance of detailing all characteristics of the menstrual cycle. There is evidence of the AUB approach by health professionals demonstrating failures in care, with anamnesis and clinical investigation that do not always include parameters considered important by women experiencing this condition[11].

The level of negative impact caused by menstruation on quality of life is also relevant, even among women who did not report self-perception of AUB. The National Institute for Health and Care in the United Kingdom (NICE-UK) has made recommendations that any intervention in abnormal bleeding should focus on improving quality of life and not just controlling blood loss. Studies that seek to understand the scenario in which women with AUB are inserted show that the main points of concern are related to blood leaking on clothes, the need for frequent changes of menstrual absorbents, cycle unpredictability, and how the bleeding period changes plans of work and leisure activities[11,12]. The days of menstrual bleeding are sometimes also related to a drop in productivity and absenteeism, which are important aspects for public health.

We highlight as strong points that this study evaluated multiple aspects related to AUB among the different regions of Brazil in a comparative and probably unprecedented way, analyzing objective and subjective parameters, as well as access to healthcare. A weak point was the fact that this study was performed in hospitals and university centers; therefore, a portion of the female population in worse economic conditions, with even more difficulty in accessing medical care, may not have been included. Considering AUB as a very frequent cause of demand for gynecological care, the discrepancies in a continental country are evident, alerting health professionals and managers regarding the implementation of policies aimed at facilitating access to healthcare services, with specialized actions in abnormal bleeding.

CONCLUSION

The prevalence of AUB in women of reproductive age was significantly higher in the North and Northeast regions, followed by the Southeast, South, and Central-West regions. There was a worsening of the quality of life during menstruation. Considering the inequity in access to healthcare services between the geographic regions of Brazil, with greater difficulty in the North and Northeast regions, such results can be a warning of the attitudes of health professionals and the direct actions of public health managers for better control and treatment of AUB.

AUTHORS' CONTRIBUTIONS

GPR: Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Sofware, Visualization, Writing – original draft. **CLBP:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, Sofware, Supervision, Validation, Visualization, Writing – review & editing. **DAYG:** Data curation, Formal Analysis, Resources, Validation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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Early breast cancer: concept and therapeutic review

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Brazilian Society of Mastology

SUMMARY

OBJECTIVE: Breast cancer treatment has evolved significantly over the years, both in terms of local and systemic approaches. Halsted's radical mastectomy gave way to modified mastectomies and to conservative surgeries, along with breast reconstruction and repair. Although the use of new drugs has directly increased the survival of patients submitted to adjuvant or neoadjuvant systemic therapies, the de-escalation of drugs may also be beneficial in numerous cases. Therefore, breast cancer treatment must be increasingly customized and assessed using a multidisciplinary approach. This study aimed to review the concept and therapy of early breast cancer.

METHODS: A narrative review of the literature was carried out in the PubMed database in December 2022, where the keywords for the searches were as follows: early breast cancer, surgical treatment of breast cancer, systemic treatment of breast cancer, neoadjuvant chemotherapy in breast cancer, adjuvant treatment of luminal breast cancer, early triple negative tumor, and early positive Her-2 tumor. Articles that were historically important in the treatment of breast cancer and articles that impacted management with scientific relevance were selected for this review.

DISCUSSION: As new evidence continues to update existing knowledge, breast cancer treatment is becoming increasingly personalized and must now take into account the different tumor variants and their clinical stages, the age of patients and relevant comorbidities, as well as personal expectations and desires.

CONCLUSION: This literature review of current studies shows that the primary therapy for patients with early breast cancer continues to be surgery, although a customized and multidisciplinary approach is now required.

KEYWORDS: Breast neoplasms. Cancer treatment protocols. Breast conserving surgery.

INTRODUCTION

Breast cancer treatment has evolved significantly over the years, both in terms of local and systemic approaches. Halsted's radical mastectomy gave way to modified mastectomies and to conservative surgeries, along with breast reconstruction and repair.

Although the use of new drugs has directly increased the survival of patients submitted to adjuvant or neoadjuvant systemic therapies, the de-escalation of drugs may also be beneficial in numerous cases. Therefore, breast cancer treatment must be increasingly customized and assessed using a multidisciplinary approach.

Although surgery is recommended as the primary therapy for patients with early breast cancer, neoadjuvant systemic therapy is recommended as the primary treatment for patients with[1] triple-negative and HER-2-positive tumors equal to or greater than 2 cm in size or with clinically active axillary lymph nodes, and for some selected cases of triple-negative tumors with a size between 1 and 2 cm or[2] luminal tumors in cases in which downstaging is favorable for an axillary approach or reduction of the tumor volume is favorable for breast surgery.

This study aimed to review the concept and therapy of early breast cancer.

Surgical treatment

Historically, breast surgery has been the most widely applied treatment for breast cancers, regardless of their clinical stage. More specifically, the radical mastectomy as described by Halsted in 1894 reflected the prevalent belief in the local spread of tumors and thus that the more radical the procedure, the better the patients' recovery[1]. In fact, this approach was an outstanding development, since it helped reduce the overall mortality of breast cancer patients by nearly 20% and close to 50% when performed in patients with early tumors[2].

With the evolution of knowledge on breast cancer, radical mastectomies gave way to modified radical mastectomies. Patey and Dyson[3] described a modified radical mastectomy that preserved the pectoralis major, whereas Auchincloss[4] and Madden[5] described a mastectomy that also preserved the pectoralis minor[3-5]. The next developments were the skin-sparing mastectomy and the skin- and nipple-areola

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complex-sparing mastectomy, which are currently performed in patients who meet certain clinical-oncological criteria[6,7].

In the 1980s, other major breakthroughs came with the publication of the Milan studies, conducted by Umberto Veronesi, and of the NSABP (National Surgical Adjuvant Breast and Bowel Project B-06) study, conducted in the US by Bernard Fisher. The updated 20-year follow-up on these studies demonstrated not only the oncological safety of conservative surgery followed by radiotherapy, but also the psychosocial benefits they offered to patients[8,9].

Immediate breast reconstruction, either by myocutaneous flaps or implants, has become a standard practice in the surgical treatment of breast cancer. In fact, when there are no contraindications to this procedure, it should be offered to patients due to the numerous benefits it provides, such as its contribution to the patients' body image and the consequent improvement in their quality of life[10].

Oncoplasty, an association of oncological surgery and plastic surgery techniques, can now be used when unsatisfactory cosmetic results may arise from purely oncological surgery. Since this combination of techniques can also be used in conservative surgery for larger tumors, it has also helped increase breast preservation. The benefits of breast preservation cannot be overstated, and include improved recovery and adherence to treatment, higher self-esteem, better quality of life, higher survival rates, benefits on affective life and marital relationships, as well as an earlier return to work[11,12].

The belief that distant metastasis occurs via the lymphatic and hematogenous routes is one of the chief drivers of conservative surgery, decreasing the radicality of surgical treatment[13].

Systemic treatment, on the contrary, has also seen significant evolution.

Systemic treatment

In 1975, the NSABP demonstrated that treatment using oral adjuvant 1-phenylalanine mustard improved patients' prognoses. This study thus confirmed the hypothesis that the worse prognosis in some patients was caused by the presence of distant micrometastases. This is how Fisher arrived at the concept that invasive diseases are systemic in character and, thus, the early treatment of micrometastases benefits patients[14].

As this concept became established, adjuvant systemic therapy – whether through chemotherapy or hormone therapy – grew increasingly important in post-surgical treatment[15].

The effectiveness of drugs in adjuvant treatment soon prompted studies in neoadjuvant settings, which aimed to render inoperable tumors operable. A particularly significant study on this procedure was conducted in Milan by Bonadona.

Subsequently, NSABP studies B-18 and B-27 not only demonstrated that the prognosis was identical for patients submitted to neoadjuvant or adjuvant chemotherapy, but also yielded higher breast preservation rates compared to mastectomies when systemic treatment was performed before surgery. Study B-18 treated patients with Adriamycin and Cyclophosphamide, and the cohort that began treatment with chemotherapy achieved higher rates of conservative surgery (19.8 vs. 59.8%) with comparable rates of local recurrence. Although the study indicated no difference in overall survival (OS), a 9-year follow-up study demonstrated that patients with pathological complete response (pCR) to neoadjuvant chemotherapy had 50% lower risk of death[17]. Study B-27, on the contrary, associated taxanes with the treatment and reached similar results to study B-18 in terms of OS and disease-free survival (DFS) when neoadjuvant or adjuvant treatment was performed, albeit with increased DFS and OS in patients who achieved pCR. Moreover, it is worth noting that the association of taxanes in B-27 led to higher pCR rates[18]. Based on this evidence and other studies, neoadjuvant chemotherapy has become an established practice to[1] render inoperable tumors operable[2], transform radical surgeries into conservative ones, and[3] provide initial treatment to locally advanced tumors (T3, T4, and N2-3)[19].

Three milestones that contributed to customized treatments were as follows[1]: the identification of estrogen and progesterone receptors by immunohistochemistry[2]; the advent of in situ hybridization techniques to detect HER-2 amplification; and[3] the study by Perou and Sorlie[21] that classified breast cancer into five molecular subtypes (luminal A, luminal B, HER-2-positive, triple-negative/basal-like, and triple-negative/normal-like)[20,21].

The increased use of chemotherapy, anti-hormone treatments, and targeted therapies has not only increased the recommendation of neoadjuvant chemotherapy for the previously mentioned indications, but also allowed the in vivo assessment of the tumor response to the agent used in the neoadjuvant therapy.

Among the targeted therapies, the use of the monoclonal antibody trastuzumab deserves special mention. Studies such as the NSABP B-31 and BCIRG 006, comparing commonly used chemotherapy schemes with and without the association of trastuzumab, found that the combined treatments provided higher DFS and OS rates[22,23]. In the neoadjuvant setting, the highest pCR rates are usually associated with triple-negative and HER-2-positive tumors (and for the latter, especially when associated with the target therapies). Thus, the current practice is to conduct neoadjuvant chemotherapy in tumors with smaller dimensions and with these biomolecular characteristics[24,25].

In the NOAH and GEPARQUINTO studies, the combination of trastuzumab and chemotherapy in tumors with positive

HER-2 expression yielded pCR rates of approximately 50%, or almost twice the result of treatments without this association[24-26]. Dual blockade with trastuzumab and pertuzumab achieved the highest pCR rate, with a nearly 20% rise compared to schemes that only used trastuzumab. In the NeoSphere study, the pCR rate amounted to 45.8% in the dual blockade group and 29% in the trastuzumab group. The data published in the AFFINITY study on adjuvant therapy (2017) ensured the definitive approval of the dual blockade[27]. The dual blockade in neoadjuvant therapy for HER-2-positive tumors, on the contrary, grew following the publication of the KATHERINE study, which randomized patients with[1] HER-2-positive tumors and residual invasive diseases in the breast or axilla after initial chemotherapy and[2] anti-HER-2 therapy (trastuzumab with or without pertuzumab). In the study's 14 postoperative cycles, these patients received either transtuzumab-entasine (TDM-1) or trastuzumab. Although these randomized patients had tumors of varying sizes and with or without axillary, skin, or chest wall involvement, none of them had metastases. The study also excluded patients with tumors smaller than 1 cm and axilla with no lymph node involvement. Although the group receiving TDM-1 had a 50% lower risk of recurrent invasive diseases, the benefit in OS was statistically insignificant[28].

With the aim of reducing cardiotoxicity, studies were carried out to assess the non-use of anthracyclines in neoadjuvant therapy associated with dual blockade schemes. The TRAIN-2 study analyzed 418 patients with stages II and III HER-2-positive tumors with no previous treatment. These patients were then randomized into (i) 206 patients treated with six cycles of paclitaxel+carboplatin+trastuzumab+pertuzumab followed by paclitaxel+carboplatin+trastuzumab+pertuzumb and (ii) 212 patients treated with six cycles of 5-fluoracil+epirubicin+cyclophosphamide+trastuzumab+pertuzumab followed by paclitaxel+carboplatin+transtuzumab+pertuzumab. A complete pathological response was seen in 141 patients in the anthracycline group and 140 patients in the non-anthracycline group. The updated analysis of the 48.8-month follow-up study indicated no difference in DFS and OS between these groups, although the anthracycline-free group had lower rates of cardiac toxicity[29].

If, on the one hand, new therapies have emerged, on the other, an attempt is being made to de-escalate adjuvant treatment in patients with positive HER-2 expression. Due to new evidence, this can be applied in some situations. In the APT trial, 410 patients with HER-2-positive breast cancer, tumors up to 3 cm, and negative lymph nodes were treated with paclitaxel associated with trastuzumab for 12 weeks. The trastuzumab was later maintained for another 9 months. After a median follow-up of 6.5 years, DFS stood at 93% and OS at 95%. It is worth mentioning that 91% of study participants had tumors of up to 2 cm, whereas 64% had tumors with positive estrogen expression[30].

Regarding the triple-negative tumors, the appropriate response to neoadjuvant therapies was widely known and consisted mainly of an association of anthracyclines and taxanes. Current studies have shown higher rates of pCR following the use of carboplatin, as seen in the ALLIANCE study, which reached pCR in the breast at 44 versus 60% and response in the breast and axilla at 54 versus 41%, both statistically significant, although reflecting no OS gains to date[31,32]. The indication of chemotherapy as primary therapy in triple-negative tumors increased with the results of the CREATE-X study, in which 910 HER-2-negative patients with residual invasive tumors and following neoadjuvant therapy with anthracyclines, taxanes, or both were randomized to 6–8 cycles of capecitabine or placebo. In 5 years, the cohort receiving the treatment reached higher DFS and OS. The subgroup of patients with triple-negative tumors achieved better results both in terms of DFS and OS. In this study, 15.4% of patients had tumors of up to 2 cm, and the remaining participants had larger tumors[33].

Similar in design, the study GEICAM/2003-11_CIBOMA/2004-01 did not deliver the same promising results. The study analyzed 876 patients with triple-negative tumors equal to or larger than 1 cm in size, with positive or negative lymph nodes, who were undergoing neoadjuvant chemotherapy using anthracyclines with or without taxanes. The study then randomized the patients who received no treatment or capecitabine for 14 consecutive days during 8 cycles of 21 days. After a 5-year follow-up study, the group treated with capecitabine reached higher DFS and OS, albeit with statistically insignificant results. Although the subgroup analysis suggested that capecitabine had benefited the non-baseline triple-negative patients, the results were statistically insignificant[34]. Published recently, a systematic review carried out a meta-analysis of nine randomized clinical trials comprising 3,842 patients with triple-negative tumors that were treated with neoadjuvant or adjuvant capecitabine. Bearing in mind the low heterogeneity of the samples, the meta-analysis showed that the association of capecitabine yielded statistically significant increases in DFS and OS. On the downside, capecitabine treatments have been associated with increased risks of diarrhea, stomatitis, and hand-foot syndrome[35].

Among the new drugs that have been researched in neoadjuvant treatment for patients with triple-negative tumors, immunotherapy stands out. The KEYNOTE-522 study analyzed stages II and III patients with previously untreated

triple-negative tumors. All patients underwent four cycles of 3-week treatments, receiving paclitaxel and carboplatin associated with either pembrolizumab (784 patients) or placebo (390 patients). Both of these groups then received four additional cycles of pembrolizumab or placebo, respectively, associated with doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. After surgery, these patients then received up to nine cycles of 3-week treatments with adjuvant pembrolizumab or placebo. Immunotherapy yielded higher pCR rates with a statistically significant difference between the groups, and patients with stage III or lymph node tumors benefited the most from this treatment. A median 39.1-month follow-up study indicated a higher DFS with statistical significance[36].

For patients with luminal tumors in early clinical stage, surgery is still the recommended primary therapy. The SENTINA and ACOSOG-Z71 studies discussed neoadjuvant therapy used for axillary downstaging, that is, with the aim of searching the sentinel lymph node in the primarily compromised axilla[37,38]. These studies assessed neoadjuvant hormone therapy, considering that the response rate of luminal tumors to chemotherapy is much lower when compared to triple-negative and HER-2-positive tumors. However, a systematic meta-analysis review showed that neoadjuvant therapy with aromatase inhibitors (AI) yielded a clinical response similar to chemotherapy, a similar radiology response, and similar rates of conservative surgery, but with the added benefit of lower toxicity.

Compared to tamoxifen, AI also achieved superior clinical and radiological responses with statistical significance[39].

A study with 97 patients with luminal tumors randomized the chemotherapy treatment (epirubicin+cyclophosphamide followed by docetaxel every 21 days, during four cycles) with hormone therapy (exemestane 25 mg for 24 weeks). From the patients undergoing chemotherapy, 51% were premenopausal; from those undergoing hormone therapy, 56% received goserelin with exemestane. A subgroup analysis showed significantly improved clinical response rates for premenopausal patients undergoing chemotherapy (75 vs. 44%, p=0.027) compared to postmenopausal patients (57 vs. 52%, p=0.78)[40].

METHODS

A narrative review of the literature was carried out in the PubMed database, where the keywords for the searches were early breast cancer, surgical treatment of breast cancer, systemic treatment of breast cancer, neoadjuvant chemotherapy in breast cancer, adjuvant treatment of luminal breast cancer, early triple negative tumor, and early positive Her-2 tumor. Articles that were historically important in the treatment of breast cancer and articles that impacted changes in conduct with scientific relevance were selected for this review.

DISCUSSION

As new evidence continues to update existing knowledge, breast cancer treatment is becoming increasingly personalized and must now take into account the different tumor variants and their clinical stages, the age of patients, any relevant comorbidities, as well as personal expectations and desires. With the exception of patients with stage IV tumors, inoperable tumors, or without the necessary clinical conditions for surgical treatment, the mandatory treatment for breast cancer continues to be surgery – which may also be associated with systemic approaches such as neoadjuvant, adjuvant, or both. Specifically for HER-2-positive tumors, the target therapies yielded high pCR rates, and the dual blockade treatment stands out in this particular. In the KATHERINE study, adjuvant treatment with TDM-1 increased the DFS in patients with no pCR for invasive diseases. The APT study, in turn, ensures the non-inferiority of trastuzumab associated with adjuvant paclitaxel with no anthracyclines for initial tumors with no lymph node tumors. The CREATE-X study is a milestone in the treatment of triple-negative tumors, since adjuvant capecitabine after neoadjuvant chemotherapy in patients with no pCR for invasive diseases yielded a higher DFS and OS, and the KEYNOTE-522 study with immunotherapy yielded higher pCR rates and higher DFS. The recommendation of neoadjuvant therapy based on the size of the tumor remains controversial, since the conclusions provided by different studies are inconsistent in this particular. Surgery continues to be the primary therapy for early luminal tumors, and a few special cases in this particular involve strategies for reducing tumor or axillary disease volumes.

CONCLUSION

This literature review of current studies shows that the primary therapy for patients with early breast cancer continues to be surgery, although a customized and multidisciplinary approach is now required. Neoadjuvant therapy, on the contrary, is the primary treatment for triple-negative tumors equal to or greater than 2 cm and can be considered in selected cases of tumors between 1 and 2 cm and HER-2-positive tumors equal to or greater than 2 cm, or with axillary lymph node tumors and luminal tumors in which the axilla is involved, and the goal is to reduce the volume of the axillary disease.

AUTHORS' CONTRIBUTIONS

MCSB: Conceptualization, Formal Analysis, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **APA:** Resources, Writing – original draft. **FB:** Conceptualization, Methodology, Resources, Supervision, Writing – original draft. **VMO:** Conceptualization, Methodology, Resources, Supervision, Writing – original draft.

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ORIGINAL ARTICLE

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Disability prevalent conditions in women

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SUMMARY

Women and men can have the same illnesses, but with different prevalence and reactions to symptoms.

OBJECTIVE: This study aimed to emphasize that distinct traits between men and women require a different approach for each of them.

METHODS: PubMed and Google Scholar were searched using the following terms: Disability Evaluations, Women's health, Osteoporosis, Osteoarthritis, and Lymphedema, Pregnancy.

RESULTS/CONCLUSION: Disease management can go beyond the symptoms, assessing the long-term consequences and possibly the disabilities they can generate, compromising the quality of life of the person, his/her family members, and eventually caregivers.

KEYWORDS: Disability evaluations. Women's health. Osteoporosis. Osteoarthritis. Lymphedema. Pregnancy.

INTRODUCTION

Men and women respond differently to illness and pain. Most people around the world with chronic pain are women[1], with a higher prevalence of disable conditions in adults between 25 and 44 years[2]. The fact that women take on greater responsibilities in caring for home, children, and older family members may not only increase stress, but also intensify the progression of diseases[3]. Women feel more pain and experience painful stimuli more intensely than men. They also have a lower pain threshold and lower pain tolerance from mechanical, thermal, and electrical stimuli. Men perceive pain at lower intensities but have more anxiety related to this condition. The causes of this difference between both sexes are unknown, but hormonal and psychological characteristics, with an emphasis on anxiety, can have a great influence[1].

OSTEOPOROSIS

People with osteoporosis can become progressively disabled, and those who have mobility limitations and pain will become more osteoporotic.

Osteoporosis is characterized by low bone mass, alteration, or disruption of bone microarchitecture, which leads to increased skeletal fragility, decreased bone strength, and consequently increased risk of fracture.

The lifetime risk of any osteoporotic fracture is remarkably high and ranges from 40 to 50% in women and 13 to 22% in men[4].

Fractures are associated with pain and decreased physical function, social relationship, well-being, and quality of life.

Women have approximately twice as many hip fractures as men[5]. One year after a hip fracture, 40% of patients are still unable to walk independently, 60% have difficulty with at least one essential activity of daily living, and 80% have difficulty driving and shopping[6].

Women have far more Colles fractures (fractures of the distal third of the radius) than men, in a ratio greater than 10:1 by the age of 75 years[7]. More than 1 million postmenopausal women will have a spinal fracture each year[7]. When compared to men, women have twice as many spine fractures. Symptomatic and radiographic (morphometric) fractures are significantly associated with greater morbidity and disability[5].

Chronic pain is quite common in a more advanced state of osteoporosis. Pain is associated not only with fractures, but also with postural changes or sequelae of fractures, which may include sensory, affective, and cognitive aspects. Patients with chronic pain can become disabled and dependent, requiring long-term care, especially when older. The prevention and treatment of pain are linked to adequate treatment of osteoporosis, which includes, in addition to specific medication to

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improve bone mass, pain management in a multidimensional, pharmacological, and non-pharmacological approach aimed at improving bone mass and quality of life[8].

Surgical treatment for fracture stabilization, such as arthroplasty, vertebra, or kyphoplasty, may be indicated, as well as exercises for increasing bone mass and gaining coordination, balance, and muscle strength. All exercises must be performed safely with a gradual progression of difficulty. Pharmacological treatment includes medications to improve bone quality, pain, and quality of life.

OSTEOARTHRITIS

Osteoarthritis (OA) is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro and/or macro injuries that activate maladaptive repair responses, including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism), followed by anatomic and/or physiological derangements (cartilage degradation, bone remodeling, osteophyte formation, joint inflammation, and loss of normal joint function) that can culminate in illness.

Osteoarthritis is the most prevalent rheumatic disease and the leading cause of physical disability and reduced quality of life in the population aged over 65 years. Patients experiment with limited function in daily life: 25% cannot do normal activities, and 80% are limited with movement. OA also increases the risk of cardiovascular disease, diabetes, hypertension, and death[9]. It is a common and growing disease, affecting 240 million people worldwide, and women are twice as affected as men. Research suggests that women are more likely to experience joint pain, aching, and stiffness caused by OA. For example, women aged 50–60 years may be three times more likely to develop hand OA than men in the same age group[10], and they are 40% more likely to develop knee OA than men.

One possible reason for such a difference between men and women is hormonal[1]. During stages of the menstrual cycle, increased hormone levels may cause joint laxity, which is associated with instability and injury. The relationship between menstruation, joint laxity, and OA is perhaps most clear in the case of female athletes and knee OA: women are two to eight times more likely than men to tear the anterior cruciate ligament (ACL), and ACL injury leads to a much higher risk of developing knee OA in the affected side[11]. Women's risk of developing OA increases significantly after menopause, and women may notice joint pain appears or worsens during this time. Estrogen levels drop during menopause. This drop may contribute to changes in the body that accelerate the OA process.

Another important reason could be the excess body weight. According to the National Institutes of Health, women in the United States (US) are more likely to be obese or extremely obese than men. The percentage of women who have severe obesity (11.5%) is higher than that of men who have severe obesity (6.9%)[12]. Obesity increases the risk of OA because the extra weight puts more stress on load-bearing joints, such as the hips, knees, and ankles, and it is associated with low-grade systemic inflammation and insulin and leptin resistance. Studies found that high levels of leptin have inflammatory characteristics and can change articular homeostasis, leading to cartilage degeneration. This inflammation may contribute to OA development in any joint, including non-weight-bearing joints, such as the hands. Obesity is currently considered a major public health problem around the world, already reaching epidemic characteristics, and it is the major risk factor for type 2 diabetes, hypertension, dyslipidemia, and osteometabolic diseases, including osteoporosis and OA[13]. It becomes increasingly clear that the link between obesity and OA transcends excessive loading.

The third reason could be the differences in biomechanics and musculoskeletal system, because they modify how women stand, walk, and run and how their joint surfaces move in relation to one another (joint articulation). Evidence suggests that women's knees contain less cartilage when compared to men's knees, and women are more likely to suffer from cartilage degeneration than men[14]. Over time, these anatomical differences and the associated joint strain may contribute to the development of OA.

Despite this innate vulnerability, women can take steps to feel healthier and decrease their joint pain. Physical activity and changes in diet composition can reverse the inflammatory and leptin resistance, reducing the progression or preventing the onset of OA. Walking, physical therapy, and gentle exercises are generally considered safe because they help maintain and build muscle with minimal joint strain.

To promote individual well-being for each patient, holistic mind-body exercises are recommended (e.g., tai chi and yoga), as well as aquatic exercises, because of the benefits of warm water in relaxing and pain relief, and the possibility of cardiovascular improvement without articular overload. Everyone should receive education to be active, exercise, and manage body weight[15].

LYMPHEDEMA

An increase in breast cancer survival has been achieved due to advances in surgical, radiotherapy, chemotherapy, and biological treatments of neoplasms. However, patients experience

discomfort from the treatment, and numerous complications can arise, including lymphedema related to breast cancer and after mastectomy. This is mainly characterized by local lesions to the normal lymphatic vessel and an increase in limb volume greater than 10%[16]. Breast cancer survivors have risk of developing lymphedema in the short and long term, with a mean onset of 14 months after starting treatment and a 14–40% risk of occurrence after completing cancer treatment. Currently, there is no precise way to distinguish which patients have a higher risk of developing lymphedema after cancer, but there is a consensus regarding some risk factors, such as wide dissection of axillary lymph nodes, use of radiotherapy, the presence of a high body mass index, a high number of cancer cell-positive lymph nodes, and tumor capsular invasion[17].

Clinical manifestations of lymphedema vary widely and include local discomfort, pain, swelling, decreased hand function, hardening and fibrosis of affected tissues, reduced motor dexterity, as well as an increased risk of infections caused by the protein-rich fluid environment of static lymph. Symptoms vary according to the severity and evolution of lymphedema, and this process ranges from a mild initial condition to progressive structural changes, often occurring over a period of several weeks or months. Lymphedema after cancer severely affects the quality of life of patients and their occupational activities and functional status, as well as producing psychosocial and professional changes[18].

Despite having a strong impact on the quality of life, today there are numerous treatments for lymphedema[18]. Although lymphedema can lead to changes in various aspects of life and lead to adaptations and changes in routine, it does not necessarily prevent a habitual lifestyle or complete and productive activities. In addition, although the way in which lymphedema affects a woman's quality of life depends greatly on its degree and location, numerous other long-term physical and psychological conditions related to post-cancer treatment also impact and interfere negatively with the edema's evolution. In this sense, the treatment of lymphedema demands an interdisciplinary therapy that acts in the different spheres of a woman's life and health.

Active surveillance of this condition during cancer treatment is essential and can be used to identify and diagnose subclinical disease in the early stages, providing opportunities for early intervention and treatment, as well as optimizing costs and reducing its incidence in the medium term. In addition, the use of complex decongestive therapy, numerous lymphatic physiotherapeutic intervention techniques, including manual lymphatic drainage, skin care, compression bandages and gloves, and long-term education on self-management of lymphedema, are widely used with good results. Moreover, it is widely known that a sedentary lifestyle leads to overweight or obesity, factors that are strongly associated with an increase or worsening of the incidence of lymphedema. Therefore, physical exercise during and after breast cancer treatment can improve psychosocial and physical conditions, resulting in an active lifestyle that improves cancer survival and reduces complications of its treatment, such as lymphedema[19]. Patients with lymphedema commonly reduce exercise because of worries about exacerbating the condition. But studies have already shown that physical exercise does not cause lymphedema or make the disease worse. Quite the contrary, it is a key support element to treat the complications of cancer treatment at all stages of neoplasm follow-up[20].

Therefore, lymphedema is a chronic condition but not necessarily a disability. Its treatment presupposes a new vision of life, possibilities, and limits. Coordinated multidisciplinary therapies that include behavioral measures and physical exercise can reduce the volume of lymphedema and its complications, maintaining the functionality and quality of life of patients and their families.

DISABILITY AND PREGNANCY

It is noted that one-tenth of women aged 18–49 years has a disability[21]. In Brazil, the prevalence of women with disabilities in reproductive age is near 8.4% and it increases as socioeconomic status decreases[22].

There are data showing that the number of pregnant women with some previous chronic disability that affects their mobility is increasing worldwide. It is estimated that one in four women in the USA lives with a functional impairment[23].

The most prevalent disabled conditions in pregnant US women were arthritis and back or neck problems[24].

While disabilities vary in their causes and impacts, they all cause activity limitations. Pregnancy in women with disabilities has dramatically changed in the past 20 years – for example, pregnancy in women with multiple sclerosis (MS) was extensively studied, and nowadays counseling is scientifically based[21]. In the past, stigma associated with disability and sexuality and medical factors limited childbearing to women with disabilities. Recent surveys showed similar proportions of women with and without disabilities getting pregnant[21].

Disability conditions like paraplegia or MS affect neither the fertility nor the course of pregnancy itself; however, there is evidence that any maternal disability is associated with increased risk for perinatal complications[21].

Caregivers for women need to reinforce their knowledge about reproductive and gestational particularities. It is also important

to recognize the double vulnerability that implies being a woman and a person with a disability and to know their rights[25].

Women with disabilities experience barriers to obstetric care, including physically inaccessible health care facilities and care protocols that do not consider their singular needs. Research in this special area is growing[21], but it is necessary to develop public health care guidelines and offer educational programs that can help health care professionals find easy access to informational material.

The integral care of women with disabilities and the special approach certainly influence the quality of care and are better for families and community.

AUTHORS' CONTRIBUTIONS

PGP: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **RBC:** Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **MDS:** Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **FM:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Does the use of oral contraceptives or hormone replacement therapy offer protection against the formation or rupture of intracranial aneurysms in women?: a systematic review and meta-analysis

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SUMMARY

OBJECTIVE: The aim of this study was to carry out a systematic review of the literature with meta-analysis to evaluate the effect of using oral contraceptive and hormone replacement therapy as a protective factor in the formation of intracranial aneurysms and subarachnoid hemorrhage.

METHODS: This is a systematic review of the literature with meta-analysis, using PubMed and Embase as databases and the PRISMA method. Case-control and cohort studies published until December 2022 were included in this review.

RESULTS: Four studies were included in this review; three of which were eligible for meta-analysis. Regarding the use of oral contraceptive and the development of subarachnoid hemorrhage, there was a lower risk of aneurysm rupture with an odds ratio 0.65 (confidence interval 0.5–0.85). In the analysis of patients using hormone replacement therapy and developing subarachnoid hemorrhage, there was also a lower risk of aneurysm rupture with an OR 0.54 (CI 0.39–0.74). Only one article analyzed the formation of intracranial aneurysm and the use of hormone replacement therapy and oral contraceptive, and there was a protective effect with the use of these medications. oral contraceptive: OR 2.1 (CI 1.2–3.8) and hormone replacement therapy: OR 3.1 (CI 1.5–6.2).

CONCLUSION: The use of hormone replacement therapy and oral contraceptive has a protective effect in intracranial aneurysm rupture and formation.

KEYWORDS: Subarachnoid hemorrhage. Combined oral contraceptive. Hormone replacement therapy. Intracranial aneurysm.

INTRODUCTION

Subarachnoid hemorrhage (SAH) due to the rupture of an intracranial aneurysm (IA) is an extremely serious situation whose mortality reaches approximately 50% of affected patients[1]. Approximately 65% of patients with IA are female[2]. There are several hypotheses that try to justify this higher incidence of IA in women, such as hormonal factors, endothelial factors, changes in the collagen content of the vessel wall, hemodynamic changes, genomic actions, endothelial factors, and the effects of environmental risk factors such as smoking, but the reason for this high prevalence is still unclear[3,4].

The use of oral contraceptives (OCs) has become common among women since the 1960s, initially with the aim of controlling menstrual symptoms and as birth control[5]. Also in the 1960s, hormone replacement therapy (HRT) began to be used to treat climacteric and menopausal symptoms[6]. Over the decades, dosages and types of hormonal combinations have been changing due to adverse effects. Increased risk of venous thromboembolism, thrombosis and thrombophilia, stroke, acute myocardial infarction, and breast cancer, among others, were being diagnosed more frequently in these populations. It was also evaluated that the use of these medications exerted some

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protective factors in some other diseases, such as endometrial and ovarian cancer, and, in some studies, there was also a reduction in the incidence of IA and a decrease in the risk of SAH, but the results of these protective factors related to the use of OC and HRT presented conflicting results in the literature[7].

The objective of this study was to answer the question of whether the use of OC and HRT has a protective effect against the formation of IA and the incidence of SAH.

METHODS

We used the PRISMA methodology to do this review[8]. The clinical question was: Do women who use HRT or OC have a lower incidence of IA or a lower risk of SAH when compared to women who do not use HRT or OC? The structured question in the PICO format was prepared as follows: population—women; intervention—use of OC or HRT; comparison—no use of OC or HRT; and outcome—incidence of IA or incidence of SAH secondary to ruptured IA.

Eligibility criteria

PICO components, cohort or case-control studies, no restrictions on time, just articles written in English, Portuguese, or Spanish with the full text or abstract containing the desired data. The results must be expressed in terms of relative risk with a confidence interval and the number of participants involved.

Exclusion criteria

Review articles, *in vitro* experimental articles or animal studies, case series or case reports, and observational or non-comparative studies.

Sources of information consulted and search strategies

Medline via PubMed, manual search; keywords used and search strategy: oral contraceptive AND brain aneurysm. Embase *via* Scopus, manual search; keywords used and search strategy: Intracranial AND aneurysm AND risk AND of AND rupture AND follow AND up AND oral AND contraceptive AND (LIMIT-TO (DOCTYPE, "air")) AND (LIMIT-TO (LANGUAGE, "English") OR (LIMIT-TO (LANGUAGE, "Portuguese ")) OR (LIMIT-TO (LANGUAGE, "Spanish")) AND (LIMIT-TO (EXACTKEYWORD, "Human")). Manual search in the references of selected articles.

The studies were selected according to the inclusion and exclusion criteria after reading the title and abstract. If there was any doubt regarding the inclusion or not of the article, we proceeded with the reading of the complete article, and if there were not the necessary data for the elaboration of this review, they would be discarded from the analysis. The reading and selection of articles were carried out solely by the main author. After choosing the articles, the extracted data were registered, and duplicates were excluded.

Risk of bias and quality of evidence

For this review, only the articles whose results presented the relative risks and confidence intervals of the questions that were formulated were selected. To define the cases, it was necessary to prove it with an imaging exam identifying an IA (digital angiography of intracranial vessels, angio-tomography, or angio-resonance) and/or SAH (computed tomography scan). Historical controls were accepted in this analysis as long as relative risk data and confidence intervals were also available. To collect data on the use of HRT or OC, an interview with the patient or a trusted close person was necessary, either by telephone or in person.

Extracted data

Author, year of publication, type of study, number of cases, number of controls, relative risk and confidence interval in the intervention group, relative risk and confidence interval in the comparison group, article quality, summary of findings, and textual result of findings (positive, negative, or inconclusive association).

If there was the possibility of comparing any of the data presented, these would be submitted to a meta-analysis using the *RevMan software* version 5.4.1 (*Cochrane*).

RESULTS

After the textual search using the Embase database, according to the criteria established in the methodology, 42 results were obtained; of which 6 were selected for abstract analysis, and of these, 1 article was selected for this review based on the exclusion and inclusion criteria. With the PubMed database search, 34 results were obtained, 10 of which were selected for abstract analysis. In the end, 2 of these articles were included for analysis. After reviewing the bibliography of the articles included in this study, one relevant article was also added (Figure 1). The risk of bias and the quality of the evidence are shown in Table 1.

The meta-analysis included 4 articles where the following aspects were analyzed: findings of IA in patients taking OC versus those who were not taking OC; the presence of IA in patients taking HRT versus those who were not taking HRT; findings of SAH among patients taking OC versus those who were not taking these drugs; and SAH findings among patients who take HRT versus those who did not take HRT.

CHARACTERISTICS OF THE INCLUDED PAPERS

Chen 2011[9]

A case-control study that interviewed in person or by telephone a group of cases (women with a finding of ruptured or unruptured IA) and a group of controls matched by age and demographic data without a history of treatment or diagnosis of IA. In this interview, they were asked about OC and HRT use and calculated the *Odds ratio* (OR) of HSAe and IA in those two groups. As a result, an OR 2.1 (CI 1.2–3.8; p=0.01) was obtained in the IA group in patients using OC and an OR 3.1 (CI 1.5–6.2; p<0.05) in the IA group in patients using HRT. There was no statistical difference regarding the risk of SAH in patients using OC and HRT compared to those who did not. As a summary of this article, a protective effect can be inferred regarding the formation of IA in patients who used HRT or OC. As for rupture, there was no statistical difference between the groups.

Longstreth 1994[10]

A case-control study that interviewed patients with a history of SAH in *King County, Washington*, whose controls were matched by sex and age, with a sample of 2 controls for each case, randomly chosen through the telephone number. The interviews took place in the patient's homes, directly with them or with close family members, lasting about 1 h, with questions about OC and HRT use and other risk factors for SAH too. As a result, an OR of 0.52 (CI 0.25–1.10; p<0.002) was obtained for patients using OC and at risk of SAH and an OR of 0.47 (0.26–0.86; p<0.002) for patients using HRT and risk of SAH. Both drug groups had a protective effect regarding the risk of SAH.

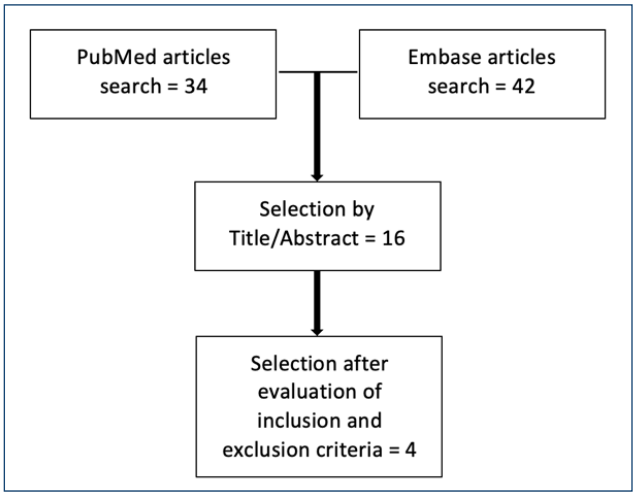


Figure 1. Flowchart of selected papers.

Qureshi 2016[11]

A cohort study was conducted to follow-up women between 50 and 79 years old who participated in the *Women's Health Initiative* (WHI) study for 12 years to analyze the risk of SAH during follow-up and to analyze which patients used and did not use HRT. A total of 93,676 patients were followed up in this study, and of these, 114 developed SAH during the follow-up. The relative risk (RR) of developing SAH (after adjusting for other confounding risk factors) in patients using HRT was 1.5 (CI 1.0–2.2). The article suggests that postmenopausal women diagnosed with IA, with a family history of aneurysm, and with cardiovascular risk factors should be advised not to use HRT. If it is necessary, preference should be given to combined drugs (estrogens associated with progestins).

Murchu 2001[12]

A multicentric case-control study that evaluated 268 women with a history of SAH and conducted personal interviews with patients or close family members defined 286 controls matched by sex, age, and city of residence randomly selected through electoral rolls and conducted interviews with the controls in the same way as cases. In the interview, the use of HRT and ACO was asked, as well as other risk factors related to SAH. The RR for SAH was 0.97 (CI 0.58–1.60) in patients using OC, without statistical significance, and 0.75 (CI 0.47–1.18) in patients using HRT, demonstrating a protective effect of HRT on the development of SAH.

Table 1. Risk of bias and quality of evidence.

Author/year	RR or OR and CI	Image exam to define the case	Personal interview or by telephone
Chen, 2011			
Longstreth, 1994			
Qureshi, 2016			
Mhurchu, 2001			

RR: relative risk; OR: odds ratio; CI: confidence interval. Green chart: the absence of bias.

META-ANALYSIS

Hormone replacement therapy and subarachnoid hemorrhage risk

According to Graph 1, three articles were included in this analysis, with the result showing the benefit of the intervention group.

Oral contraceptive and subarachnoid hemorrhage risk

According to Graph 2, three articles were included in this analysis, with the result showing the benefit of the intervention group.

Oral contraceptive and hormone replacement therapy and intracranial aneurysm formation

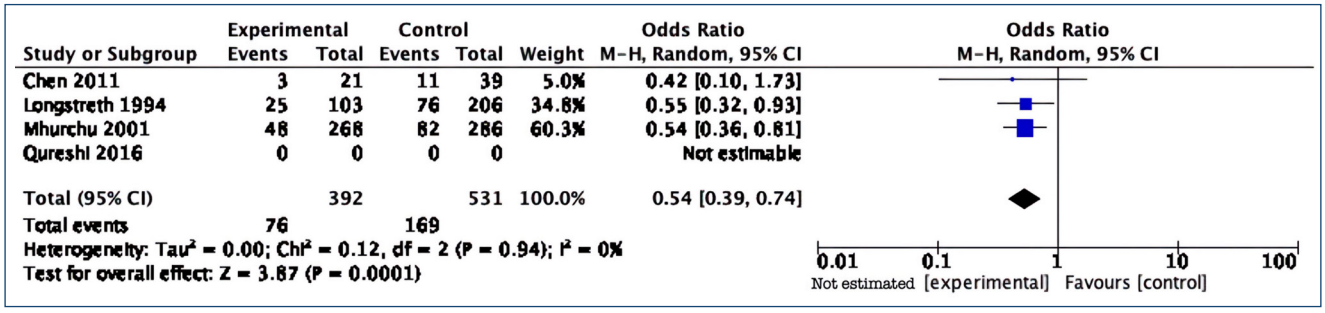
Only one article analyzed the formation of IAs and the use of HRT and OC, and there was a protective effect with the use of these medications. OC: OR 2.1 (CI 1.2–3.8) and HRT: OR 3.1 (CI 1.5–6.2). In this case, the meta-analysis was not performed[9].

DISCUSSION

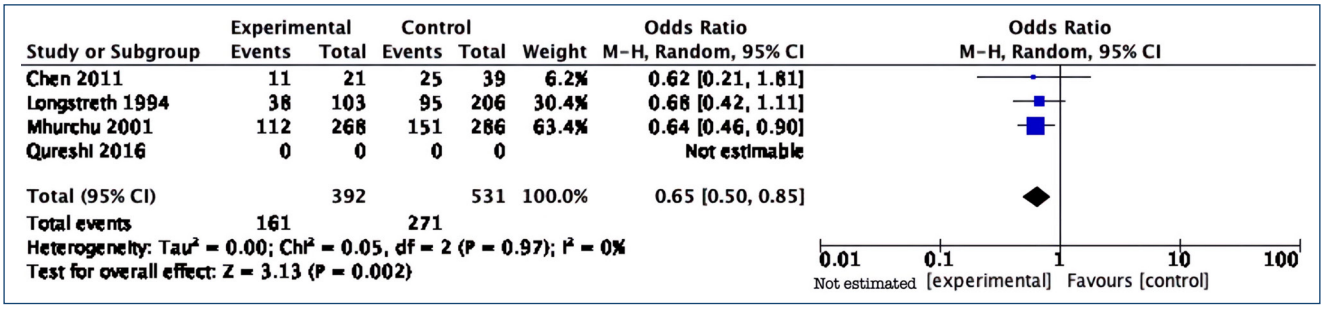
The use of HRT and OC has always been a very controversial topic in the medical literature due to the various associations of the use of these medications with increased cardiovascular risk, the development of malignant neoplasms, the association with thrombotic and thromboembolic events, and several other pathologies[13]. These associations have changed a lot over the decades, mainly due to changes in medications, dosages, and associations in the formulations studied, and we currently see a trend toward the use of lower doses of hormones and different combinations of estrogen and progestins or isolated progestins (as a contraceptive method) or isolated estrogen (as a treatment for menopausal symptoms in hysterectomized women), increasingly with fewer side effects and risks of developing diseases. The therapies have been individualized according to the characteristics of the patients, associated morbidities, and idealized goals with the treatments[14].

The diagnosis of IA is extremely challenging, mainly due to the risks of SAH, as this is an event of great morbidity and mortality[15]. Over the decades, discovering factors associated with a decrease in the risk of bleeding in these patients has always been a very important objective, especially in women, most affected by this disease[16,17]. Studies that demonstrate a lower risk of developing IA and SAH in women who use HRT and OC can bring much hope to the treatment of these diseases.

Some articles were excluded from this analysis mainly because they were experimental studies, case studies, and/or



Graph 1. The forest plot of the comparison analyzes the risk of subarachnoid hemorrhage in the group that used hormone replacement therapy versus the group that did not use hormone replacement therapy.



Graph 2. Forest plot of the comparison analyzing the risk of subarachnoid hemorrhage in the group that used oral contraceptive versus the group that did not use oral contraceptive.

review articles, for which it would not be possible to draw a statistical inference about the use of these medications as a protective factor. Something to consider in all the studies carried out was the fact that the controls did not undergo any type of imaging exam that would prove the non-existence of IA. This is a possible bias in these studies.

Other articles were not based on personal interviews with the patients involved; they only inferred the probable use of OC if the woman was married, divorced, or single, which is something subject to much criticism and currently inconceivable.

This review has some limitations, mainly due to variations in the baseline characteristics of the patients evaluated, variations in the medications used and their dosages, and a lack of control over the use of other medications. There are no controlled studies for this type of evaluation since it is unethical to use a placebo group in studies of contraceptive drugs in women of childbearing age, and, in addition, it is known that IAs and SAH are rare events in the general population.

CONCLUSION AND SUMMARY OF EVIDENCE

From the results of this meta-analysis, it is possible to infer that the use of OC and HRT has a protective effect in relation to the risk of SAH in women. There is limited data in the literature so far to infer that the use of ACO and TRH has a protective effect on the formation of IAs.

AUTHORS' CONTRIBUTIONS

DLPS: Formal Analysis, Writing – original draft, Writing – review & editing. **MBG:** Writing – review & editing. **VMHZ:** Writing – review & editing. **EGF:** Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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The use of contraceptives and their nutritional impact on medical students

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SUMMARY

OBJECTIVE: This study aimed to analyze the impact of contraceptives on medical students at the Federal University of Paraná and verify adherence, consequences, and lifestyle effects of the contraceptive method used.

METHODS: This is an observational, cross-sectional study in which 214 participants answered an online questionnaire composed of 30 questions. For statistical analysis, the Stata® 16.0 software was used, and the mean and standard deviation were estimated to characterize continuous variables with a normal distribution and percentages for categorical variables. For group-to-group comparisons, a one-way ANOVA was used for normal continuous variables and Fisher's exact test for categorical variables.

RESULTS: Almost 10% (9.3%) of women used condoms only, and double protection (condom+oral contraceptives) corresponds to 23.4%. Of the 214 participants, 38 reported making exclusive use of long-acting reversible contraception, and 13.6% of the interviewees used oral contraceptives exclusively. More than 88% of the interviewees believe that the medical course provided adequate education on contraception. Regarding lifestyle habits, 71.5% of the students reported alcohol intake, tobacco use, and/or other drug use.

CONCLUSION: There was a great diversity of combinations between contraceptive methods used by the medical student at Federal University of Paraná, the most prevalent being the oral contraceptive associated with male condoms. There was a greater association in the use of long-acting reversible contraception in married students. Although 88.3% of the participants believed that they had a good education about contraception at university, only half of them use condoms in sexual relationships. The rate of adherence to alcohol and tobacco among students is considerable, and such practices can negatively affect a nutritional profile, a healthy lifestyle, and safe sexual practices. Brazilian medical schools are fundamental for the advancement of medical education in contraception and for the creation of public policies on family planning.

KEYWORDS: Contraceptive agents. Women. Medicine. Students. Alcohols.

INTRODUCTION

The use of contraception by female medical students can be explained by the time-consuming nature of pregnancy. Female doctors are known to face many challenges in family planning. In North America, most female physicians enter residency after the age of 25 years, which is the average age at which a North American woman would complete her first pregnancy[1].

A survey carried out with university students in the state of Rio Grande do Sul showed that contraceptive methods are used by approximately 90% of students, with condoms being the most commonly used. It is believed that a higher level of education, as well as better sociodemographic indicators, have a greaet influence on knowledge and adherence to contraceptives in this population[2].

The use of hormonal contraceptives in young women might have a negative impact not only on family planning but also on nutritional profile, lifestyle, and vitamin levels. Previous studies have shown that the use of hormonal oral contraceptives may be associated with lower serum levels of vitamin B12 and folic acid[3].

This study aimed to analyze the contraceptive profile of university medical students at the Federal University of Paraná (UFPR) on the Curitiba-PR and Toledo-PR campuses to verify adherence and knowledge about the contraceptive method used by the student.

METHODS

This is an observational, cross-sectional study. Female students participated in the research, from the first to the twelfth period of the medical course at the Federal University of Paraná, on the Curitiba-PR and Toledo-PR campuses, aged 18 years or over.

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Data collection was carried out in March 2022. The students were approached online through pre-established social media groups among university students. The invitation to participate in the research, which contained the link to the online form, along with the free and informed consent form (TCLE), was sent to the groups mentioned above. In the invitation sent, there was an explanation on the purpose and importance of participating in the study, as well as on the right to voluntary participation and confidentiality of information. In addition, there were data about the researchers and the number of the Certificates of Presentation of Ethical Appreciation issued by the Ethics and Research Committee of the Health Sciences Sector. The participants had their voluntary participation, answering the questions only if they felt free to do so. Response time was predicted to be 6 min.

There were 30 questions on the online form, and 2 of them were open-ended. The questions on the form were divided into five categories, namely, socioeconomic, sexuality, and previous pregnancies, contraceptive methods and knowledge, and finally side effects.

Medical students at the Federal University of Paraná on the Curitiba and Toledo campuses, from the first to the twelfth period of the course, were included in the research. Students under the age of 18 years and students who, after being exposed to the TCLE and the questionnaire, refused to participate in the research were excluded from the study.

After sending the invitation, the students had a period of 7 days to respond. A second invitation was made after 7 days to include students who could not respond at the first opportunity. The data obtained were compiled in Excel® and sent for statistical analysis.

The medical course at the Federal University of Paraná has 812 female students, with 613 enrolled on the Curitiba campus and 199 enrolled on the Toledo campus. The links were sent to all medical classes on both campuses; however, only 215 students accessed the invitation, and after exclusion criteria (refusal to participate or non-acceptance of the TCLE), 214 participants were involved.

A statistical analysis of the data obtained was performed using the mean and standard deviation to characterize continuous variables with a normal distribution. For categorical variables, percentage calculations were used. Regarding comparisons between groups, one-way ANOVA was used for normal continuous variables and Fisher's exact test for categorical variables. A p-value<0.05 was considered significant. The Stata® 16.0 software was used.

The study was approved by the Ethics and Research Committee of the Health Sciences Sector (CAAE: 49561921.8.0000.0102) on December 28, 2021.

RESULTS

The study included 214 female university students, 169 of them were from UFPR Curitiba and 45 were from UFPR Toledo.

The mean age was 25.5 years, with a standard deviation of 2.9. Approximately 54% claim to have a family income of more than R$6,060.00, which is equivalent to about five Brazilian minimum wages today. In general, this is a woman with good purchasing power, since only 9.3% of the interviewees claim to have a family income between R$1,212.00 and R$2,424.00. Only one student participating in the study claimed to have an income of less than R$1,212.00. The other characteristics of the population are described in Table 1.

Regarding life habits, 71.5% of the students reported using alcohol, tobacco, and/or other drugs (Figure 1).

Table 1. Characteristics of the population.

	n	%
Age (years)		
23.5 (2.9)*		
Campus		
Curitiba	169	79
Toledo	45	21
Family income		
Less than R$ 1,212.00	1	0.4
R$ 1,212.00 – R$ 2,424.00	20	9.3
R$ 2,424.00 – R$ 6,060.00	76	35.5
More than R$ 6,060.00	117	54.6
Relationship status		
Single	84	40.7
Dating	112	52.3
Married	15	7
Fixed partner for more than six months		
Yes	132	61.7
No	82	38.3
Number of partners in the last six months		
No fixed partner	25	11.7
Between one and two partners	172	80.3
Three or more	17	7.9
Sexual orientation		
Homosexual	9	4.2
Heterosexual	153	71.5
Bisexual	49	22.9
Others	3	1.4

Source: Author (2022). (*) Average age. In parentheses: standard deviation.

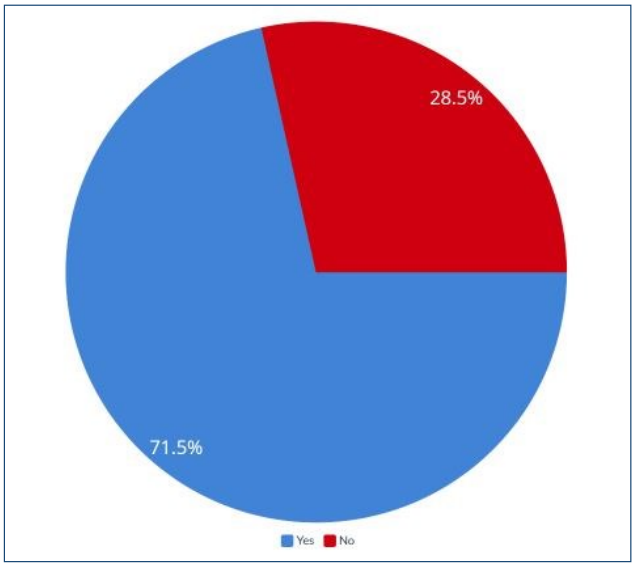

Figure 1. Consumption of alcoholic beverages, tobacco, and/or other drugs. Source: Author (2022).

The methods of contraception chosen by the students varied. In the questionnaire, it was possible to choose more than one contraceptive method alternative, generating several combinations. For statistical analysis, contraceptives were divided into 14 groups (Table 2).

Regarding the medical student's contraceptive profile, the use of condoms alone corresponds to 29 (9.3%) of the users. When used in conjunction with oral contraceptives, this index rises to 50 (23.4%). The rates of condom use associated with hormonal and non-hormonal LARCS were 15 (7%) and 10 (4.7%), respectively. Notably, 10 students said that they associated condom use with behavioral contraceptive methods (table, coitus interruptus, and body temperature). Of the 214 participants, 38 reported using LARCS exclusively as a contraceptive method, corresponding to 17.7% of the total. In all, 19 students do not use contraceptive methods. Approximately 29 (13.6%) of the interviewees use only oral contraceptives (combined/progestogens). In addition, 27 (12.6%) of the students claim to use behavioral methods in association with some contraceptive method. Regarding the time of use, 132 (60%) students have been using the chosen contraceptive method for more than 2 years. Regarding knowledge about contraceptive methods, 88.3% of respondents believe that the medical course provided adequate education on contraception.

When comparing relationship status with a contraceptive method of choice, Fisher's exact test showed a statistical difference ($p<0.001$). Married women had a greater preference for hormonal LARCS (40%), while the others used condoms and oral contraceptives together (19.6 and 28.7%).

Table 2. Contraceptive profile of the medical student.

	n	%
Use of contraceptive method		
No	19	89
Yes	195	91.1
Contraceptive method of use		
Male or female condom	20	9.3
Oral contraceptive	29	13.6
Non-hormonal larcs	8	3.7
Hormonal larcs	30	14
Condom and oral contraceptive	50	23.4
Comdom and non-hormonal larcs	10	4.7
Comdom and hormonal larcs	15	7
Comdom and behavioral methods	10	4.7
Oral contraceptive and behavioral methods	5	2.3
Non-hormonal larcs and behavioral methods	1	0.5
Hormonal larcs and behavioral methods	3	1.4
Triple protection (including behavioral methods)	8	3.7
Others	6	2.8

Source: Author (2022). Note: Oral contraceptives consist of combined contraceptives or progestogens alone; non-hormonal long-acting reversible contraception (LARCS) is characterized by a copper/copper and silver intrauterine device (IUD), and hormonal LARCS consists of Mirena, Kyleena, and Implanon; behavioral methods are considered table, coitus interruptus, and body temperature; vaginal rings, a monthly injection, and the morning-after pill with or without a condom were classified as "other" methods.

DISCUSSION

Approximately 91.1% of medical students at UFPR use some form of contraception, which is in line with a similar study carried out at the Faculty of Medicine in Valença-RJ, which showed that 90% of students used contraception. The most commonly cited method is the contraceptive pill alone, followed by that associated with the male condom. These indicators are maintained when observed among students in stable relationships, showing that the married medical student in Valença also opts for the contraceptive pill alone. In addition, the research showed that the studied population was predominantly composed of women who were not in stable relationships[4].

The adherence rate to alcoholic beverages, tobacco, and other drugs is noteworthy when it is found that 71.5% of students use some type of substance. A limitation of the present study was not exploring the circumstances in which its use occurs. A similar study carried out with 125 medical students at the Centro Universitário de Anápolis in the state of Goiás found that 71% of the interviewees had already practiced sexual activity

under the influence of alcohol or other drugs, and of these 35% stated that this practice interfered with the use condom[5].

In addition, reduced absorption of vitamins such as B1 (thiamine), B2 (riboflavin), B6 (pyridoxine), vitamins A, C, and folic acid can be caused by the use of alcoholic beverages. The abusive use of the substance results in the worsening of this condition as well as in the reduction of the intake of foods that contain vitamins, minerals, proteins, carbohydrates, and fats[6].

A study carried out by the University of Sydney, seeking to understand the impact of oral contraceptives on plasma levels of vitamins B6, B12, and folate in university students of reproductive age, found reduced serum levels of vitamin B12 in OAC users, compared to the placebo group. It was also found that 50% of the participants were consuming lower levels of the aforementioned vitamins in their diet, showing the need to better understand the relationship between the eating behaviors of university students[3].

It was surprising to note the diversity of combinations of contraceptive methods used by the UFPR medical student. However, the most cited ones do not differ from the literature. Medical students usually prefer the oral contraceptives associated with condoms, possibly due to their facility and availability. A study carried out with medical students at the University of Southern Santa Catarina that included 279 women showed that 86% used some form of contraception, the most cited being combined oral contraceptives, followed by condoms[2].

The use of LARCS draws attention. Adding the hormonal and non-hormonal LARCS combinations with other methods, the percentage reaches approximately 31%. When used in conjunction with a condom, this rate decreases to 11.7%. An interesting association was the predominant use of LARCS among married academics, going in the opposite direction of the study carried out by Gabriela et al.

In a married student, the choice of contraceptive method seems to demonstrate that she prioritizes the end of college and pregnancy since LARCS are currently considered the safest method. The low adherence to long-acting reversible contraceptive methods among single medical students shows the need for a greater approach to their use at the university. A study carried out with medical students at the Federal University of São Carlos (UFSCAR) showed that of the 104 participants, 60.19% of them did not know the terminology "LARC". Despite showing interest in LARCS use, the high cost and difficulty of access were the main reasons for non-adherence to the method[7], which also seems to have occurred in our study.

Another fact that stands out is the use of condoms. When used alone, it corresponds to only 9.3% of the students. However, its adherence rises to 52.8% when associated with another contraceptive method. At the Federal University of Paraná in 2001, it was observed that 50% of the female students interviewed did not use safe sexual practices, that is, not using condoms[8]. It is therefore possible to note that the rate of condom use among students remained similar during the more than 20 years that separate the two studies. Added to this fact, the prevalence of behavioral methods associated with other contraceptive methods is highlighted. In this regard, it is relevant to question the fact that 88.3% of the students stated that the education on contraception offered in the medical course was adequate. However, the data obtained in the current study show that there is a gap in care with respect to protection against sexually transmitted infections (STIs).

Evaluating the medical student's contraceptive profile is important when data obtained show that students who value adequate contraceptive practices, as well as safe sex, are more comfortable discussing sexuality with their patients, thus transmitting knowledge and information that is so necessary today[1].

Among the limitations of the study, the difficulty of accessing the students can be mentioned. Despite the wide access to social networks, which would seem to facilitate the dissemination of the research invitation, it was noted that the students had difficulty joining, possibly due to a lack of interest. This is mainly reflected by the large difference in participation among students across the campus.

Addressing contraception not only in an academic way but also to carry out sexual health education is fundamental for advances in medical education and the creation of public policies in family planning. The medical student at the Federal University of Paraná presents heterogeneity in her socioeconomic profile. Although there is a great diversity of combinations among the contraceptive methods used, these women opt for easily accessible methods, as demonstrated by the predominance of condom and oral contraceptive pill use.

Concern about STI prevention should be encouraged, given that there are still a considerable number of students who do not use condoms. It is necessary to better understand the effects that oral hormonal contraceptives have on the vitamin profile of women of reproductive age as well as the effectiveness of vitamin supplementation in women using oral contraceptives, since there is less recent literature on the subject.

AUTHORS' CONTRIBUTIONS

JCV: Investigation, Methodology, Writing – original draft.
LGS: Writing – original draft, Writing – review & editing.
FSF: Writing – original draft, Writing – review & editing.
VFA: Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Breast and gynecologic cancers as a Brazilian health priority

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Brazilian Society of Clinical Oncology

SUMMARY

OBJECTIVE: Cancer imposes a profound burden on low- and middle-income countries where 65% of the global cancer deaths occurred in 2020. The objective of the present review was to describe female cancer epidemiology in Brazil, barriers to prevention, screening, and treatment, and to propose strategies to a better control.

METHODS: For the process of literature search and scientific acquisition, we have utilized the terms "female cancer" AND "breast cancer," AND "cervical cancer" AND "endometrial cancer" AND "ovarian cancer" AND "Brazil" in PubMed. References of the articles included in this review were manually searched in order to identify relevant studies on the topic. The official Brazilian epidemiology data were extensively analyzed at the governmental site www.inca.gov.br.

RESULTS: Considering cases of breast and gynecologic cancers together, 105,770 new cases are expected to be diagnosed yearly, positioning female cancer as the highest cancer incidence in Brazil. Female breast cancer is the most common and the leading cause of death from cancer in the female population in all regions of Brazil, except in the North, where cervical cancer ranks first. Cervical cancer, a preventable disease, corresponds to the third-most common neoplasia in women, with higher incidences in the North and Northeast regions of Brazil. An upward trend has been observed in endometrial cancer incidence, a tendency that follows the increase of its two most common risk factors: population aging and obesity. Ovarian cancer currently occupies the eighth position among female cancers in Brazil, but it is the most lethal gynecologic cancer. The main strategies to reduce female cancer mortality rates are the reduction of inequalities in healthcare services and the early diagnosis of cases. The lack of a specific national cancer program results in a reactive and unplanned approach to healthcare provision, ultimately leading to suboptimal resource utilization and higher expenditure.

CONCLUSION: Analyzed together, breast and gynecologic cancers correspond to the leading cause of cancer in Brazil. A heterogeneous group, female cancer includes diseases with a high primary and secondary prevention potential. The organization of a female cancer program in Brazil prioritizing primary and secondary prevention strategies, such as adequate mammography screening and human papillomavirus vaccination coverage, could significantly improve female cancer control in the country.

KEYWORDS: Neoplasms. Women. Epidemiology. Prevention and control.

INTRODUCTION

Cancer imposes a profound burden on low- and middle-income countries (LMICs), where 65% of the global cancer deaths occurred in 2020[1]. The Brazilian National Cancer Institute (INCA) expects more than 704,000 new cancer cases annually for the triennium from 2023 to 2025. Excluding non-melanoma skin cancer, 483,000 new cases are expected, with 50.5% of them (244,000 cases) in women. In the female population, breast cancer (BC) is the most common neoplasia with 73,610 new cases per year, followed by colorectal cancer with 23,660 cases, and cervical cancer (CC) with 17,010 cases[2]. Considering cases of breast and gynecologic cancers together, 105,770 new cases are expected to be diagnosed yearly, positioning female cancer as the highest cancer incidence in Brazil.

BC is the most common incident, excluding non-melanoma skin cancers, and the most prevalent tumor in all Brazilian regions[2]. It is also the leading cause of death from cancer in the female population in all regions of Brazil, except in the North, where CC ranks first. The BC mortality rate adjusted for age was 11.84 deaths per 100,000 women in 2020, with the highest rates in the Southeast and South regions, with 12.64 and 12.79 deaths per 100,000 women, respectively. In the Brazilian cancer mortality rate historical series, it is possible to observe an upward trend over the past few decades, with a certain deceleration and stabilization in the South and Southeast regions, and an increase in the other regions, between 2000 and 2015[3]. Limited data on the clinical characteristics, treatment, and outcomes of patients diagnosed with BC are

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available in Brazil. The AMAZONA retrospective cohort study enrolled 4,912 patients within 28 Brazilian institutes from June 2008 to January 2009[4]. Over 2,200 women were included in the analysis. A high proportion of patients diagnosed with BC younger than 50 years old was reported (41%), and approximately 70% of the patients had hormonal-receptor-positive disease. The characteristics of those young women with BC were later evaluated in the prospective AMAZONA III study. Out of 2,888 women diagnosed with BC, 486 (17%) were younger than 40 years old and presented more frequently with stage III, T3/T4, grade 3 tumors, HER-2-positive, luminal B-like disease, and triple-negative subtypes[5].

The lifetime risk of BC for a woman is about 12%, a percentage with the potential to increase significantly when a pathogenic variant in a gene predisposing to BC is found. For instance, the cumulative risk of BC by the age of 80 years is 72% for *BRCA1* mutation carriers (mut) and 69% for *BRCA2mut*. It is of utmost importance to perform a genetic evaluation in case of suspicion of hereditary BC.

The CC incidence rate is approximately 15 per 100,000 women, which corresponds to the third-most common neoplasia in women, with higher incidences in the North and Northeast regions of Brazil[2,6]. The CC-adjusted incidence rate for the whole population fell from 21.15 per 100,000 women in 2000 to 11.44 per 100,000 women in 2015, an annual percentage change of -4.6 from 2000 to 2011 and -10.3 from 2011 to 2015[7]. Incidence rates were higher in the Northern region (20.48 per 100,000), followed by the Northeast region (17.59 per 100,000)[6]. The mean age of CC diagnoses is 48.7 years. It was also observed that 62% of the patients have less than 8 years of schooling and 60% are diagnosed in stages II–IV, locally advanced disease. Squamous cell carcinoma is the most common histology (79%), followed by adenocarcinoma (9.5%)[7]. Recent data have shown that, as for mortality, between 2000 and 2020, 108,590 deaths from CC occurred nationwide. The mean age-adjusted mortality rates according to race/skin color were 3.7/100,000 for white, 4.2/100,000 for black, 2.8/100,000 for yellow, and 6.7/100,000 for indigenous women. Taking the mortality rates in white women as a reference, there was a 27% increase in death risk in black women (RR=1.27) and 82% in indigenous women (RR=1.82)[8].

Uterine cancer has recently surpassed ovarian cancer and become the second-most common gynecologic cancer in Brazilian women with an estimated risk of 7.08 new cases per 100,000 women[6,7]. This tendency follows the increase of the two most common risk factors for uterine cancer: population aging and obesity. According to the Ministry of Health, 33% of Brazilian women were overweight and 32% were obese in 2022, in contrast to 29 and 16.5%, respectively, in 2010[9]. Regarding population aging, life expectancy in Brazilian women increased and reached 80.5 years in 2021[10]. The highest incidence rates of uterine cancer were seen in the higher-income regions of the country, such as in the southern and southeastern states. The mean age at diagnosis was 61.9 years with 55% of the patients reporting less than 8 years of schooling. The majority of uterine cancer patients are diagnosed with early-stage disease (68% with stages I–II)[7].

Ovarian cancer occupies the eighth position among female cancers in Brazil and is more common in the Southeastern and Southern regions. Between 2000 and 2005, the adjusted incidence rate for the population declined from 8.62 to 6.62 (an annual percentage change of -5.1), remaining without significant changes until 2015. The mean age of diagnosis for ovarian cancer is 53.3, with 51% having less than 8 years of schooling and 67% diagnosed in stages III–IV[7]. Approximately 25% of ovarian cancer patients have a genetic predisposition to cancer, half of them with a pathogenic variant in *BRCA1* or *BRCA2*. Genetic testing is essential for hereditary ovarian cancer control and to tailor maintenance therapy with PARP inhibitors.

BARRIERS TO DISEASE CONTROL AND STRATEGIES TO OVERCOME IT

Despite the existence of a publicly funded healthcare system offering universal coverage, there are still wide socioeconomic and ethno-racial inequities in access to healthcare in Brazil[11]. Brazil reports a global health expenditure of 9% of its gross domestic product. However, only half of this budget is provided by the government to cover 75% of the population under the public healthcare system, and the other half is paid by the remaining 25% of Brazilians through their private health insurances[12,13].

Starting with screening, mammographic screening has been described as an effective method to detect early BC. Women who regularly participate in a screening program can have their risk of dying of BC reduced by up to 60%[14]. INCA issued an official recommendation for BC screening in 2004, updated in 2015, which recommends mammography biennially for women aged 50–69 years. However, in Brazil, mammographic screening has been an opportunistic procedure. Despite educational campaigns, mammography coverage is currently around 35% of the target population, well below the 70% recommended worldwide[15].

Changing gears to CC, this is a highly preventable neoplasia with periodically performed Pap smears and vaccinations. In 2020, the World Health Organization (WHO) launched a

global Cervical Cancer Elimination Initiative and stated that 90% of girls should be vaccinated by the age of 15 years, 70% of women should be screened with high-performance tests by the ages of 35 and 45 years, and 90% of precancerous lesions should be treated. The coverage of fully vaccinated girls in Brazil was only 57.1% in 2021, although an increase was seen compared to 2020 (46.7%)[16]. Multiple barriers to vaccination can be listed: limited understanding of human papillomavirus (HPV) and HPV-related diseases, being unaware of or forgetting about the need for additional doses, safety concerns about the vaccine, discomfort related to talking about sexual behavior, lack of time for discussions about the vaccine among clinicians, lack of a clear recommendation from a healthcare provider, and parental belief that their children is too young for the vaccine and/or not sexually active[17]. The advent of HPV prophylactic vaccination offers a potential large step toward CC prevention. Based on the high incidence of HPV-related cancers, the strong carcinogenic potential of certain HPV strains, and numerous trials proving high efficacy of vaccines, prophylactic immunization is considered one of the most important tools to alter the incidence of HPV-associated cancers in countries throughout Latin America and other LMICs worldwide. Large-scale HPV immunization can reduce lives lost due to preventable cancers and relieve health systems strained by costly treatment of late-stage cancers. However, despite its proven efficacy and safety, vaccine uptake has been lower than expected, and among the several reasons for this are high cost of the HPV vaccine and requirement for multiple doses, limited knowledge of HPV vaccine efficacy and safety, cultural barriers, insufficient provider recommendations, and inadequate implementation strategies. Brazil is in danger of repeating the low adherence to Pap smear screening for HPV vaccination. Brazil has a long history of high vaccination coverage with robust national immunization programs, especially compared to other developing regions. So, the country needs to properly utilize its existing vaccination platform. Regarding Pap smear, Brazilian consolidated coverage is around 20%, and it is not homogeneous among all regions, with the highest rate in the South and the lowest in the Northeast. The main reasons reported by Brazilian women not to perform it are as follows: feeling that it is not necessary (45%), having no formal recommendation to perform (14%), and being ashamed (13%)[18].

Unfortunately, there is no reliable screening test to detect ovarian cancer in its earlier stages, leading to a diagnosis at advanced stages (FIGO III and IV) in around 75% of the cases. Every woman with a diagnosis of ovarian cancer should be offered germline *BRCA1/2* testing since this information helps delineate treatment and, when a mutation is detected, should also trigger germline testing in healthy relatives. For women who carry mutations in a propensity gene, it is recommended to perform prophylactic salpingo-oophorectomy[19]. Unfortunately, access to genetic testing is still dismal in the public health system as well as the availability of genetic counseling.

Timely access to proper treatment continues to be an issue in Brazil. The time interval between diagnosis and treatment of BC and the impact of health insurance coverage were analyzed in a cohort from the AMAZONA III study, with 1,709 stage I–III patients[20]. The diagnosis-to-treatment interval was higher in women treated in the public versus in the private system (56 vs. 34 days, $p<0.0001$), independent of clinical stage, type of treatment (systemic vs. surgery upfront), subtype, and country region[20]. According to the Panorama of Gynecologic Cancer in Brazil, the time to start treatment after having a confirmatory biopsy is over 30 days in more than 70% of gynecologic cancer patients. Access to proper treatment is also an issue. For instance, endometrial cancer is usually diagnosed in its early stages (FIGO stages I–III), where treatment consists mainly of surgery and radiotherapy. Surgery has evolved in the past 10–15 years and is done preferentially via minimally invasive surgery (MIS). Unfortunately, access to MIS (laparoscopic or robotic) is not a reality in the public health system. Brazil also faces a lack of radiotherapy facilities (including brachytherapy), and the distribution is not homogeneous across the country[21]. CC, which is usually diagnosed in locally advanced stages (FIGO stages II–IV) where radiotherapy is necessary, also struggles with this challenge. Another common issue in gynecologic cancers is the lack of trained specialists since there is no formal gynecologic oncology subspecialization or society in Brazil.

Access to cutting-edge systemic treatments is fundamental for improving survival outcomes. In Sistema Único de Saúde, there is still no access to therapies like cyclin inhibitors, pertuzumab, immunotherapy, and PARP inhibitors, among others, that provide clinically meaningful benefits. Of note, some of these treatments are already officially incorporated into the public system, but, for several reasons, patients still do not have access to them.

There is a great need to expand hereditary cancer testing and counseling in Brazil, and changing current policies is essential to accomplishing this goal. Vigilance in the ongoing implementation, understanding Brazil's unique social and structural barriers, and mounting a strong and timely response to this public health problem are crucial to attaining a significant impact. Increased knowledge and awareness of genetics education among nongenetic healthcare professionals, as well as the general population, public health officials, and patient organizations, would not only increase access to genetic services

for patients, but also advance translational efforts to improve cancer care and outcomes.

Focusing on minorities, worldwide, the transgender patient population remains underrepresented in cancer research and cancer care standards. Additionally, the acceptance of transgender rights does not translate automatically to competence in administering equitable patient care. In one study of surveyed healthcare providers, only 35% felt comfortable and 29% felt equipped to provide routine gynecologic care to transgender females and transgender males, respectively[22]. In the same study, 59% of providers were unaware of BC screening recommendations for transgender females[22]. Furthermore, transgender patients frequently report significant distrust of the healthcare system related to experiences of discrimination and marginalization[23].

Recently, INCA launched national recommendations on healthy nutrition and exercise to educate the population about the risks of a sedentary lifestyle and poor eating habits and their relationship to cancer. Concerted efforts now need to be made to ensure that these primary prevention measures reach the public.

The main international strategies to reduce female cancer-mortality rates are the reduction of inequalities in healthcare services and the early diagnosis of cases. In many countries, the lack of specific National Cancer Control Programmes results in a reactive and unplanned approach to healthcare provision, ultimately leading to suboptimal resource utilization and higher expenditure[12]. The organization of a comprehensive female cancer program in Brazil prioritizing primary and secondary prevention strategies could improve breast and gynecologic cancer control.

AUTHORS' CONTRIBUTIONS

ANR: Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **DDR:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **DAS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **EP:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **LCGL:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **MS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **MRM:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **PMH:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Applicability of vaginal energy-based devices in urogynecology: evidence and controversy

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SUMMARY

OBJECTIVE: This study aimed to analyze the evidence and controversies about the use of vaginal energy-based devices (laser and radiofrequency) for treatment of genitourinary syndrome of menopause, recurrent urinary tract infection, urinary incontinence, and genital prolapse through a literature review.

METHODS: A search of literature databases (PubMed, Medline) was performed for publications in December 2022. Keywords included genitourinary syndrome of menopause, vaginal laxity, vaginal/vulvovaginal atrophy, urinary tract infection, urgency incontinence, frequency, urgency, stress urinary incontinence, genital prolapses AND energy-based devices, AND vaginal laser, AND vaginal radiofrequency, AND CO2 laser, AND Er:YAG laser. Publications in English from the last 7 years were reviewed and selected by the authors.

RESULTS: The literature regarding vaginal energy-based devices in the treatment of urogynecological conditions is primarily limited to prospective case series with small numbers and short-term follow-up. Most of these studies showed favorable results, improvement of symptoms with low risk, or no mention of serious adverse events. Consensus statement documents from major medical societies suggest caution in recommending these therapies in clinical practice until more relevant data from well-designed studies become available.

CONCLUSION: The potential of the vaginal laser and radiofrequency as a therapeutic arsenal for the evaluated urogynecological conditions is great, but qualified research must be done to prove their efficacy and long-term safety, define application protocols, and recommend the use of these technologies in clinical practice.

KEYWORDS: Genitourinary syndrome of menopause. Female urogenital diseases. Urinary tract infection. Urinary incontinence. Genital prolapses AND "laser therapy" AND "radiofrequency therapy".

INTRODUCTION

Genitourinary syndrome of menopause (GSM) is a common clinical condition, and its symptoms affect about 50% of postmenopausal women, with a great impact on their quality of life. Since the first use of vaginal laser in 2014, there has been growing enthusiasm regarding the use of vaginal energy-based devices (EBD) to treat vaginal atrophy and other associated urogynecological conditions. Several publications describe the potential use of these devices, especially the laser, which demonstrates that their use is already a reality in clinical practice despite limited evidence regarding long-term efficacy and safety[1-4].

There are three main types of non-surgical (for tissue remodeling) EBD with applicability for vaginal use: micro ablative fractional CO_2 laser, Er:YAG laser, and temperature-controlled radiofrequency (RF). As they have not yet been recommended for general use, they are not treatments covered by health insurance or affordable for the general population[3,4].

In July 2018, the Food and Drug Administration (FDA) issued a public warning about the use of EBD to perform vaginal rejuvenation or vaginal cosmetic procedures because the safety and efficacy for treatment of these conditions have not been established[5]. Some more recent research is disparate from the FDA's safety communication. A review in the American Manufacturer and User Facility Device Experience (MAUDE) database and the Bloomberg Law database showed a low rate of reported side effects or no claims asserting harm from vaginal EBD use, which suggests they have an acceptable safety profile[6-8].

Through this narrative review of the literature, we aimed to analyze the current evidence for recommending the use of these vaginal EBD in urogynecology, especially in GSM,

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recurrent urinary tract infection (UTI), urinary incontinence, and genital prolapses.

METHODS

A structured search of literature databases (PubMed, Medline) was performed for all publications, full texts, and abstracts, written in English from January 2015 to December 2022. Keywords included genitourinary syndrome of menopause, female urogenital diseases, urinary tract infection, urinary incontinence, genital prolapses AND "laser therapy" AND "radiofrequency therapy". The articles were reviewed and selected to present the evidence and discuss each proposed clinical indication.

RESULTS

A total of 32 studies were selected and analyzed by the authors, of which 14 evaluated the effect of energy-based therapies in GSM, 5 recurrent urinary tract infection, 11 urinary incontinence, and 3 pelvic organ prolapse.

All the studies except five were prospective or retrospective case series without a control group. Most of them were of low quality and had short follow-up and the clinical outcomes measured were subjective.

DISCUSSION

Vaginal energy-based devices in the treatment of genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM) describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract. Symptoms associated with GSM are highly prevalent, affecting approximately 27% to 84% of postmenopausal women, and can include vaginal dryness, dyspareunia, burning, itching, and dysuria. GSM is generally progressive without effective therapy[1].

According to the North American Menopause Society (NAMS), the first-line recommended treatment for mild GSM is the use of non-hormonal therapies such as lubrificants and moisturizers; gentle vaginal stretching exercises or regular sexual activity can also be recommended. When we face a moderate-severe GSM, it is recommended to start with local estrogen products, which are considered the "gold standard" and the most effective therapy as long as there are no contraindications to its use. Alternative options for those patients for whom estrogenic therapies are not recommended have been studied[2].

Mension et al.[3] published in 2021 a systematic review on the use of vaginal laser for GSM. A total of 64 studies were available, of which only 10 were controlled intervention studies, and only 4 were considered of good quality. All selected studies had a short follow-up time, less than 6 months, and used three CO_2 laser sessions. One recent publication analyzed in this review was highlighted by Salvatore et al.[9], in which the CO_2 laser was compared with a placebo (sham-laser) and compared the intensity of vaginal dryness, dyspareunia, sexual desire and satisfaction, urinary frequency, and urinary incontinence through the visual analog scale (VAS), Female Sexual Function Index (FSFI), and Urogenital Distress Inventory (UDI-6). At the end of the 4th month, the incidence of vaginal dryness, dyspareunia, and sexual dysfunction was lower in the laser group compared to the placebo; there was no difference in urinary symptoms, and there were no significant adverse events. Most studies used symptom scores and not objective measures to assess outcomes.

The International Continence Society (ICS) and the International Society for the Study of Vulvovaginal Diseases (ISSVD) elaborated a consensus paper on the use of vaginal laser for the treatment of urogynecological conditions, aiming to bring recommendations for use based on a literature review and pointing out existing evidence until publication (2018). The authors pointed out that there is little known about the histology of vaginal mucosa after laser therapy for vaginal rejuvenation or functional remodeling; what is reported is based on small studies of patients over a short period of time and cannot prove tissue remodeling in fact, ending up not to recommend the use of laser for "vaginal rejuvenation" or indicate it for routine treatment of vulvovaginal atrophy or GSM[10].

The American Urogynecologic Society (AUGS) provided guidance for the use of vaginal EBD by convening a panel of experts to compile a clinical consensus statement in 2020. In the publication, the authors agreed that the evidence is limited by the scarcity of randomized and controlled studies, in addition to the short follow-up to assess safety and long-term effects. However, the use of laser to treat vaginal atrophy and dyspareunia associated with menopause has shown efficacy for up to 1 year with a favorable safety profile[11].

Paraiso et al. published in 2020 a multicenter, randomized trial comparing the effect of CO_2 laser with vaginal estrogen cream after 6 months. They included 62 menopausal women with significant vaginal atrophy symptoms and did not find a statistical difference in the score VAS, which evaluated dryness and dyspareunia, as well as in the other analyzed scores FSFI, UDI-6, and Day-to-Day Impact of Vaginal Aging (DIVA). The measurements of vaginal pH and vaginal maturation index

(VMI) with objective data showed statistical differences, with improvement in the group that used estrogen, although baseline and 6-month follow-up VMI data were only available for 34 participants (16 laser, 18 estrogen)[12].

Another study published in 2022 by Quick et al.[13] evaluated the effectiveness of three CO_2 laser sessions, separated by intervals between 30 and 45 days, for GSM symptoms in 67 women treated for breast cancer. In all, 33 women completed the 2-year follow-up. VAS, UDI-6, FSFI, and Female Sexual Distress Scare Revised (FSDS-R) scores were evaluated. There was an initial improvement in vaginal and urinary symptoms in all indexes after the first 4 weeks of treatment, with a decrease in the improvement in most evaluations after 1 and 2 years. Sexual function was the only area that sustained significant improvement over time. No grade 3 or higher adverse events were identified at the 2-year follow-up.

Regarding the use of vaginal RF for GSM treatment, there are still fewer publications of well-designed, randomized, and long-term studies that assess genitourinary symptoms. Wattanakrai et al. published, in 2021, a prospective, randomized, double-blind study evaluating the effect of RF and PEMF (pulsed electromagnetic field-based device) versus sham for vaginal laxity. They included the Vaginal Laxity Questionnaire (VLQ), the FSFI, perineometer measurements, Brink scores, and vaginal histological analysis. There was an improvement in parameters in the treated group compared to the control group without significant adverse events in both groups, and itching was significantly higher in the sham arm. Histological analysis demonstrated signs of neocollagenesis, neoelastogenesis, and neoangiogenesis. Authors concluded that RF+PEMF was safe and improved all studied parameters at least 12 weeks post-procedures (short-term follow-up)[14].

The authors agreed that there is no robust scientific evidence to support the widespread use of EBD for the treatment of GSM. On the contrary, the potential benefit and low rate of serious adverse events must be recognized. Well-designed, multicentric, long-term case-control studies are required to further investigate the potential benefits, safety, and efficacy of vaginal EBD therapy for treating GSM. In addition, to establish application or reapplication protocols, it is necessary to define the real cost-benefit ratio of these technologies.

Vaginal energy-based devices in the treatment of recurrent urinary tract infection

There are no publications, in the reviewed databases, that have specifically analyzed the action of vaginal EBD in preventing UTIs, despite the relationship between GSM and the recurrence of such infections. In postmenopausal women, there is an impactful transition in vaginal microbiome; lactobacilli concentration and diversity tend to be lower, and pH also usually elevates. All these changes can be correlated to vulvovaginal atrophy and estrogen deficiency[10,15].

Athanasiou et al.[16], evaluated vaginal laser therapy with CO_2 in 53 postmenopausal women and demonstrated a decrease in vaginal pH and an increase in the number of lactobacilli. In contrast, another study, published by Becorpi et al.[17], showed no change in the vaginal microbiome in 20 women after breast cancer treatment who underwent vaginal CO_2 laser sessions but recorded significant changes in the patterns of inflammatory cytokines and immunomodulators in the vaginal epithelium, suggesting that the benefits of laser treatment in this group of patients are related to a possible anti-inflammatory effect.

Sarmento et al.[18], evaluated the effect of fractional micro ablative RF on the vaginal microbiota, vaginal pH, and cell maturation of 55 postmenopausal patients. They demonstrated a drop in pH and an increase in the flora of vaginal lactobacilli 30 days after application without serious adverse effects. The short follow-up time, the lack of a control-group, and the failure to assess the UTI rate did not allow for more assertive conclusions.

The potential of the use of vaginal EBD, laser, and radiofrequency in the prevention of UTI recurrence needs to be better evaluated through well-designed studies with this specific purpose.

Vaginal energy-based devices in the treatment of urinary incontinence

Fistonić et al.[19] conducted the first study on the efficacy and safety of the laser in the treatment of Stress Urinary Incontinence (SUI). They included 73 patients between 18 and 70 years of age with pure SUI not associated with pelvic organ prolapses (POP) who were treated with a single session of Er:YAG laser. In 6 months, only 47 patients remained in the study; 34/47 (72.3%) of patients experienced improvement on the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQUI SF), and 18/47 (38.3%) had an ICIQUI SF score=0. Patients who were overweight (body mass index >25 kg/m^2) and aged over 60 years had the least improvement in the questionnaire. The short-term follow-up, lack of control group, and high loss of follow-up were important limitations.

Gambacciani et al.[20] conducted a non-randomized prospective study with long-term follow-up in 235 patients undergoing vaginal Er:YAG laser. Of these, 114 had SUI and were evaluated with the ICIQUI SF questionnaire, excluding patients with POP. There was a significant decrease in ICIQUI SF scores

after the third month, which remained lower until 12 months after the last application. However, after 18 and 24 months, there was no significant difference compared to baseline values. A total of 96 patients desired to repeat the procedure, and 9 patients remained satisfied after 24 months.

Blaganje et al.[21] published the only prospective randomized controlled trial (RCT) evaluating the effect of the vaginal laser on SUI. In all, 114 premenopausal women were classified into treatment group with Er:YAG laser in a single session and a control group with placebo (sham laser). The primary result was evaluated with the ICIQUI SF questionnaire. Of note, 21.4% of patients in the laser group were dry (ICIQUI SF score=0) after 3 months, when compared to only 3.6% of the control group. Age, BMI, and parity had no effect on the outcome, but severe SUI was a negative predictive factor.

González et al.[22] published the first long-term study of CO_2 vaginal laser in patients with SUI. A case series of 161 postmenopausal women with mild SUI without POP underwent four sessions of micro ablative CO_2 fractional laser, followed by annual protocol at 12, 24, and 36 months. There was a reduction in ICIQUI SF scores up to 36 months and also a significant improvement in the 1-h pad test.

Few studies have presented an objective evaluation of the improvement of urinary incontinence. Tien et al.[23] consecutively evaluated 28 women with urodynamic SUI. Of them, 39.3% (11/28) had an objective cure with a single session of Er:YAG laser and other 39.3% (11/28) showed improvement. The best results were for mild SUI. Other studies, such as that by Kuszka[24] suggest that laser treatment should be reserved for milder cases.

Another randomized, no-blinded study[25], of short follow-up, evaluated vaginal CO_2 laser in postmenopausal women with genitourinary syndrome. The effect on SUI was analyzed with the ICIQUI SF questionnaire. In all, 72 patients were classified into three groups: group 1 received three sessions of fractional vaginal CO_2 laser, group 2 received vaginal promestriene, and group 3 received vaginal lubricant. At 14 weeks, there was a reduction in ICIQUI SF scores only in the laser group.

A meta-analysis by Wang et al.[26] investigated the safety and efficacy of the vaginal laser (Er:YAG and CO_2) for the treatment of SUI. It included 16 studies involving 899 patients, excluding patients with POP, with only 1 prospective RCT[22]. There was an improvement in the ICIQUI SF score up to 6 months and in the 1-h pad test up to 12 months after treatment. Three sessions of treatment achieved a greater improvement compared to the results from 1 or 2 sessions, and no benefit was achieved with more than 3 sessions[19,22,24,27]. The data showed that the laser can be effective in the long term, but only two studies had follow-up time of up to 24 or 36 months[19,22]. Premenopausal women had a greater chance of sustained results in 2 years[20], and most studies suggested the need for an annual maintenance session[19,21,27,28]. Only six studies reported side effects, with vaginal discharge being the most frequent, in a small number of patients. There have been reports, even less frequent, of de novo urgency (2 patients), low-intensity pain (6 patients), vaginal itching (3 patients), vulvar discoloration (5 patients), and vaginal bleeding (2). None of the effects required medical intervention.

Regarding RF, the number and quality of studies that evaluate their applicability to SUI are even lower. However, the Brazilian study by Slongo et al. deserves to be highlighted[29]. It was a randomized clinical trial including 117 climacteric women who were classified into three groups: group 1 received three monthly sessions of vaginal micro ablative RF; group 2 received 12-weekly pelvic floor muscle training (PFMT) sessions; and group 3 received RF+PFMT simultaneously. Assessment at 30 days after treatment using ICIQUI SF demonstrated improvement in all three groups; however, it was significantly greater in the RF+PFMT group than in the RF and PFMT alone groups (p=0.002). Urinary loss in the 1-h pad test decreased by 7.72 g on average after treatments but with no differences between the three groups.

The authors concluded that vaginal EBD may have applicability for SUI, especially for mild cases, but randomized and controlled trials with a greater number of patients are necessary.

Vaginal energy-based devices in the treatment of genital prolapses

Few studies evaluate the effectiveness of vaginal EBD for the treatment of POP. Most works that evaluate the laser for other conditions exclude patients with POP. Athanasiou et al.[30] compared Er:YAG laser with observation in a randomized prospective study in 30 postmenopausal patients with cystocele or retocele stage ≥2, excluding patients with apical prolapse. In all, 15 patients received three monthly laser sessions, and 15 were observed. No patients in the laser group had objective cure of prolapse (considered stage ≤1); 2/15 had a decrease of 1 point in the prolapse stage, and 2/15 worsened. Pelvic Floor Distress Inventory Questionnaire short-form (PFDI-20) and Pelvic Floor Impact Questionnaire short-form (PFIQ-7) scores did not show statistically or clinically meaningful differences with laser treatment.

Another study evaluated three CO_2 laser sessions in women with postmenopausal genitourinary syndrome and POP stage ≤2, observing improvement in PFDI-20, Pelvic Organ Prolapse Distress Inventory, and Urinary Distress Inventory questionnaires,

which evaluated urinary, sexual, and functional symptoms related to prolapses. However, there was no control group, and there was no direct evaluation of the improvement of the prolapse[31].

Ogrinc[32] demonstrated significant improvement of cystocele grades 2 to 4 with 2 to 5 sessions of Er:YAG laser, with reduction of prolapse to grades 0 or 1 in 85% of cases in 12 months of follow-up. However, this is a single-arm, pilot, and observational study with 61 patients, using only the Baden-Walker scale for POP staging and without the use of validated questionnaires.

The authors concluded that there is no recommendation for EBD in the treatment of genital prolapses.

CONCLUSION

The lack of quality in studies regarding the use of vaginal laser or radiofrequency for urogynecology raises the question about whether these therapies provide long-term risk-free benefit. Based on the available scientific evidence, after this literature review, although the vaginal EBD seems promising for select indication at present, it should not be recommended for the treatment of GSM, urinary incontinence, recurrent urinary tract infection, and genital prolapses outside of a research context where patient is aware of efficacy and risks.

AUTHORS' CONTRIBUTIONS

ACM: Data curation, Resources, Writing – original draft. **LMPPJ:** Data curation, Resources, Writing – original draft. **LGMT:** Methodology, Supervision, Writing – review and editing. **CLZR:** Methodology, Supervision, Writing – review and editing.

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REVIEW ARTICLE

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Asthma and pregnancy

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INTRODUCTION

Asthma during pregnancy is a significant public health issue because it is one of the most potentially serious medical problems to complicate pregnancy. Studies have shown that having asthma during pregnancy puts both mother and baby at risk for complications[1].

Several studies indicate that pregnancies in patients with asthma are associated with an increased risk for adverse obstetric outcomes, such as preeclampsia, gestational diabetes mellitus, cesarean section rate, preterm birth (PB), low birth weight (LBW), and intrauterine growth restriction[2].

Different prevalence rates of asthma during pregnancy are described. In Canada, asthma affects only 0.43% of pregnant women, while this rate can reach 8.4% in the United States. In Brazil, although there are not many studies on the subject, it is estimated that the prevalence of asthma in this population is closer to American standards, ranging from 5 to 8%[3].

An observational study using secondary data from a birth cohort study in the metropolitan area of Aracaju applied a questionnaire to 4,757 women and identified that 299 had a diagnosis of asthma before or during pregnancy, corresponding to a prevalence of 6.3%[4].

ASTHMA DIAGNOSIS IN PREGNANT WOMEN

Asthma is characterized by respiratory symptoms such as shortness of breath, wheezing, cough, and chest tightness that are often worse at night and may vary over time and intensity, together with variable airflow obstruction. Symptoms can be triggered by viral infections, exposure to allergens, smoke, exercise, changes in weather, and irritants. Detailed anamnesis and physical examination support asthma diagnosis. Additionally, documented expiratory airflow limitation and excessive variability in lung function corroborate the diagnosis[5].

Symptoms of asthma are similar in pregnant and nonpregnant patients. However, if a pregnant woman complains of shortness of breath or chest tightness, the asthma diagnosis should be carefully made based only on her symptoms[6]. Frequently, pregnant women complain of shortness of breath or chest tightness (approximately two-thirds) during the pregnancy period[7].

During pregnancy, several physiological and structural changes can contribute to a sensation of dyspnea, such as the dilated uterus, elevated diaphragm, and increased anteroposterior and transverse diameter of the thorax. Such changes are compensated by a reduction of thoracic compliance, and as a result, the functional residual capacity (FRC) and total lung function (TLC) decrease by 20 and 5%, respectively[8].

Spirometry parameters such as forced expiratory volume in first second (FEV1), forced vital capacity (FVC), and FEV1/FVC do not change during pregnancy compared to reference values in the nonpregnancy period. Spirometry may help asthma diagnosis in pregnant women by detecting reversible airway obstruction and helping monitor response to treatment. Bronchial provocation tests are not advisable to be carried out in pregnant women to prevent maternal hypoxia and fetal distress.

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Phenotyping asthma allows optimizing disease management and treatment choice, as well as identifying pharmacological pathways that are more likely to respond positively to treatment. In asthmatic pregnant women, identifying the primary phenotype as allergic or non-allergic may be enough. Serological tests for allergen-specific immunoglobulin E (IgE) are preferred to skin and provocation tests, which should be postponed until after birth because of possible, though rare, anaphylactic reactions[9]. During the pregnancy period, Th2 upregulation and other immunity changes may lead to bronchial asthma exacerbation.

PREGNANCY EFFECTS ON ASTHMA

Data about the specific mechanisms by which pregnancy might affect asthma symptoms and control are still weak. Despite that, it is known that pregnancy can cause worsening of asthma in around 30–40% of women[5,10].

The worsening of asthma, with more frequent exacerbations and poor symptom control that occurs in some pregnancies, is thought to be caused by different factors, including mechanical or hormonal changes[5]. Pregnancy might also increase the susceptibility to viral respiratory infections[11]. On the contrary, sometimes, it might be challenging to differentiate the real worsening of asthma from pregnancy-induced dyspnea. The lung function evaluation, especially FEV1, not substantially affected during pregnancy, along with other associated asthma symptoms, might be a clue for making the difference between these situations[12].

EFFECTS OF ASTHMA ON PREGNANCY

The impact of asthma during pregnancy on maternal, fetal, neonatal, and childhood outcomes has been already demonstrated in several studies. Some data suggest that asthma severity and the intensity of treatment, rather than control or exacerbations, may be related to the increased risk of preeclampsia in asthmatic women[12,13].

Other studies indicate that pregnant women with asthma, in addition to preeclampsia, are at significantly increased risk of outcomes including emergency cesarean section, LBW and PB, and neonatal intensive care unit (NICU) admissions[13].

Uncontrolled asthma can lead to hypoxia and other physiological abnormalities that could decrease fetal blood oxygen and result in abnormal growth and development of the fetus. Acute asthma exacerbations or a recurrent loss of asthma control during pregnancy have been identified as the most significant events to affect fetal morbidity and mortality than inhaled corticosteroids (ICS) use[13,14].

A significantly increased risk of LBW infants was noted in subjects experiencing asthma exacerbation during pregnancy (RR 3.02) and using oral corticosteroids (OC) (RR 1.41) [12]. On the contrary, controlled asthma during pregnancy appears to protect the fetus from adverse outcomes[13,15,16].

ASTHMA SEVERITY AND CONTROL

Asthma control assessment should be part of the anamnesis of all pregnant women diagnosed with asthma. Asthma control can be assessed using simple and easy-to-apply questionnaires, the main ones being Global Initiative for Asthma (GINA), Asthma Control Questionnaire (ACQ-7), and Asthma Control Test (ACT) (Table 1)[5,17].

Medication adherence and inhalation technique should always be evaluated[17]. In 2005, data from Australian pregnant women with asthma demonstrated that in their initial visit with an asthma nurse educator at 20 weeks of pregnancy, women with asthma had poor adherence, with 40% self-reported nonadherence with ICS, insufficient knowledge about asthma medications (42% were inadequate), and poor device technique (16% had inadequate inhaler technique)[18].

In addition, common comorbidities such as rhinitis, gastro-esophageal reflux, overweight/obesity, and smoking which can contribute to worsening asthma, should be identified and managed[17,19].

ASTHMA TRIGGERS AND COMORBIDITIES DURING PREGNANCY

Avoiding exacerbation triggers and proper comorbidities management are critical elements of successful asthma management and control.

Pregnant patients' frequency and severity of respiratory viral infections are higher for those with asthma[7]. Among all pregnant women, influenza is associated with increased morbidity and mortality, especially in the second trimester[7]. During the H1N1 pandemic season, asthma was the most common comorbidity in 23% of cases reported in pregnant women who developed influenza A infection, and 44% of pregnant women who died of H1N1 influenza had asthma[7].

Other triggers are environmental (e.g., dust and pollutants) and occupational exposure. Aspirin, other nonsteroidal anti-inflammatory drugs, and beta-blockers (in oral or ophthalmic formulations) may cause bronchospasm[17].

Pregnancy is a moment of unique psychological variability due to neuroendocrinal changes, excessive maternal weight gain,

Table 1. Definition of asthma control by different instruments.

Instrument/items	Controlled asthma	Partially controled asthma	Uncontrolled asthma
GINA			
Daytime asthma symptoms more than twice/week?	None	1–2 items	3–4 items
Any night waking due to asthma?			
SABA reliever for symptoms more than twice/week?			
Any activity limitation due to asthma?			
ACQ-7			
Number of nocturnal awakenings	≤0.75	0.75 to <1.5	>1.5
Intensity of symptons			
Limitation of activities due to asthma			
Intensity of dyspnea			
Wheezing (how long)			
Rescue medication			
Pre-bronchodilator FEV1			
ACT			
Limitation of activities due to asthma	≥20	15–19	≤15
Dyspnea			
Nocturnal awakenings due to asthma			
Rescue medication			
Self-assessment of asthma control			

GINA: Global Initiative for Asthma; ACQ-7: 7-item Asthma Control Questionnaire – 0-7 points per item; ACT: asthma control test – 0-5 points per item. The ACQ can be used without spirometry; in this case, it is referred to as ACQ-6. If used without spirometry or rescue medication, it is referred to as ACQ-5. Reference: Pizzichini et al.[17].

and additional stress regarding fetus safety[12]. Predictably, anxiety and depression potentially impact patient-related outcomes in 6–15% of pregnant asthmatics, including an increased risk of unplanned caesarian delivery and poor asthma control[20].

Obesity and gastroesophageal reflux are prevalent comorbidities in pregnant asthmatics. Maternal obesity during pregnancy represents a unique phenotype and endotype associated with increased airway obstruction, ICS resistance, upregulation of inflammatory pathways, frequent exacerbations, and increased incidence of asthma in children[21]. Exercise and combined dietary interventions significantly improve asthma control and avoid excessive maternal weight gain throughout pregnancy.

GESTATIONAL COMPLICATIONS IN PREGNANT WOMEN WITH ASTHMA

Asthma is strongly associated with preeclampsia, placental abruption, placenta previa, and obstetric hemorrhage. Decades of research have linked asthma to increased rates of cesarean delivery[7]. In addition to obstetric complications, asthma is associated with multiple comorbid maternal conditions[7]. Pediatric complications associated with poorly controlled maternal asthma include LBW and small for gestational age (SGA), with the risk of LBW increasing with asthma severity[7,16]. Table 2 shows the main gestational complications in pregnant women with asthma and fetus[7].

TAILORED ASTHMA TREATMENT IN THE PREGNANCY

Asthma education is critical to building partnership care during pregnancy. The obstetric population often needs better asthma self-management skills and knowledge, regardless of disease severity[18]. Parents should be aware that poor asthma control in pregnancy increases the risk of maternal complications and poor neonatal outcomes[13,22].

Active self-management education plays a key role in obstetric care by improving treatment adherence, asthma control, and inhaler technique and developing a written plan for unstable asthma.

Maternal smoking during pregnancy significantly increases the risk of suboptimal fetal growth and PB, enhances the risk of asthma exacerbations, impairs the effectiveness of ICS, and increases mortality[23,24]. Smoking cessation programs should

Table 2. Main gestational complications in pregnant women with asthma.

Maternal and obstetric complication	Fetal complications
Miscarriage	Low weight at birth
Gestational diabetes	Restricted intrauterine growth
Premature birth	Congenital malformations
Preeclampsia	Increase in perinatal mortality
Gestational hypertension	Fetal anomalies
Pre and pos partum hemorrhage	
Cesarian delivery	
Pulmonary embolism	
Premature rupture of membrane	

Reference: Bonham et al.[7].

ideally involve a multidisciplinary approach with periodic brief counseling interventions and cognitive behavioral therapy. Data about the safety of pharmacological approaches to smoking cessation in pregnancy are limited[25].

PHARMACOLOGICAL TREATMENT

Pharmacological treatment in asthmatics during pregnancy aims to achieve asthma control and prevent future risks, such as exacerbations, accelerated lung function decline, and adverse effects of treatment[17]. Although drug safety for pregnant women and the fetus is a general concern during pregnancy, the use of ICS, short-acting B2-agonists (SABA), short-acting anticholinergic (SAMA), long-acting B2-agonist bronchodilators (LABA), montelukast, and theophylline is not associated with a significant increase in fetal abnormalities[5,26].

As bronchial inflammation is a critical pathogenic mechanism in asthma, the use of ICS is the mainstay of pharmacological asthma treatment, as monotherapy or in association with LABA[17]. According to GINA, ICS withdrawal is not recommended during pregnancy[5].

Even though LABA monotherapy should be avoided due to increased asthma-related mortality, the combined therapy of ICS/LABA is the preferred option as an add-on therapy for patients who failed to achieve control with low/moderate doses of ICS. There was a recent paradigm shift in the management of mild asthma with the recommendation of a fixed-dose ICS/formoterol as maintenance and reliever therapy[5].

Add-on therapy with tiotropium provides functional gain and reduces exacerbations in uncontrolled asthmatics under moderate-high doses of ICS/LABA[5,17]. The small number of pregnant women with asthma in randomized clinical trials difficult to conclude on the efficacy and safety of long-acting muscarinic antagonist (LAMA) in this population.

Leukotriene receptor antagonists (LTRA) are recommended as an add-on medication to other maintenance therapies in pregnant women[5].

As in the general population, severe asthma in pregnancy is defined by persistent symptoms and/or exacerbations despite proper inhaler technique and good treatment adherence in patients treated with a medium-high dosage of ICS combined with other classes of asthma maintenance therapy[5,27]. Although a study has suggested a relationship between a high dose of ICS and fetal malformations, this should be explained by asthma severity based on the relationships between exacerbations and congenital malformations demonstrated by the same group[28].

Some patients with severe asthma may require regular OC use to achieve adequate asthma control. OC use has been associated with an increased risk of PB and LBW infants in exposed women. An increased risk of orofacial clefts was reported in a meta-analysis of case-control studies, but this increased risk was not confirmed in a large cohort study[15].

Recently, biological agents have been used in patients with severe refractory eosinophilic allergic or non-allergic asthma, but data on the use of these biologics in pregnancy are sparse[2,29]. Omalizumab (anti-IgE therapy) is one of the options for moderate-severe allergic asthma. It is currently the only asthma biological with limited available human safety data from the EXPECT pregnancy registry that reported no increased risk of congenital anomalies, stillbirths, premature birth, and SGA[30].

EXACERBATION MANAGEMENT

Studies showed that nearly half of the pregnant asthmatic women experience exacerbations, and one-fourth will experience severe exacerbations, necessitating emergency department (ED) visits or hospitalizations[29,31].

Early and aggressive interventions are necessary to treat severe acute asthma exacerbations in pregnant women to minimize maternal and fetal hypoxia risk[32].

A short story and focused physical examination should be performed rapidly with particular attention to vital signs, maternal oxygen saturation, lung function, and the work of breathing, as outlined in Table 3[5]. If feasible, fetal monitoring should be performed to evaluate fetal distress[5,33].

Recommended primary pharmacological treatment is similar for both pregnant and general adult populations and includes immediate use of inhaled ß2-agonists, inhaled ipratropium, and timely (within 30–60 min) administration of systemic corticosteroids (prednisone 60 mg orally daily up to 5 days)

Table 3. Initial severity assessment of acute asthma in pregnancy.

Findings	Mild/moderate	Severe
Speaking in	Sentences or phrases	Words or unresponsive
Respiratory rate	18–19/min	>30/min
Heart rate	100–120 beats/min	>120 beats/min
Peak flow/FEV1 (%predicted)	50–75%	<50%
Pulse oximetry (room air)	90–95%	<90%

Reference: GINA[5].

or 2 mg/kg methylprednisolone IV in the ED. Oxygen supplementation is recommended in hypoxemic patients to maintain arterial oxygen saturation between 94 and 98%[29].

Status asthmaticus gravidus is a life-threatening asthma syndrome that may require additional therapy (i.e., magnesium sulfate and Heliox), most of which have limited efficacy data in pregnant patients. Intubation and mechanical ventilation are indicated in patients with refractory respiratory failure[29].

SAFETY OF ASTHMA MEDICATIONS DURING PREGNANCY

Despite the lack of evidence for the adverse effects of asthma treatment in pregnancy, many women and doctors remain concerned[5]. Some published data summarize the evidence for human pregnancy safety data for asthma medications[12,26,34,35]. There is evidence for ICS safety during pregnancy (Evidence A) [26,36]. Budesonide is considered the first-line IC to initiate therapy because it is the most IC studied in pregnancy and shows no increased risk of congenital anomalies or stillbirths. However, another IC may be continued if asthma is controlled[12,26].

SABAs are recommended as safe in pregnancy, with salbutamol being the most studied as a rescue medication. There is evidence for **LABA** safety during pregnancy (Evidence A)[26,36], although **LABAs** are only recommended in fixed-dose combination with ICSs to moderate-severe asthma. There is no preference among available LABAs (i.e., formoterol or salmeterol). No data are available for using ultra LABAs (i.e., indacaterol and vilanterol) during pregnancy[26].

The risk of congenital anomalies of ICS/LABA combination versus high-dose ICS alone in the first trimester was similar in moderate-severe asthma, suggesting safety in pregnancy[37]. On the contrary, there is limited data on ICS/formoterol combination safety as a maintenance and reliever therapy[26].

SAMA associated with **SABA** has been recommended for managing severe asthma exacerbation not responding to SABA monotherapy. No well-controlled studies of tiotropium [LAMA] have been performed in pregnant women[12,26].

The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy Trial (EXPERT)[30] showed similar rates of major congenital anomalies in both groups (omalizumab vs. control). Therefore, treatment may be continued during pregnancy if the benefits outweigh the risks; however, it is not currently recommended to start omalizumab in pregnant women[26,30].

There are no available prospective data regarding the safety of other monoclonal antibodies (i.e., mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab) for severe asthma during pregnancy. Animal studies found no teratogenic effects. Pregnancy registries https://mothertobaby.org/ongoing-study/nucalamepolizumab/, https://mothertobaby.org/ongoingstudy/fasenra/, and https://mothertobaby.org/ongoing-study/dupixent/ are ongoing for all of them, except for tezepelumab[26,38].

For the patient who requires OC for asthma control, its benefit in preventing severe exacerbations outweighs the potential risk of congenital abnormalities[26,34,35].

MANAGEMENT DURING LABOR AND DELIVERY

There are no published studies specifically addressing intrapartum management in women with respiratory disease and whether there are any clinical benefits of cesarean section *versus* vaginal birth[35]. Although there is a higher planned cesarean rate among moderate-severe asthmatics compared with mild asthma patients, labor induction is rarely indicated due to asthma[22,39].

Controller asthma medications should be maintained, as well as a reliever, if needed, during labor and delivery[5,35]. Asthma exacerbations are uncommon; however, bronchoconstriction may be induced by hyperventilation during labor and should be managed with SABA[5]. In asthmatics receiving OC, there is a potential risk of maternal hypothalamic-pituitary-adrenal axis suppression and a dose of hydrocortisone intravenously during active labor, or cesarean section should be used[35,40].

Pre-delivery evaluation and multidisciplinary planning are the cornerstones in managing women with respiratory disease[35],

decreasing severe respiratory complications[41], probably to close collaboration between obstetricians and respiratory physicians regarding pregnant asthmatic women[22].

Some obstetric considerations must be made. The use of prostaglandin E2 for labor induction or oxytocin (second and third labor stages) has not been associated with worsening lung function or asthma exacerbation[35]. Nevertheless, ergotamine may cause bronchospasm, particularly in association with general anesthesia. Oxytocin is the uterotonic choice for the active third stage of labor[35,40]. Epidural anesthesia is preferred during delivery because it reduces oxygen consumption and minute ventilation. In an emergency cesarean section, this can be extended into proper anesthesia, avoiding the need for airway management. Ketamine and halogenated anesthetics, with a bronchodilator effect, are preferred if general anesthesia is necessary[40].

Post-partum hemorrhage may be increased in women with asthma[35]. Medications used for its management may affect the respiratory system reinforcing the need for collaboration between the obstetric and respiratory teams to optimize management[35].

CONCLUSION

Asthma during pregnancy is a significant public health issue. Studies have shown that having asthma during pregnancy puts both mother and baby at risk for complications. Although there is concern about the use of asthma medications during pregnancy, disease control and exacerbations prevention outweigh the potential risk. Close collaboration between obstetricians and respiratory physicians is essential to improve clinical outcomes in asthmatic women during pregnancy.

AUTHORS' CONTRIBUTIONS

RMCP: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **JEDC:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **LSBC:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **ASM:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **DCB:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **GFG:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **RGF:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **TPB:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Acupuncture for pregnancy-related pain in the lower back and posterior pelvic girdle

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INTRODUCTION

Low back pain and pelvic pain are common conditions during pregnancy, and they can persist even after delivery[1]. The etiology of this phenomenon is complex, likely involving mechanical, circulatory, hormonal, and psychosocial factors[2]. Although there are no organic or specific diseases in most cases, the effects of pain can be considerable, negatively affecting sleep quality, physical condition, work performance, social life, and leisure activities, as well as leading to economic losses due to absenteeism[1,3].

The experience of pain during pregnancy is widespread, and its treatment poses significant challenges[4]. Some pain-relieving medications can pose dangers to both the fetus and the mother, while inadequate pain management can lead to severe maternal consequences such as depression and high blood pressure[4].

Due to limitations concerning pain management, acupuncture becomes an important treatment[5]. Acupuncture has been increasingly integrated into Western medicine as a complementary therapy for various conditions, especially pain, and has been shown to have analgesic, anti-inflammatory, and neuromodulatory effects[6]. Several studies have suggested that acupuncture can relieve pregnancy-related pain in the lower back and posterior pelvic girdle by improving blood circulation, relaxing muscles, reducing inflammation, and regulating hormones[7–9].

OBJECTIVE

The main objective of this review article was to update scientific knowledge regarding the use of acupuncture for back pain in pregnancy.

METHODS

A literature review was performed in the following scientific databases: Medline/PubMed, EMBASE, SciELO, LILACS, and Cochrane. The following terms were used: acupuncture AND low back pain in pregnancy, acupuncture AND pelvic pain, acupuncture AND pregnancy pain.

This review included randomized controlled trials (RCT) or quasi-RCT studies with patients who received only acupuncture (defined as the insertion of needles into acupoints, including traditional acupuncture, Western, segmental, and trigger point), as well as comparative studies with patients in other groups who received conservative treatment with sham, analgesia, and kinesiotherapy. Included studies had at least one of these primary outcomes: pain or functionality. Studies of laser acupuncture and auricular acupuncture without body acupuncture were excluded.

The articles were selected and evaluated independently by two authors (MYBPP and AH). The authors met to reach a consensus on the inclusion and exclusion of articles in the review.

Only human clinical studies were included. Articles in Portuguese and English were included. The search was limited to articles published between 2000 and 2022. Repeated articles in databases, animal experimentation studies, and case reports were excluded.

RESULTS

A total of 85 articles were initially identified through electronic search. After review of the title and abstract, 23 full-text papers were reviewed, with 8 articles fulfilling the inclusion criteria. Duplicate articles were manually removed. The included studies comprised 1,087 patients. All articles

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were published in English. A flowchart of the study selection process is shown in Figure 1.

Tables 1 and 2 summarize the characteristics and main findings of the eight included trials.

Acupuncture versus waiting lists or standard care

Bishop et al. compared acupuncture with standard care (SC) for pelvic girdle and low back pain during pregnancy, enrolling 386 women to receive either SC or SC plus five acupuncture sessions. Acupuncture was more effective for reducing pain and improving functional status at 4 weeks, but not at 12 weeks. Acupuncture was also more cost-effective when accounting for employer costs[10].

Kvorning et al. assessed the pain-relieving effect of acupuncture in the last trimester of pregnancy. They involved 72 women who received either standard treatment (physiotherapy, exercises, and/or analgesics) or SC plus acupuncture. The acupuncture group had a 60% reduction in pain intensity and a 44% reduction in days with pain per week, compared to 14 and 9%, respectively, in the control group ($p<0.001$)[8].

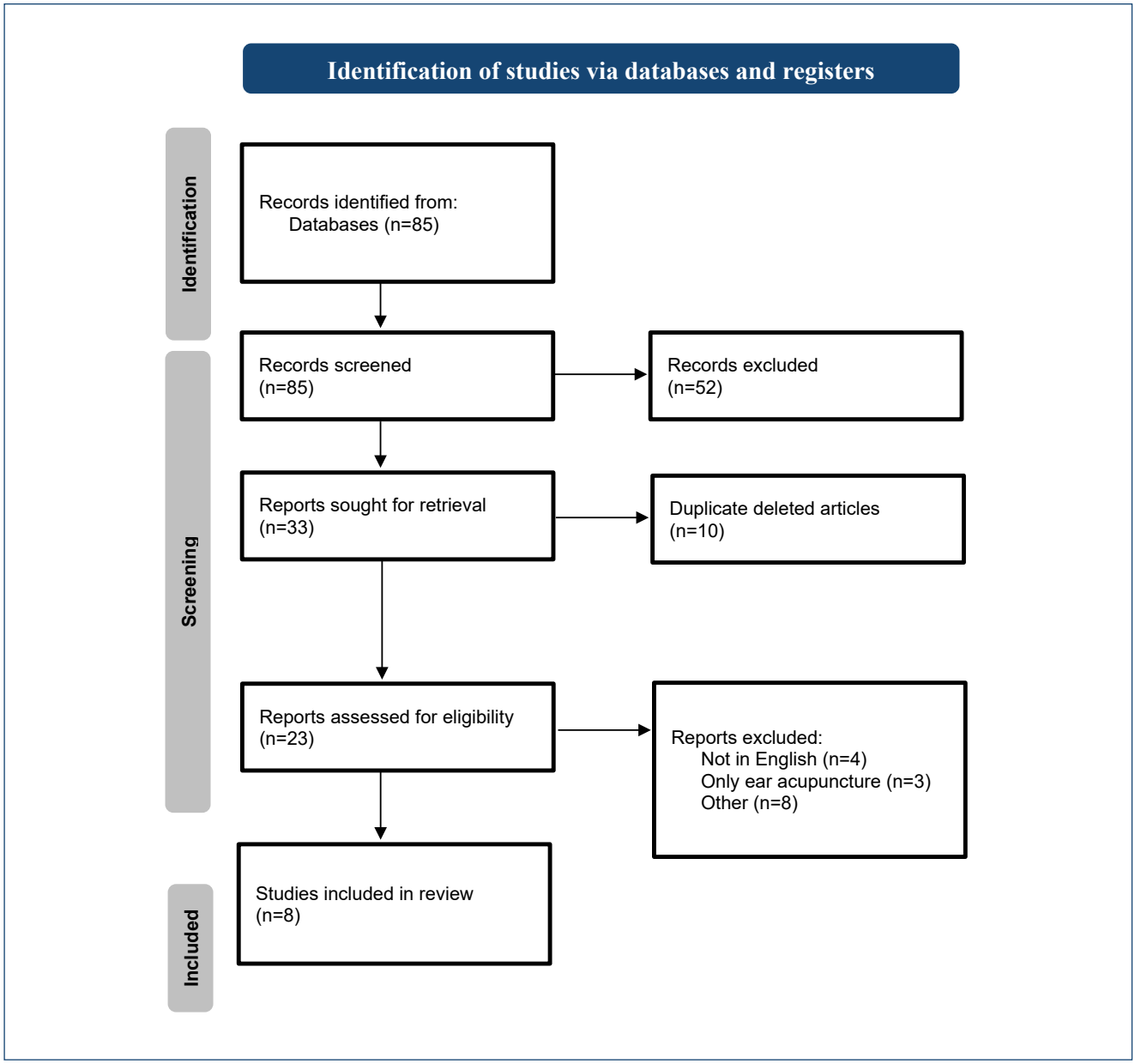

Figure 1. Flowchart of the study.

Table 1. Randomized controlled trials evaluating acupuncture for pregnancy-related low back pain.

Authors	Study	Participants	Outcomes	Interventions	Results
Wedenberg et al.[9]	RCT	n=60, pregnant women with a gestational age of no more than 32 weeks	VAS, disability (DRI)	Group 1: 10 acupuncture sessions, 3×/week, 30 min/day Group 2: 10 physiotherapy sessions, 1–2×/week, 50 min/day	Acupuncture: ↓ pain and disability versus physiotherapy
Kvorning et al.[8]	RCT	n=72, n=37 acupuncture, n=35 control group	Pain (VAS), assessments of maximal/minimal pain, daily activities, and quality of life	Acupuncture: average of 6 sessions (range 3–11)	Acupuncture: ↓ patient-reported outcomes (pain, function, quality of life). No serious adverse effects
Elden et al.[14]	RCT	n=386, n=125 acupuncture, n=130 SC, n=131 SC+exercises	Pain (VAS), severity of pelvic girdle pain before/after treatment	Acupuncture: 12 sessions, 2×/week over 6 weeks. SC: general information, advice SC+exercises: stabilizing exercises (6 sessions of 1 h for 6 weeks)	Acupuncture: ↓ pain in evening versus SC+exercise, ↓ pain in morning and evening versus SC. Greatest pain reduction versus other groups
Lund et al.[12]	RCT	n=70, n=35 superficial acupuncture stimulation versus n=35 deep acupuncture	Pain (VAS), pain, emotional reactions, and loss of energy (Nottinghan Health Profile Questionnaire)	Acupuncture: 10 sessions 2×/week for 5 weeks, 30 min/day.	Acupuncture: ↓ patient-reported outcomes (pain, function, and quality of life)
Elden et al.[11]	RCT	n=115, n=58 acupuncture+SC versus n=57 nonpenetrating sham acupuncture+SC	Pain (VAS), frequency of sick level, functional status, and quality of life	Acupuncture: 12 sessions, 2×/week for 4 weeks, 1×/week for 4 weeks, 30 min/day Sham: same protocol	Acupuncture: no significant effect on pain or degree of sick leave versus chan. Some improvement in daily activities
Guerreiro Silva[7]	Quasi-RCT	n=61, n=27 acupuncture, n=34 control, women with 15–30 weeks of pregnancy	NRS, disability (general activities, work, and walk)	Group 1: 8–12 sessions, 1–2×/week over 8 weeks Group 2: SC with paracetamol+hyoscine	Acupuncture: ↓ NRS, ↓ disability score, ↓ use of paracetamol
Bishop et al.[10]	Pilot RCT	n=124, 42 acupuncture and SC, 41 nonpenetrating acupuncture+SC, 41 SC	Pain (VAS), Functionality+Global Rating of Change	True acupuncture group: 6–8 sessions over 6 weeks, 20–30 min/day Nonpenetrating needles: 6–8 sessions over 6 weeks SC: self-management booklet	Acupuncture: ↓ patient-reported outcomes (pain, function, and quality of life)
Nicolian et al.[13]	RCT	n=199, n=96 acupuncture, n=103 SC	Efficacy (NRS), disability score, cost-effectiveness	Group 1: 5 acupuncture sessions, 2×/week (1st week, 1×/week (following weeks) Group 2: (pregnancy belt, lifestyle recommendations, and exercises)	Acupuncture: ↓ NRS, ↓ disability score, ↓ average total costs compared to SC

Guerreiro Silva et al. examined the effects of acupuncture on low back and pelvic pain during pregnancy in real-life settings. They enrolled 61 pregnant women and quasi-randomly allocated them to either acupuncture or standard treatment. The acupuncture group had a 54% decrease in pain intensity score and a 65% decrease in analgesics used per week, compared to 12 and 16%, respectively, in the control group[7].

Acupuncture versus sham acupuncture

Elden et al. evaluated superficial versus deep acupuncture using nonpenetrating sham acupuncture. The study found no significant difference between treatments regarding the patients' pain during movement and the degree of sickness leave. Acupuncture had some degree of improvement in performing daily activities according to "daily activity limitation[11]."

Lund et al. compared superficial versus deep acupuncture. The superficial group had similar changes in pain intensity, while the deep group had more significant changes. The authors concluded that there was no clear difference between the groups[12].

Acupuncture cost-effectiveness

Nicolian et al. found that acupuncture was cost-effective when compared to SC. It was both cheaper (€1512 versus €1452 per

Table 2. Details on acupuncture point selection and type of stimulation for the included studies.

Authors	Type of stimulation	Needles	Points
Wedenberg et al.[9]	Manual, stimulation 15 min after insertion	2–10 needles, ear-acupuncture+body-acupuncture	Fossa triangularis for ear-acupuncture. BL 26, BL 27, BL 28, BL 29, BL 30, BL 60, CW 20, local points
Kvorning et al.[8]	Manual, stimulated	Periosteal stimulation used when possible, associated with tender points, up to 8 points	R3, GV 20, local tender points (initial), BL 60, SI 3, BL 22-26+tender points
Elden et al.[14]	Manual, stimulation to elicit De Qi every 10 min	Segmental and extra-segmental points	GV 20, LI 4, BL 26, BL 32, BL 33, BL 54, KI 11, BL 60, EX 21, GB 30, SP 12, ST 36
Lund et al.[12]	Manual, stimulation to elicit De Qi 5× during the session	Deep acupuncture: inserted intramuscularly Superficial acupuncture: inserted subcutaneously, minimal manipulation	Local: BL 27, BL 28, BL 29, BL 31, BL 32, BL 54, KI 11, CV 3 Distal: SP 6, LR 2, LI 4
Elden et al.[11]	Manual, stimulated every 10 min	Segmental and extra-segmental points, on tender acupuncture points and/or trigger points. Point selection: clinical experience	Local: EX 21, BL 26, BL 28, BL 32, BL 33, GB 30, BL 54 Distal: KI 11, ST 36, BL 60, GV 20, LI 4
Guerreiro Silva et al.[7]	Manual stimulation to elicit De Qi.	Average of 12 needles. TCM point-based selection	K 13, S 13, BL 62, BL 40, TE 5, GB 30, GB 41 and Huatuojiaji points
Bishop et al.[10]	Manual stimulation to elicit De Qi.	6–10 bilateral points (between 12 and 20 points total). Point selection: Western acupuncture+trigger points	Local points: BL 23-28, BL 54, BL 31-33, GB 30, HJJ L4, HJJ L5. Distal points: GB 34, ST 36, LR 3, LI 4, BL 60, BL 62
Nicolian et al.[13]	Manual stimulation to elicit De Qi.	Points needled bilaterally. Point selection: pain location and TCM	BL 40, 40V, Ah Shi points

patient) and more effective (3.9 more days with visual analog scale [VAS] ≤4 per patient) over 12 weeks[13].

Adverse effects

The selected articles did not report significant adverse effects, such as pneumothorax, neurological, dermatological, or allergic effects. Adverse effects found were minimal local pain, with VAS<3, not requiring interruption of therapy application, and also local erythema.

DISCUSSION

The outcomes of most studies favored acupuncture for pain management. Patients given acupuncture showed significant improvement in pain intensity. The above findings are further validated by the significantly lower use of analgesic drugs and nonacupuncture analgesic techniques in patients given acupuncture compared to control patients[7].

There is significant heterogeneity among acupuncture trials regarding study design, intervention protocol, control group, outcome measures, patient characteristics, and quality assessment tools[13]. Studies included in this review followed different acupuncture point selections, with most based on traditional Chinese medicine (TCM) diagnosis, with local and distal points used[10]. Some protocols followed a standardized point selection, while others allowed extra points based on patients' complaints[8]. This can affect the comparability and consistency of the results.

Within these limitations, our review's main findings are consistent with a recent systematic review and meta-analysis, which also included ear acupuncture[15]. Our results are also consistent with the hypothesis that acupuncture is an effective and safe treatment for back pain in pregnancy and that it is a safe procedure with only a few and minor reported adverse events. Another systematic review found that acupuncture as an adjuvant to SC was more effective than SC alone and physiotherapy in reducing mixed pelvic/back pain. Moreover, women experienced greater pain relief with acupuncture plus standard therapy than with standard treatment alone or stabilizing exercises plus standard treatment[16].

Safety and side effects

While acupuncture is generally considered safe, there are potential risks associated with the treatment. Common, less serious adverse effects can include minor bruising or bleeding, temporary soreness at the needle site, and nausea or dizziness[5]. Serious adverse effects can include infection, punctured organs, and nerve injury, which were not found in any of the reviews included in this study.

Limitations

Blinding of participants, practitioners, and assessors is a significant challenge in acupuncture clinical trials, as the intervention is not easily concealed. Finding an appropriate control group is difficult in acupuncture studies, as sham acupuncture is often

used as a control. Long-term follow-up can be challenging, as participants may become discouraged or lose interest over time. The wide range of patient responses to the treatment and the difficulty in standardizing acupuncture treatments can lead to variability in results from different studies. These issues can make conducting clinical trials in acupuncture difficult, and the results of such studies can be unreliable.

CONCLUSION

Acupuncture is a promising treatment for low back and pelvic pain during pregnancy. The current evidence supports the effectiveness and safety of acupuncture for these conditions, but more high-quality, standardized trials are needed to confirm and strengthen its evidence base. Acupuncture may offer a valuable option for pregnant women who suffer from low back and pelvic pain and who seek a safe and effective non-pharmacological intervention.

AUTHORS' CONTRIBUTIONS

MYBP: Investigation, Writing – original draft. **AH:** Investigation, Writing – original draft. **LC:** Methodology. **MM:** Methodology. **LCSS:** Writing – review & editing. **AWWT:** Supervision.

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REVIEW ARTICLE

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Anesthesia and women's peculiarities

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INTRODUCTION

An important issue is the establishment of concepts when the topic of discussion involves sex and gender. So, sex is a term used for the biological determinant (chromosomal), and gender is a social construct with a broad spectrum (cis, trans, etc.).

Both gender- and sex-related peculiarities may influence many aspects of anesthetic planning, although the different concepts of sex and gender are precious, as well as pregnancy status; gender and pregnancy are beyond the scope of this article.

The physiological and pharmacological aspects are extensive and, by themselves, deserve special attention. From the preoperative evaluation to the postoperative management, the anesthesiologists must know these differences and how they may influence the outcome.

However, only the main factors influencing anesthetic management and its results will be highlighted.

PHYSIOLOGICAL AND PHARMACOLOGICAL DIFFERENCES

Some physiological and pharmacological women's singularities may interfere with anesthesia management[1], and many of them result from direct or indirect actions of female sex hormones. Differences in the metabolism of drugs exist at various levels, possibly due to the genomic and nongenomic action of sex hormones. A detailed understanding of the effect of sex and its related conditions on the metabolism of drug molecules will help clinicians determine the effective therapeutic doses of drugs depending on the patient's condition and disease. As if that were not enough, female hormones vary according to ovulation. For example, vasodilatation occurs when estrogen production is high due to nitric oxide liberation[2]. Younger women, compared with men, have better diastolic function and a larger left ventricular ejection fraction, but the differences are not favorable regarding the pulmonary system. For example, women's ventilatory responses to CO_2, hypoxia, and the apneic threshold are lower[3]. No measurable effect on renal blood flow, renal vascular resistance, or filtration fraction was detected with estrogen variation; other differences include body mass index, waist circumference, body fat composition, which are usually 5–10% higher, and decreased total body water (15–20%)[4]. All these factors have implications for variances in the rate and extent of drug distribution and variations in plasma binding protein levels that can alter drug-free fractions. The free fraction is the active form of the drug.

Fluctuations in the menstrual cycle modify the volume of distribution, but few studies have examined the effect of this variability on drug volume of distribution. Nevertheless, body fat composition influences the volume of distribution of water-soluble drugs, like muscle relaxants, and consequently, less drug dosage is required for the same effect when compared to men. For lipid-soluble drugs, the opposite effect occurs and is observed with propofol and benzodiazepines.

Drug metabolism plays the most significant role in pharmacokinetic differences between the sexes[5]. The hepatic enzyme activity is crucial for the drug's hepatic clearance, and hepatic enzymes play a significant role in determining women's pharmacokinetic variability. Finnstrom et al. have demonstrated essential sex differences in some key cytochrome P450 enzymes[6], and Craft pointed to more significant analgesic effects with opioid agonists in females than in males[7].

Huhn et al. suggested that they may also influence opioid pharmacokinetics, which may produce systematic sex-based differences in opioid abuse liability[8] by modifying opioid receptor binding and density in the hypothalamus; these effects could also change opioid receptor availability, impacting how opioids are subjectively experienced. These findings may explain why men and women respond differently to pain syndrome and probably to postoperative nausea and vomiting (PONV) predisposition.

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PREOPERATIVE EVALUATION

A preoperative evaluation is essential for safe anesthesia management and should be performed before surgeries and procedures. The pre-anesthetic evaluation has several objectives: evaluating the patient's physical state, establishing anesthetic management based on exchanging information between the anesthesiologist and the patient, and obtaining the "Free and Informed Consent Form," as recommended by CFM Resolution 2174/2017[9]. Usually, anesthesiologists do not have many opportunities to meet the same patient, so the anesthesiologist should use this valuable preoperative meeting to establish mutual trust through empathic listening.

However, sex differences can interfere with disease prevalence, treatment outcomes, morbidity, and mortality[10]. As well as worldwide, cardiovascular diseases represent women's leading cause of death in Brazil[11,12], and diabetes, hypertension, obesity, sedentary life, etc. are the most common risk factors observed in clinical practice. However, oral contraceptive use is a sex-specific risk factor. Although endogenous estrogens usually protect women against cardiovascular disease, women have more microvascular dysfunction than men's large coronary artery obstruction, which may explain why they are often underdiagnosed[13]. In addition, cardiologists may not even evaluate symptoms of myocardial Ischemia as early in women as in men, underestimating risk factors, so anesthesiologists should investigate more accurately during the preoperative interview about previous suggestive symptoms. Ohkuma et al.[14]. showed by a meta-analysis that both diabetes types (1 and 2) were stronger risk factors for heart failure in women than in men[15]; consequently, the importance of a systematic sex-specific approach is necessary. In addition, women have a higher risk of venous thromboembolism during fertile years, with oral contraceptive use increasing it fourfold. Chronic obstructive pulmonary disease and asthma are more frequent in women[16].

PONV following surgery is three times more frequent in women than in men, although the rate decreases after menopause remains higher in women than in men. The incidence is higher in the follicular phase than in the luteal phase and highest during menstruation. Therefore, it may be relevant to consider scheduling elective surgery during the luteal phase of a patient's menstrual cycle when the patient has a previous history of PONV.

The female has been identified as one of the risk factors closely linked to specific sex differences and may be associated with a lower level of satisfaction. Therefore, successful preoperative anesthesia evaluation and education may improve such adverse outcomes. Nowadays, telehealth is an additional tool to attend to these objectives.

ANESTHESIA MANAGEMENT

The physiological and pharmacological peculiarities of women must be considered during the clinical anesthesia scenario. Some of the most important are the responses to hypnotics, especially the need for higher infusion rates to achieve the same anesthesia depth; this effect is observed with common lipid-soluble drugs, such as propofol and midazolam. In addition, anesthesia recovery in women is faster than in men[17].

Another drug class used in the anesthesia setting that is influenced by sex is the neuro-muscular blocking agents; their water solubility determines a lower distribution volume in women, so fewer drug doses are needed than in men for the same muscle relaxant effect[18].

Another relevant difference is the response to the analgesic and respiratory depressant effects of opioids; women are more sensitive than men[19], and the total opioid dose is approximately 30% lower in women than in men[20].

Concerning inhalational anesthetics, the sexes have no clinically relevant differences[21].

The relevance of these aspects, possible comorbidities, and the interventions to which they will be submitted are essential. So, the anesthesia choices must attend to the identifiable singularities on a case-by-case basis. In a general assessment, significant pharmacological differences are observed in the usual anesthetics most commonly utilized in care practice, such as propofol, opioids, and neuromuscular blockers. However, it should be considered that most of these agents are used by continuous infusion, including target-controlled devices. This practice allows accurate monitoring of the effects and necessary adjustments.

POSTOPERATIVE CONSIDERATIONS

The prophylaxis and treatment of postoperative pain and avoiding PONV are highly relevant and equally important goals of anesthesia, which are the subjects of recent consensus recommendations[22].

Pavlin et al., in a prospective study, examined what factors affected discharge time, including sex, and observed that, at outpatient procedures, the discharge time in women was fastest after propofol induction/maintenance and can be explained by a trend toward fewer emetic symptoms[23]. In the same way, Myles et al., comparing the overall quality of recovery from anesthesia between men (n=241) and women (n=222), observed that women emerged significantly more quickly than men, although women had a slower return to baseline health status[24].

Sex as a risk factor for chronic postsurgical pain (CPSP) was the object of a systematic review in the adult population

after any elective nonobstetric surgery[25] and confirmed a higher risk of developing CPSP in the female. Thurston et al., in a systematic review of literature considering differences in postoperative pain and postoperative pain management, racialized minorities, female sex, and individuals of lower socioeconomic status (SES), found that optimal postoperative pain relief continues to be a challenge for individuals who self-identify as racialized minorities, females, and those of lower SES[26].

CONCLUSION

Differences between men and women should be considered in the operating theatre practice. The physiological and pharmacological differences are also evident, although many studies must be conducted to clarify some aspects. In many studies, when scrutinized, confounding factors can be detected. Therefore, the anesthesiologists should make the anesthetic planning with caution and knowledge, considering the existing guidelines and the best practices.

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REVIEW ARTICLE

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Immunobiography and women's health: repercussions from conception to senility

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INTRODUCTION

In recent years, some researchers have questioned whether changes that occur in the adaptive immune system during aging could explain all the changes observed in the elderly and if the innate response could also have some participation in the process. Currently, it has become evident that both types of immunity participate in immunosenescence[1].

Immunosenescence is a key concept that translates into a growing and permanent decrease in the immune system's cellular growth. Senescent cells in various organs and tissues are inherent in the aging process, but when in great intensity and quantity, they are associated with chronic diseases, autoimmunity, and cancers[2].

The immune system is highly complex, presenting some specific properties, such as each receiver's ability to recognize different molecular patterns, cells capacity to interact and form a network (network), and their adaptability to different situations (plasticity). Based on these particularities, a model was proposed in the form of a "bow tie," called bow-tie architecture[3]. In this model (Figure 1), the bow-tie knot represents the immune system, and each side represents structures that can receive different input signals (fan in) and, after processing, produce a series of output signals (fan out).

Immune system cells are also able to adapt and change according to the numerous stimuli they receive. The type of stimulus, intensity, and temporal sequence are critical for the type of response generated, such as strong or weak, absent (tolerance or anergy), autoimmune, inflammatory, and memory. The immune responses generated will be unique to each individual and will compose the immunological history or "immunobiography" in the timeline, represented by the sum of all immune experiences that may be experienced throughout life[4].

Events during prenatal and neonatal life, as well as the so-called antigenic eco-space to which individuals are exposed from birth to adulthood and into senescence, form the bricks with which immunobiography is constructed[4].

When it comes to women's health, there are some important particularities because care for the biopsychic body becomes necessary in order for the conceptus to be received in a healthy way due to the condition of motherhood. Therefore, this article is intended to describe the behavior of the immune system – immunobiography – in the face of impairments and external agents from conception to senility.

METHODS

The research was carried out from December 2022 to February 2023 in the PubMed/Medline, Lilacs, and SciELO databases, using the following keywords: immunobiography, women's health, immune system, immunosenescence, inflammaging, and autoimmunity, using AND and OR Boolean logic. The filters used to prepare the proposal were as follows: articles published in the past 10 years, in English, Spanish, and Portuguese.

After screening by reading titles and abstracts, publications such as comments, editorials or letters, and duplicate articles were excluded. From then on, the full reading began, including more articles, through the references of the studies that had been preselected initially and reviews published on the subject, through manual search.

After selecting the articles, we tried to divide the theme into three topics in order to build the narrative of the factors that

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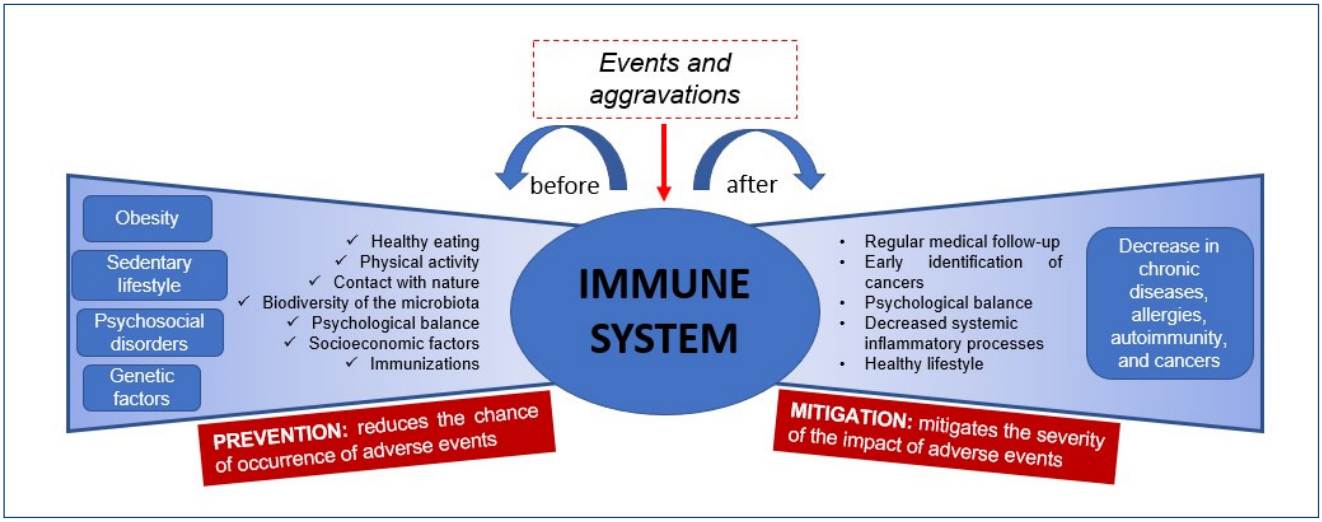

Figure 1. Bow-tie model of representation of factors related to prevention and mitigation of chronic diseases, allergies, autoimmunity, and cancers.

are involved in the immunological development from conception to immunosenescence.

RESULTS

Through the search in the databases, 33 articles were selected that address the following three sections: 1. Early events of conception and the immune system; 2. Exposures in early extrauterine life and the immune system; and 3. Events that occur in adulthood and senescence.

Early events of conception and the immune system

Intrauterine stimuli

Prenatal influences on immunobiography include numerous aspects, such as the health of future parents before conception, genetic predisposition, demographic and economic determinants, maternal health during pregnancy, and influences of the uterine environment and maternal biopsychic and cultural organisms during pregnancy[5].

In the context of individual-environment interaction, the Biodiversity Hypothesis has arisen in view of these new observations of the interaction between the external microbiota (soil, natural waters, plants, and animals) and the internal microbiota (intestine, skin, mucous membranes, and airways), enriching the human microbiome, aiming at promoting balance in immune tolerance and protecting against inflammatory and allergic disorders[6].

Numerous external agents can alter the epigenome, directly and indirectly influencing the development and immune programming of the conceptus. Among them are cited: environmental exposures during pregnancy, including diet, nutrient intake, nutritional status (obesity × malnutrition), use of vitamins and folic acid, smoking, infections and use of antibiotics, effect on the hypothalamus-pituitary-adrenal axis due to psychological stress, alcohol use, and exposure to indoor and outdoor toxins and pollutants (Figure 2). Consequently, understanding some of these factors will be essential in identifying individuals at risk and in the possible development of interventions for the prevention of chronic, allergic, and autoimmune diseases[7].

Maternal diet

The developing fetus depends on the mother to provide molecular precursors, as well as certain vitamins that are essential for immunity and system development[8].

Regarding the maternal diet, the intake of fish and fish oil during pregnancy seems to protect against allergies, although some studies have found the opposite. One study found that increasing intake of fish by mothers during pregnancy protected children against eczema, atopy, and wheezing by the age of 6 years, especially those who were not breastfed. Maternal supplementation with polyunsaturated fatty acids during pregnancy also reduces atopic eczema and egg sensitization in the first year of life[9].

Folate, another important nutrient, is recommended for pregnant women to prevent congenital anomalies (neural tube defects) in the fetus. While most studies report that elevated folate levels are associated with an increased risk of allergic diseases, there are a few publications reporting adverse effects. Thus, there is still no consensus on the subject, but it seems prudent to avoid excess folate during pregnancy[10].

Levels of other vitamins during pregnancy, from diets and supplements, also affect the risk of allergic diseases. Intake of vitamins A and E is inversely associated with the risk of allergic

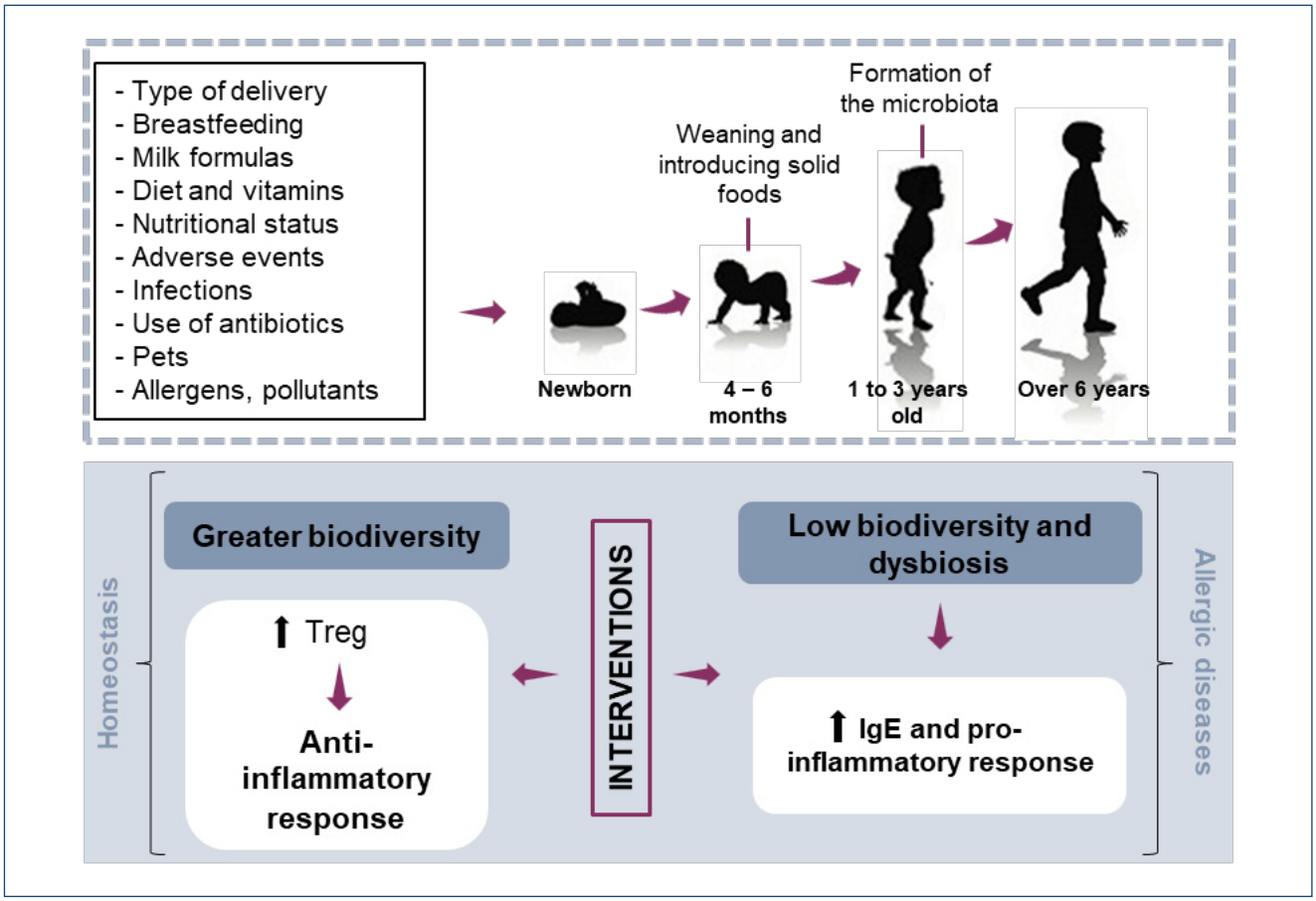

Figure 2. Multiple factors that interact between the host and the environment. Complexity of interactions of prenatal and postnatal factors in immunobiography.

rhinitis in childhood. Higher levels of vitamin C in the maternal diet reduce the risk of allergic diseases and wheezing, and vitamin D consumption during pregnancy alters neonatal airway epithelial cell responses and is inversely associated with the risk of asthma[11].

Some studies, including systematic reviews, have suggested that maternal ingestion of probiotics and prebiotics may cooperate in fetal immune development, with benefits of protection against atopic dermatitis, especially if used during prenatal care and in the first 6 months of postnatal life[12].

All these data seem to indicate that maternal intake of different nutrients may play a relevant role in the development of the immune system and other systems and may modify the risk of atopy in children. However, current knowledge on this topic remains uncertain.

There is still no universal recommendation regarding the prevention of allergic diseases through specific food supplementation during pregnancy or the exclusion of certain foods for consumption by pregnant women[13]. Well-designed intervention studies are needed to resolve these uncertainties.

Type of delivery and intestinal microbiome

The mode of birth influences the risk of allergic diseases: children born by cesarean section have an increased risk of developing allergies due to the acquisition of a microbiota with less diversity and consisting mostly of bacteria that provide little stimulus to the responses of type helper 1 (Th1) cells and regulatory T cells (Tregs). It is important to emphasize that the passage through the birth canal provides a birth experience in respiratory, endocrine, neuroimmune, and vaginal microbiome exchange fullness, which will certainly imprint a favorable potential on the baby's immunobiography[14].

There is suggestive evidence that the human microbiome is seeded in uterus, and it is likely that bacteria play a significant role in the development of the immune system. There is an increased rate of bacterial translocation through the intestine and increased traffic of live bacteria around the fetus in the last trimester, which may suggest that bacterial exposure increases or perhaps begins toward the end of pregnancy[15].

In turn, the administration of antibiotics during pregnancy and at birth acts unfavorably on the neonatal microbiome. It is

known that direct transmission of antibiotics through the placenta or breast milk can occur. As a result, antibiotics can cause temporary dysbiosis in the mother, resulting in transmission of her altered microbiota to her baby during critical early life phases[16].

Premature birth also confers a series of alterations that have been associated with neonatal dysbiosis. In particular, preterm infants are more frequently admitted to neonatal intensive care units, whose environment is likely to influence the neonatal microbiome. These babies are more likely to receive antibiotics and consume formula or pasteurized breast milk, as well as having little skin-to-skin contact with their mothers, negatively influencing the formation of their immune system[16].

Indoor and outdoor environmental factors

It is well known that smoking is one of the most studied environmental factors due to its association with epigenetic alterations. Pre- and postnatal exposure to tobacco is associated with higher levels of DNA methylation, decreased gene expression of IFN-γ (in effector T cells), and FOXP3 (in regulatory T cells). Smoking during pregnancy also interacts with interleukin-13 (IL-13) and may influence the onset of asthma, airway hyperreactivity, and genetic variants in the 17q21 locus associated with the risk of early onset asthma[17].

Similar considerations apply to environmental pollution, both indoors and outdoors, increasing the risk of rhinitis and asthma in childhood. In some parts of the world, there is strong air pollution by toxins and heavy metals generated by industrial processes, pesticides, plasticizers, as well as polluting particles and gaseous emissions resulting from burning fuels, which lead to possible epigenetic effects related to atopy[18].

Exposures in early extrauterine life and the immune system

Breastfeeding and the microbiome

More than a third of the intestinal bacteria of breastfed babies are vertically derived from milk and breast skin contact. Source-tracking studies have shown that the skin around the areola is the source of approximately 10% of an infant's microbiome and that bottle-fed babies may therefore miss out on microbes from their mother's skin. In addition, breast milk contains prebiotics that modulate the infant gut microbiome and metabolome, persistently differing in composition, diversity, and immune function in non-exclusively breastfed infants[19,20].

There is suggestive evidence that the mechanism by which childhood gut bacteria protect against the development of asthma and allergies is through the production of short-chain fatty acids, which are intestinal bacterial metabolites and immune modulators produced as a result of the fermentation of fibers. Elevated serum acetate levels in pregnant women correlated with a reduced risk of wheezing in the offspring in the first year of life. Similarly, intestine with higher concentration of acetate at 3 months of age and of propionate and butyrate at 12 months of age correlated with a decreased risk of wheezing and asthma later in life[19].

Events that occur in adulthood and senescence

Biodiversity of the microbiota and immune system

From an ecological point of view, the human body is an ecosystem of microbes, and in particular, the intestinal microbiome – also called the "second genome" – exerts multiple protective and life-supporting functions by orchestrating the relationship between cells and the environmental metagenome. The lack of interaction with the external microbiota, present in nature, promotes altered immune responses, favoring the risk of inflammatory and allergic diseases in individuals[6] (Figure 3).

This microbiome is established gradually in the first years of life. At birth, the human gut microbiome is highly dynamic, with low biomass and low diversity. Around one year of age, it passes from a developmental stage to a transitional phase, and the composition of the microbiota changes as diversity increases. Finally, at 2 and 3 years of age, the gut microbiome matures into a nearly stable adult microbiome[21].

The diversity and stability of the microbiota are mainly promoted in early life, but the interaction between the microbial components of the outer and inner layers never ceases. Lifestyles with reduced contact with nature lead to a cycle of greater dependency on health care[21].

Responses to infections and vaccines in immunosenescence

The numerous changes that occur in the immune system during aging make immunosenescence a significant contributing factor to increased risk and severity of infections. Although the immune response to antigens may be preserved in elderly individuals, their ability to immunize against new antigens is reduced[22].

Latent Epstein-Barr virus, herpes virus, and cytomegalovirus infections have been associated with telomere shortening in CD8 T cells, specifically due to a reduction in telomerase activity associated with T-cell proliferation. These data indicate that chronic infections during aging produce significant changes in the population of CD8+ T cells. Furthermore, these cytokines are strongly involved in the pathogenesis of immunological disorders that can favor the emergence of different pathologies, including autoimmune diseases[23,24].

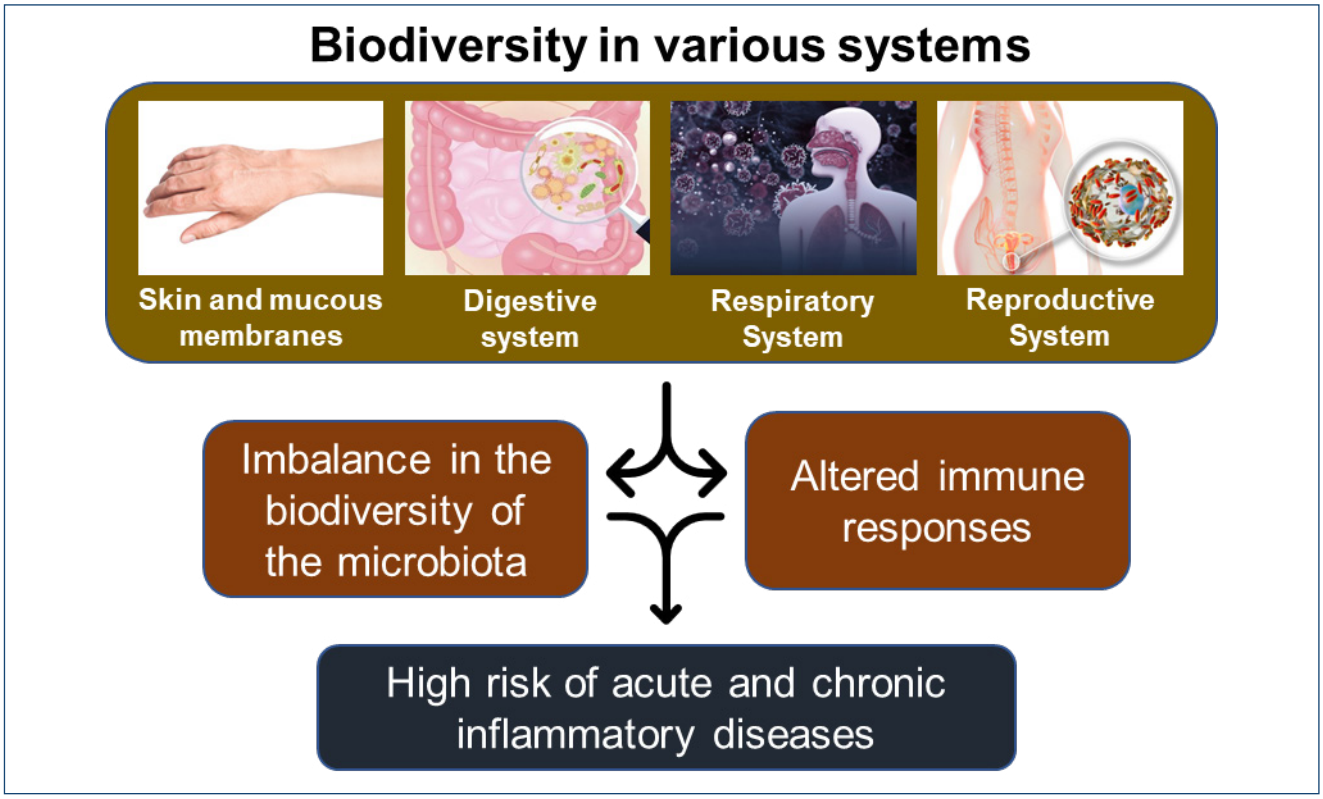

Figure 3. Lower biodiversity of the human body's microbiota and the risk of inflammatory diseases: biodiversity theory.

Among the various preventive strategies for protecting the health of the elderly, one of the most effective is vaccination against the most common infectious diseases in this age group. As a strategy to increase the immune response of the elderly to vaccines, several approaches have been described, the main ones being the increase in antigen concentration and the association of adjuvants in vaccines[25].

Autoimmunity in senility

Currently, there is no doubt that the changes that occur in the immune system during aging influence the onset of autoimmunity. This is due to the fact that aging is related to increased reactivity to self-antigens and loss of tolerance. In addition, it is worth remembering the epigenetic changes that occur in elderly people that can affect important genes involved in the development of autoimmune diseases[26].

Another important aspect of aging is the increase in inflammatory cytokines and chemokines produced by T cells, such as tumor necrosis factor (TNF)-α, c-reactive protein, IL-8, monocyte chemoattractant protein 1 (MCP1), and RANTES, which may contribute to the development of autoimmunity in the elderly[26].

One of the important causes of dysfunctional immune responses that can lead to autoimmunity are telomere abnormalities, and an association has been demonstrated between the mean telomere length of peripheral blood mononuclear cells in different pathologies. These findings were interpreted as evidence of accelerated T-cell proliferation in the autoimmune process. Another striking fact is that the genetic predisposition for short telomeres is strongly related to the HLA-DR4 haplotype, which is shared in rheumatoid arthritis and T1DM in some individuals[27].

Inflammaging and immunobiography

In general, inflammatory processes do not decrease with age, and a sterile, chronic, and low-grade inflammation called inflammaging seems to be an almost universal phenomenon in the elderly, constituting a hallmark of immunosenescence[28].

Inflammaging is mainly associated with changes in innate immunity, where the macrophage plays a central role, characterized by hyperproduction of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), simultaneous production of anti-inflammatory mediators (IL-10), and chemokines. It is important to point out that the presence of compensatory anti-inflammatory mechanisms has also been previously described in centenarians, thus constituting adaptation pathways that possibly favor longevity. This apparent paradox can be explained from the perspective of immunobiography, according to which environmental

factors can shape the immune system throughout life, generating effective anti-inflammatory responses[29].

Currently, there is evidence that other types of cells not belonging to the immune system may also contribute to inflammaging, such as adipose cells, skeletal muscle cells, and senescent cells[30].

Lack of response: tolerance

The immunosuppressive network involves several regulatory T (Treg) and B (Breg) cell subtypes, as well as regulatory phenotypes of macrophages (Mreg), dendritic cells (DCreg), natural killer (NKreg), and type II natural killer cells (NKT). The immunosuppressive network also includes monocytic cells and polymorphonuclear cells derived from immature myeloid suppressor cells induced by inflammatory mediators[31].

This immunosuppressive cooperative network has a significant role in the resolution of acute inflammatory conditions, but its persistent activation, as for example in tumors and inflammatory diseases, has harmful effects on the immune system and tissue homeostasis inducing immunosenescence[31].

The immunosenescence process may be associated with the activation of an immunosuppressive network, especially with the functions of myelocytic cells, suppressor macrophages, and Treg cells. Its function is best known in relation to tumor growths, autoimmune diseases, and maternal-fetal immunity[32,33].

Many clinical observations indicate that immune system remodeling occurs with aging, with increased risk of cancers, increased susceptibility to infections, decreased efficacy of vaccine response, and increased tolerance to transplants[33].

CONCLUSION

Each individual's immune responses will be unique depending on their immunobiography. Therefore, immune responses to potential antigens, including pathogens, food, and vaccines, will be quantitatively and qualitatively different according to the host's immunobiographical history, including age, sex, lifestyle, biodiversity, socioeconomic status, and psychological status, and among different populations, whose genetics and immune systems are shaped by their ecosystem and cultural habits.

AUTHORS' CONTRIBUTIONS

GVAGL: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **MAMTB:** Conceptualization, Formal Analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **MEBA:** Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **FWS:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **FRF:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **FCK:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **ESCS:** Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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The woman's hand

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INTRODUCTION

Women represent more than 50% of the Brazilian population and deserve special health care. Due to their caring and organizing nature, they often have a double shift, at work and at home, taking care of their children, other family members, and even members of the community where they live[1]. The hand is the human's main tool, an extension of the brain, playing a critical role, especially in women. It is a work, care, affection, expression, and support tool.

Although women have more diseases than men and seek for care more frequently, they statistically live longer than men[2] and, therefore, have more conditions that are typical of aging, such as arthroses, which can affect many areas of the body, including the hands.

Women's hormone pattern is very different from men's[3], with sudden changes in pregnancy, puerperium, and menopause, in whom the changes are more pronounced than in men. These changes favor specific disorders in the upper limbs, such as compressive syndromes and tenosynovitides.

In this article, we will highlight the main conditions that more frequently affect women in our specialty hand surgery.

IN THE MEDICAL FIELD

Female surgeons and interventionists experienced more musculoskeletal pain in the upper limbs than male counterparts. Some of the characteristics found in the studies were that women were generally shorter, wore smaller glove sizes, and were younger than their male counterparts. Furthermore, the size and design of the instruments and equipment handled by physicians are developed to meet the characteristics of the man's hand rather than the woman's for performing the same procedure[4,5]. We believe that such elements of harm to the health of the upper limbs in women may be present in several other occupations.

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is the most common compressive peripheral neuropathy, which affects up to 1% of the general population[6]. It is characterized by compression of the median nerve at the wrist, inside the carpal tunnel, through which nine flexor tendons of the fingers and thumb also pass (Figure 1).

It affects more women in the climacteric period due to hormonal changes[6]. The patient reports tingling in the hands, at first only during the night or in some specific activities, until symptoms become continuous. As the condition worsens, the sensitivity of the fingers decreases and there is a loss of grip strength in the hand, more selectively in the thumb. Initially, we treat with medication, orthoses, hand therapy, and hormonal correction. In patients with severe compression or in cases of failure of conservative treatment, we indicate surgical treatment, which can be performed using the open or endoscopic method.

TRIGGER FINGER

Trigger finger is caused by the friction of the flexor tendons on the pulleys, mainly the A1 pulley, located at the base of the finger, at the level of the metacarpophalangeal joint, resulting

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in an inflammatory process called stenosing tenosynovitis (Figure 2). It is one of the most frequent affections in our specialty. It is more frequent in women after the fourth decade of life[7], and the most affected fingers are the thumb, middle, and ring fingers.

Treatment is based on rest, anti-inflammatory medication, orthoses, steroid injections, and, when clinical treatment fails, surgery using the conventional open method or needle tenolysis, both with good results.

DE QUERVAIN'S STENOSING TENOSYNOVITIS

De Quervain's stenosing tenosynovitis is an inflammatory process located on the lateral aspect of the wrist, just above the thumb, which affects the tendons of the abductor pollicis longus and extensor pollicis brevis muscles, which cross an osteofibrous tunnel where they get inflamed due to friction (Figure 3). It preferably affects women in a ratio of 3:1[8]. It is often associated with hormonal changes[9] and vicious positions with the wrist, and flexion and ulnar deviation, exactly the position adopted by mothers during breastfeeding, bathing, and the act of removing the baby from the crib or stroller.

Treatment consists of correcting posturing and the hormonal profile, hand therapy, use of orthoses, and infiltration with corticosteroids, bearing the difficulty of the puerperal woman in mind, when she has to leave home to undergo hand therapy and leave her small child and perform the multiple mother functions with the use of orthoses. In cases where clinical treatment fails, surgery to decompress the extensor tunnel I is indicated.

Figure 1. Graphical representation of the carpal tunnel with the presence of the median nerve and its ramifications to the fingers.

RHEUMATIC DISEASES

Rheumatic diseases often affect the hand and wrist, causing deformities and destruction of the joint and tendon and capsuloligamentous structures. Unlike gout and ankylosing spondylitis, among others, rheumatoid arthritis and osteoarthritis commonly affect women[10]. The most common features are deformities in the fingers, with rheumatoid arthritis frequently affecting the proximal interphalangeal joints (Bouchard's node), while arthrosis preferentially affects the distal interphalangeal joints. The treatment is multidisciplinary, and the hand surgeon is responsible for preventing deformities through synovectomy and, when the deformities are already present, performing various corrective procedures, arthrodesis, and joint prostheses.

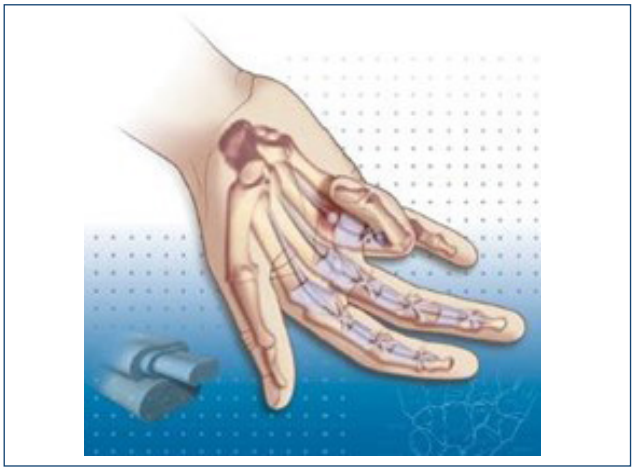

Figure 2. Graphical representation of the trigger ring finger, showing a nodule in the flexor tendon and the A1 pulley.

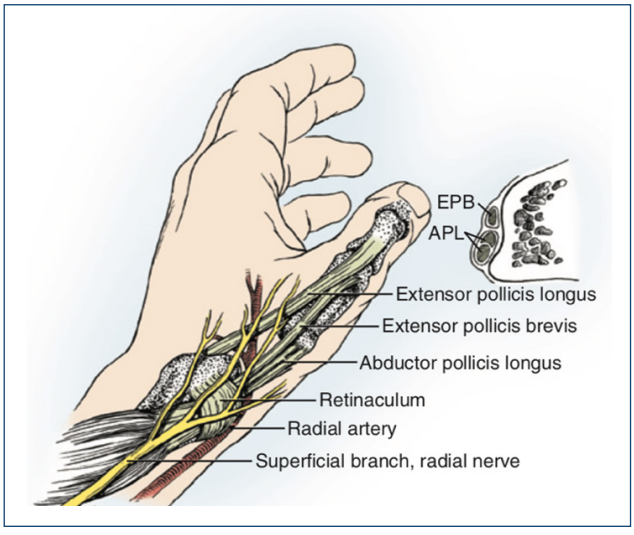

Figure 3. Anatomy of the lateral aspect of the wrist and hand, showing the first tunnel of the extensors and their anatomical relationships. EPB: extensor pollicis brevis; APL: abductor pollicis longus.

ARTHROSIS

Hands and wrists arthrosis mainly affects two regions: the distal interphalangeal joints of the fingers and the trapeziometacarpal joint of the thumb. With regard to sex, it affects women three times more than men[11].

Trapeziometacarpal arthrosis, also known as rhizarthrosis, can have a degenerative, inflammatory, traumatic, or idiopathic origin. It is a frequent condition, especially in women after the fifth decade of life, which causes weakness, pain, and deformity in the thumb, generating disability and a negative impact on the performance of daily and work activities. After the age of 55 years, rhizarthrosis affects 33% of women and 11% of men[12]. Initially, the joint becomes painful, and in the final stage, complaints of joint stiffness and deformity of the thumb in adduction arise.

Treatment consists of anti-inflammatory medication, orthoses, hand therapy, infiltration, and surgery in cases that do not respond to clinical treatment.

Arthrosis of the distal interphalangeal joints, which are the ones closest to the fingertips, causes a progressive, albeit slow, increase in volume and deformation of the joint (Heberden's nodes) with the appearance of occasional translucent mucous cysts. They are limiting because of the deformity and, mainly, of pain. It is usually clinically treated due to the lower potential for functional impairment compared to rhizarthrosis and, occasionally, surgically treated in refractory cases[13].

OCCUPATIONAL DISEASES

The demands of work for both sexes are usually similar, despite the bodily difference. Another factor is adaptation after a certain age, where postmenopausal changes are more evident in women[14]. Tenosynovitides and compressive syndromes, as mentioned before, are generally more common in women and in the postmenopausal period.

FRACTURE OF THE DISTAL END OF THE RADIUS

The radius is the most fractured bone in the human body, accounting for approximately 18% of fractures[15], and is considered a sentinel fracture, which indicates an osteoporotic process. Osteoporosis is described as a microstructural degenerative process of the bone that leads to a decrease in bone mass, leading to bone fragility. Over the years, there is an increase in osteoporosis and a consequent increase in the incidence of fractures. Women after menopause, due to estrogen deficiency, are twice as likely to have fractures of the end of the radius[16]. The worse the bone quality, the greater the fracture comminution and the more unstable the fracture, requiring surgical treatment. There are many possibilities for surgical treatment, with plate and screw fixation being the most popular method[17].

FIBROMYALGIA

Another condition that virtually affects the entire body, including the hands and wrists, is fibromyalgia. Often, due to the rich clinical picture, it simulates many common affections of the upper limbs. It is a condition with a multidisciplinary approach, which is much more frequent in women, representing 80–90% of cases[18].

COMPLEX REGIONAL PAIN SYNDROME/REFLEX SYMPATHETIC DYSTROPHY

Complex regional pain syndrome, which is also known as reflex sympathetic dystrophy, is a not very frequent complication, but with very bad consequences after surgical treatment of affections of the hands or even after trauma to the hand or wrist. It is as if the organism had a disproportionate response, much greater than the tissue aggression would require. The affected limb becomes edematous and painful, with changes in trophism and skin color. It is more common in women in the fifth decade of life and is probably related to the emotional state[19]. The treatment of this condition is a great challenge for us. It shall be addressed by a multidisciplinary team that includes a hand surgeon, a pain specialist, a physiotherapist, a hand therapist, and a psychotherapist[20].

Finally, the hand surgeon shall often differentiate and individualize the treatment when the patient is a woman, due to her different demands, her physiological pattern, and her social role.

AUTHORS' CONTRIBUTIONS

ACD: Data curation, Funding acquisition, Investigation, Methodology. **ATNF:** Data curation, Supervision. **RSMB:** Formal Analysis, Writing – original draft, Writing – review & editing. **RKO:** Project administration, Visualization **SAMG:** Software. **LRN:** Validation. MPR: Validation. **SCAS:** Visualization. **ACC:** Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Update on specific dermatoses of pregnancy

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Brazilian Society of Dermatology

INTRODUCTION

During pregnancy, changes in the immune, metabolic, endocrine, and vascular systems[1,2] can induce skin changes of three natures: (a) the physiological changes of pregnancy, (b) dermatoses and tumors influenced and/or aggravated by pregnancy, and (c) specific dermatoses of pregnancy (SDP)[3,4]. This review will address SDP, which constitutes a heterogeneous group of inflammatory dermatoses of unknown etiology, highly pruritic, and occurring during the immediate pregnancy-puerperal cycle[5]. Until 1982/1983, the nomenclature of these dermatoses was quite confusing. In 1982, Holmes et al. proposed a classification into four major groups: polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), pruritic folliculitis of pregnancy (PFP), and prurigo of pregnancy (PP)[6,7]. In 2006, Ambros-Rudolph et al. grouped PFP and PP into a group called atopic eruption of pregnancy (AEP). Furthermore, they included intrahepatic cholestasis of pregnancy (IHCP) in the SDP group[8]. AEP can be considered another specific dermatosis. However, several authors propose that PFP and PP continue to be contemplated until further studies are conducted to clarify this heterogeneous group of dermatoses[9-13]. Table 1 summarizes the SDP reviewed in this article.

Table 1. Specific dermatoses of pregnancy, according to the reclassification by Ambros-Rudolph et al.[8].

	Polymorphic eruption of pregnancy (PEP)	Pemphigoid gestationis (PG)	Atopic eruption of pregnancy (AEP)	Intrahepatic cholestasis of pregnancy (IHCP)
Frequency	Frequent	Rare	Frequent	Variable, according to geographic region and ethnic origin
Onset	Third trimester. Rare in the postpartum	Second/third trimester Rare in the postpartum	First/second trimester	Second/third trimester
Clinical feature	Urticarial papules with initial lesions in the striae, sparing the periumbilical region	Vesicobullous and urticarial lesions with periumbilical involvement	Eczematous lesions (AEP), monomorphic papules followed by pustules on the trunk (PFP), and papules and nodules on the extensor surfaces of the limbs and trunk (PP).	No primary skin lesion. Excoriations and/or prurigo due to scratching
Diagnosis	Clinical diagnosis Tests for differential diagnosis when necessary	DIF-deposit C3 BMZ IIF-anti-BMZ antibodies outlining the roof of the skin (salt-split technique)	Clinical diagnosis Elevated serum levels of IgE	Laboratory Increased bile acids, altered liver function, after ruling out other liver diseases
Fetal risk	No	Yes	No	Yes
Recurrence	No	Yes, including the use of oral contraceptives	Variable	Yes, including the use of oral contraceptives

DIF: direct immunofluorescence; IIF: indirect immunofluorescence; BMZ: basement membrane zone; PFP: pruritic folliculitis of pregnancy; PP: prurigo of pregnancy.

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POLYMORPHIC ERUPTION OF PREGNANCY

PEP has an unknown etiology. It is benign and self-limited, occurring at the end of pregnancy (between the 36th and 39th weeks) and, rarely, in the immediate puerperium[14]. The term PEP is preferred over previously used names, such as toxemic rash of pregnancy, erythema toxicum of pregnancy, erythema multiforme of pregnancy, and pruritic urticarial papules and plaques of pregnancy (PUPPP)[1,15], because this denomination encompasses all the clinical and morphological alterations involving this dermatosis[7,16,17].

It is considered the most frequent SDP[2], with an estimated incidence of 1:200 pregnancies, the vast majority occurring in primigravidae[2,7]. The suggested pathophysiology, although not yet elucidated[1], is related to an inflammatory process triggered by rapid abdominal distention, which may explain the association with excessive weight gain, twin pregnancy, and a large fetus for gestational age[4,8,18]. Recently, the authors have suggested that the immune mechanism of the upregulated Th2 cytokine profile, including IL-9 and IL-33, and the reaction against bacteria and fungi residing in the skin, may be involved[16]. A study of 517 *in vitro* fertilization (IVF) pregnancies and 1,253 spontaneous pregnancies concluded that PEP was statistically more frequent in pregnancies resulting from IVF than in spontaneous pregnancies. Also, it was suggested that prolonged treatment with progesterone might be related to a higher frequency of PEP[19].

The typical clinical feature begins with urticarial papules located along the abdominal striae, always sparing the periumbilical region, which is an essential differential diagnosis from PG[20,21]. The papules can converge, forming plaques and extending to the limbs, trunk, and buttocks, protecting the mucous membranes and face (Figure 1). They may exhibit small vesicles, target lesions, and polycyclic papules[14,22]. Generally, the condition persists for 4–6 weeks[4].

The diagnosis is clinical, with nonspecific histopathological examination and negative direct immunofluorescence (DIF) and indirect immunofluorescence (IIF)[10].

Therapy involves psychological support, clarification of doubts, and symptom treatment: use of comfortable cotton clothes, body moisturizers, and low or moderate-potency corticosteroid cream, in addition to topical antipruritics, such as water paste. Refractory cases can be treated with low-dose oral corticosteroids. There is a regression in weeks after delivery, and, in the authors' experience, a significant improvement is observed within a few hours after delivery[13,15,22]. PEP does not affect maternal and fetal prognosis, and there are no reports of recurrence in subsequent pregnancies[4].

PEMPHIGOID GESTATIONIS

Bunel recognized PG in 1811, and Milton reported it in 1872, naming it *Herpes gestationis*[1]. It is a rare, pruritic autoimmune bullous disease with clinical and pathological features similar to bullous pemphigoid (BP). Its incidence varies from around 1:50,000 to 1:60,000 pregnancies, and it is more common in multiparous women[23,24].

Autoantibodies of the IgG class form the skin lesions. These antibodies are formed against the NC16a domain of BP 180 transmembrane antigen, currently known as collagen XVII, located in the skin basement membrane zone (BMZ) and chorionic amniotic epithelia[21,24]. PG is associated with the abnormal expression of MHCII antigens HLA-B8, DR3, and DR4[24].

PG manifests commonly in the second and third trimesters of pregnancy (between 21 and 28 weeks) and, rarely, postpartum[20,21,24,25]. It usually recurs in future pregnancies, starting earlier and with a more severe presentation[7,24,25]. Also, it can relapse with menstruation and during the use of oral contraceptives[18,23-26]. The literature has reported PG associated with trophoblastic tumors such as hydatidiform mole and

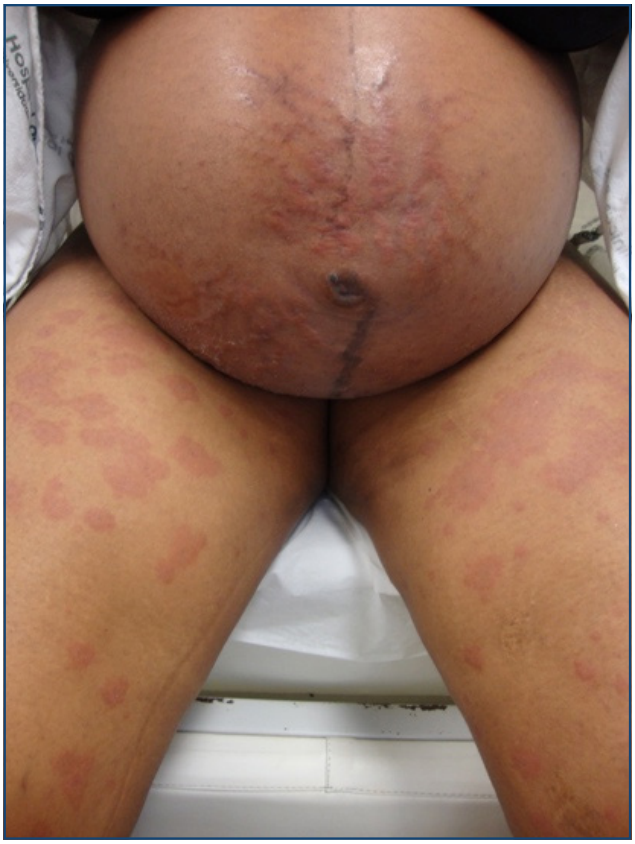

Figure 1. Polymorphic eruption of pregnancy with erythematous-urticarial papules accompanying the striae (forming fibrous cords) and sometimes going beyond the striae and forming plaques in the abdominal region, always sparing the periumbilical region. Confluent papules form plaques in the region of the thighs. Source: High Risk Prenatal Service (PNAR) at the Clinical Hospital at the Federal University of Minas Gerais.

choriocarcinoma[7,24]. The risks for the fetus are prematurity, low birth weight, and, rarely, a bullous eruption due to transplacental passage of maternal antibodies (<10%), with rapid and spontaneous resolution in most cases[14,21,24,26].

Clinically, there is an initial phase in which erythematous and urticarial papules and plaques predominate, followed by vesicles and blisters. Itching is intense and can be disabling[23]. In 90% of the cases, the lesions are initially located in the periumbilical region and spread to the abdomen and limbs[20,21,23,24]. The oral mucosa is rarely affected (15–20%)[26]. The primary differential diagnosis is PEP, where immunofluorescence studies are negative and generally spare the periumbilical region[20,21]. PG can be associated with other autoimmune diseases[23].

Histopathological examination of the initial lesions shows papillary edema with lymphocyte infiltration and a variable number of eosinophils in the dermis[24,25]. The histopathological pattern of a recent, intact blister is that of a subepidermal cleavage without acantholysis[26]. DIF of perilesional skin biopsies reveals linear deposition of C3 in approximately 30% of cases of IgG along the BMZ[20,21,24-26]. IIF in patient serum can be positive in most cases, and immunoblotting studies show that 90% of serum from patients with PG recognizes collagen XVII[21,24]. Detection of the NC16A domain of collagen XVII by ELISA has a sensitivity and specificity of 96%[21,26]. It is directly related to disease activity and helps differentiate PG from other pruritic dermatoses of pregnancy, including PEP[21]. It should also be differentiated from other bullous dermatoses, drug reactions, and erythema multiforme[27].

Mild cases with localized lesions are treated with low- to medium-potency topical corticosteroids and local skin care[23-26]. For patients with severe disease, therapy is based on systemic corticosteroid therapy[23,24]. The only criterion proposed in the literature to differentiate between mild and severe forms is the affected body surface area (< or>10%). There may be a worsening in the immediate postpartum period that may require an increase in medication dose. The drug should be discontinued 2 weeks after delivery withdrawing in 3–6 months, depending on the severity and progression of lesions[24,26]. The involvement of the multidisciplinary team is encouraged in approaching the diagnosis and management of this condition[14].

ATOPIC ERUPTION OF PREGNANCY

AEP, a term proposed by Ambros-Rudolph et al. in 2006[8], encompasses clinical conditions of atopic dermatitis that exacerbate or appear during pregnancy[4]. This dermatosis is often idiopathic, and its pathogenesis has not been fully understood. Its clinical manifestations have an earlier onset (first and second trimester of pregnancy) than the other SDP[4]. However, patients without an atopic history are more likely to have a later onset of the disease[11].

Ambros-Rudolph et al. described two clinical presentations: the eczematous type (E-type) with a classic distribution of lesions, including eczematous eruption on the face, neck, pre-sternal region, and flexors, and the prurigo type (P-type) with the presence of small, pruritic, erythematous papules, often clustered, disseminated predominantly on extensor surfaces of extremities and trunk[8]. IgE measurement has not been systematically studied in pregnancy, and its role as a diagnostic criterion is unclear[4].

There are controversies about including PFP and PP in AEP. Some authors consider them to be separate entities[9-13,15]. PFP, described in 1981 by Zoberman and Famer, constitutes an erythematous papular, monomorphic eruption found in the second and third trimesters of pregnancy[28] with spontaneous regression after delivery[12]. A prospective study found 0.03% of cases consistent with PFP in 3,192 pregnant women followed up[14,29]. PP, formerly known as Besnier's prurigo gestationis and early pregnancy prurigo, begins around the 25th to 30th weeks of gestation as pruritic and erythematous papules and nodules in the extensor regions of the extremities and trunk[30].

Regardless of the clinical manifestation and classification, the treatment of this group of SDP is symptomatic[12]. They regress after delivery and do not affect maternal-fetal health[30].

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

IHCP, described by Kehrer in 1907 as recurrent jaundice of pregnancy[1], has several names: cholestasis of pregnancy, prurigo gravidarum, and pruritus of pregnancy[13,15]. It is the only SDP that initially presents with pruritus without primary cutaneous lesions. Its prevalence ranges between 0.3 and 5.6% of pregnancies, depending on geographic and ethnic factors. A large study in Australia found a prevalence of 0.7%[14,31]. The family history is positive in 50% of the cases, and it is more frequent in twin pregnancies[1]. It occurs at the beginning of the second or third trimester of pregnancy, but there are reports of early onset, around the 8th week of pregnancy. IHCP may recur in subsequent pregnancies in 70% of cases and with the use of oral contraceptives[14,18,32].

IHCP pathogenesis is multifactorial and not fully understood. It is believed that genetic, hormonal, immunological,

and environmental factors may contribute and that the estrogen-bile acid axis plays a dominant role. Also, extracellular matrix and oxygen supply deregulation, organelle dysfunction, and epigenetic alterations may occur[33].

Clinically, it is characterized by intense, persistent, and generalized skin itching, which almost always gets worse at night and, at first, can be located only on the palmar and plantar region. Excoriations, erosions, and small papules are often secondary to scratching (Figure 2)[14]. Jaundice occurs in less than 20% of cases, and choluria and acholic stools may occur in 50% of cases, usually 2–4 weeks after the onset of pruritus[1].

There is no consensus on diagnostic criteria: some entities use persistent pruritus that disappears after delivery with bile acid concentration >10 µmol/L[33]. Liver enzymes, such as ALT, AST, and ALP, may be slightly elevated. Other causes of liver dysfunction must be ruled out[34].

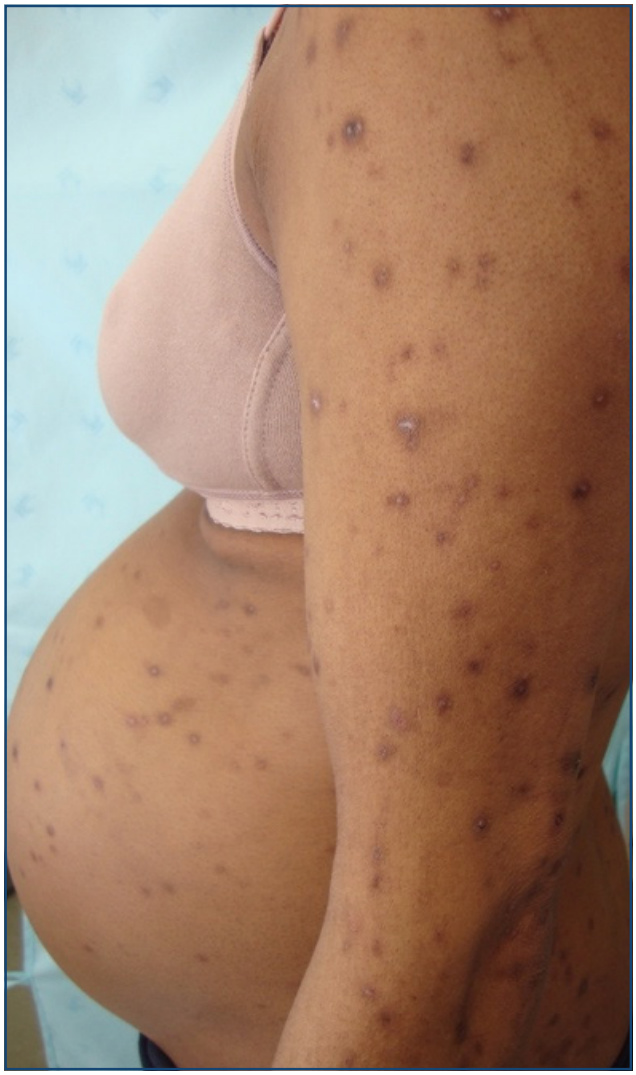

Figure 2. Pregnant woman with severe intrahepatic cholestasis of pregnancy, starting in the second trimester: excoriations, erosions, and residual hyperchromia throughout the integument secondary to scratching. Source: High Risk Prenatal Service (PNAR) at the Clinical Hospital at the Federal University of Minas Gerais.

The treatment of choice is ursodeoxycholic acid (UDCA) at 10–15 mg/kg/day to control itching and reduce bile acid levels[32]. Although UDCA is also used to improve fetal outcomes, there is controversy about its effect[33,34]. Emollients, topical antipruritic agents, and antihistamines are ineffective. In cases of prolonged cholestasis, administration of vitamin K may be necessary[35]. Pruritus usually resolves within 48 hours after delivery, and laboratory tests resolve within 2–4 weeks[30].

Maternal prognosis is usually favorable, and fetal risks are prematurity, perinatal mortality, and fetal distress. In a meta-analysis, Ovadia et al. provided evidence that IHCP is associated with a significantly increased risk of stillbirth for women with total serum bile acids of 100 µmol/L or higher. This study reinforces the inclusion of serum bile acid measurement in the diagnostic criteria for IHCP and recommends its wide use and monitoring during pregnancy[36].

The advances in the last 10 years regarding pathogenesis can bring potential targets for our drugs[33]. Intensive maternal and fetal monitoring is recommended, in addition to follow-up by an experienced multidisciplinary team to help decide the exact and safest moment for delivery[35].

FINAL CONSIDERATIONS

In SDP, the diagnosis is mainly based on clinical findings. Aside from PG and IHCP, no laboratory method is sufficient to differentiate these dermatoses, making clinical observation essential and leaving laboratory analysis for the differential diagnosis. Thus, the itching symptom should never be neglected, especially after the second and third trimesters of pregnancy. It affects the quality of life of the pregnant woman and can be a sign of several diseases.

Future elucidations of the etiology and pathophysiology of SDP will possibly bring new therapeutic modalities. Monitoring by a multidisciplinary team involving obstetricians, dermatologists, and other health professionals is encouraged in approaching the diagnosis and management of these conditions. The ultimate goal is optimal quality prenatal care for the pregnant woman and the fetus, with clinical monitoring and risk-benefit assessment on an individual basis.

AUTHORS' CONTRIBUTIONS

MLRC: Conceptualization, Writing – original draft. **GMM**: Conceptualization, Writing – original draft. **HVL:** Conceptualization, Writing – original draft.

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REVIEW ARTICLE

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Frailty in older women

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INTRODUCTION

An 85-year-old female patient has been suffering from loss of recent memory. She has received no previous medical support. Her daughter sought geriatricians as soon as she realized that her mother usually forgets the cooker on, keeps her money in biscuit jars, and she feels nervous due to apathy. She lives on her own and experiences significant tiredness. She has been operated on bilateral facetectomy alone and has no comorbidities. Her two children live nearby, and she has four grandchildren. She is a non-religious, widow, and retired private college professor who has sedentary behavior and no siblings. Her parents had Systemic Arterial Hypertension and Diabetes Mellitus. She has had some significant weight loss in the past 6 months without an apparent cause. She used to enjoy reading and watching films. She has always lived on the third floor of the same building without an elevator for the past 20 years. She will not allow her apartment to have modifications for elders; she has a fortnightly cleaner; and she neither smokes, drinks, has pets nor is allergic. She is fully vaccinated.

Geriatric data:

Normal physical examination: height 1.65 m; weight 50 kg and Body Mass Index: 18

Short Mental Test: 23/28 – Verbal Fluency Test: 9 words per minute

Get and Go Test: 20 – Rockwood Frailty Test: 4

Palliative Performance Scale: 60 – preserved hearing and vision

Densitometry – Osteopenia (-) 2.0 Femur and lumbar

Hand grip strength – unperformed

Complementary Tests:

Hemoglobin 10.5; albumin 2.1; vitamin B12 - 200; TSH 5.0; sodium 131.

CONCEPT AND FRAILTY PHYSIOPATHOLOGY

Frailty was a condition mentioned in the 1950s and 1960s and its notions were related to incapacity, comorbidity and advanced age[1]. It was first called Frailty Syndrome or Frailty in 2001[2]. Since then, healthcare workers have kept within objective parameters to diagnose frailty in the elderly. This is a multidimensional syndrome that impacts physical, nutritional, cognitive and psychosocial aspects. It has been widely studied with the elderly in the past decade[3]. There are five criteria as follows: (1) non-intentional loss of weight; (2) tiredness; (3) strength loss; (4) sedentary behavior and (5) slow walking speed. As far as our case study is concerned, this fragile elderly female suffers from fatigue and weight loss and has a slow walking speed.

There is no consensus on when her physiopathology started since there are many interlinked processes leading to the frailty phenotype. Aging and its physiological dysregulation (senescence), chronic malnutrition (caloric, protein and micronutrient restrictions), loss of muscle mass and strength (sarcopenia),

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reduction of resting metabolic rates, and reduction of energy expenditure all play important roles in the frailty spiral[4]. Other factors such as sedentary behavior, inflammaging (age-related chronic inflammation), endocrine dysregulation[5,6], cognitive deficit, alterations in the intestinal microbiota, anorexia, genetics, and epigenetics are also considered[3,7].

EPIDEMIOLOGY: FRAILTY AND VERY ELDERLY INDIVIDUALS

In 2022, the World Health Organization's (WHO) prospective figures confirmed that the very elderly (individuals over 80 years of age) are the fastest growing group both in Brazil and worldwide[8]. Such an exponential increase in this population in absolute and relative figures has an impact not only on social, economic and political aspects, but also on the treatment of the elderly by healthcare workers[9,10]. According to the platform DRG Brazil (Plataforma de Valor em Saúde), seniors are estimated to be 14% of Brazil's population and 23% of whom are hospital-care admitted. DRG Brazil has recently noted that 47% of adverse events or acquired conditions affected the elderly[11]. Hospital stays were significantly more prolonged, and death rates soared to 1.08% in under 60-year-olds and to 13.73% in over 80-year-olds[12,13].

Frailty syndrome is associated with advanced age, female gender, lower education and socioeconomic status, chronic diseases, cognitive and functional impairment, and depression. In the study "Health, Well-Being and Ageing", conducted between 2006 and 2010[14], frailty was predominant in 4.1% among 60-year-olds, 8.4% among 70-year-olds, 28% among 80-year-olds, and 55.9% among 90-year-olds and centenarians. The Fibra study has assessed 3,478 elderly individuals in their age of 60s, and frailty prevalence has reached about 9% among the whole population as it has increased among older individuals: 11.8% among 75- and 79-year-olds, and 19.7% among 80-year-olds[15-17].

One study was conducted with 33 Ribeirão Preto centenarian residents[18], representing 56% of this local super-elderly population. These were home-assessed and, according to the Fried criteria, 97% of them showed frailty syndrome.

Various diagnostic tools, stemming from developing physiopathological concepts, different cohort values and heterogeneous samples may explain such a substantial difference among frailty prevalence rates in different population studies. Population aging and the increase of frailty syndrome are significantly associated, which impacts negatively on elderly individuals' health.

DIAGNOSIS AND FUNCTIONAL CAPACITY

Frailty may be recognized as a syndrome through phenotype criteria and their respective diagnostic tools which are as follows[19]:
Weakness assessed through hand grip strength (dynamometer):

- Women with BMI<23.8: <14;
- Women with BMI 23.9–27.1: <17;
- Women with BMI 27.2–30.8: <20;
- Women with BMI>30.8: <23.

Retardation: assessed through a walking speed in a 4.6-m distance:

- Women <153 cm tall: >6 s;
- Women >153 cm tall: >5 s.

Physical Inactivity

Question: *Do you feel that you now exercise less than you did 12 months ago?*

Exhaustion

Question: *How many times did you feel this way last week?* (one point is scored if at least "2" is the answer for both questions):

"It felt like a great effort."

"I could not keep on going."

- 0: rarely or none
- 1: 1–2 days.
- 2: 3–4 days.
- 3: most of the time.

Malnutrition: assessed through unintentional body weight loss of 5% or 4.5 kg in 1 year[20-21].

An elderly individual is considered frail if they have three of these features or more, pre-frail if they have one or two, and robust if they have none of these features. There is, however, one diagnostic approach to frailty that sees it as a range of multidimensional aspects, leading to the concept of "deficit accumulation" or Frailty Index, identified through comprehensive geriatric assessment.

In clinical practice, frailty syndrome is suggested to be tracked down in 65-year-olds. FRAIL mnemonic questionnaire is a fast and simple tool that correlates Fried's physical criteria with the deficit accumulation concept:

- F — Fatigue (*Do you feel tired?)*;
- R — Resistance (*Can you not go up a flight of stairs without someone's help?)*;
- A — Aerobics *(Can you not walk one block without someone's help?);*

- I — Illness (*Do you have five or more of the following diseases: systemic arterial hypertension, diabetes mellitus, cancer (skin cancer excepted), chronic obstructive lung disease, coronary artery disease or myocardial infarction, congestive heart failure, asthma, arthritis, encephalic vascular accident, and chronic kidney disease)?;*
- L — Loss of weight (*Have you lost more than 5% of weight in the past 6 months?)*

If no points are scored, they are classified as robust; if one or two points are scored, they are classified as pre-frail; and if three or more points are scored, they are classified as frail.

FRAILTY CLINICAL OUTCOMES

Frailty matters since it poses a problem for the elderly as far as clinical and functional outcomes are concerned. It may increase the risk of falls and hospitalization rates, and lower quality of life as it may cause delirium, functional loss and higher morbimortality[22]. As chronic diseases and higher incapacity are also associated with frailty, all areas of geriatrics consider it an issue to be addressed[23-25].

FRAILTY AND HEALTHCARE

Since the elderly are faced with increased incapacities and a wide range of chronic diseases, looking after them is challenging, especially when they are socially vulnerable. Interprofessional teamwork is essential, for the frailer seniors become, the more vulnerable they are to diagnostic and therapeutic procedures.

Identifying frailty is crucial to design an individual therapeutic treatment for patients and organize state and private healthcare assistance networks. Therefore, those who are the most susceptible to health issues and medical complications can be eligible for treatment. A number of preventive, protective and therapeutic measures benefiting the elderly in every aspect of healthcare assistance will be taken[17].

As far as public health issues are concerned, both politicians and private managers must be aware of elderly affairs. Upgrading current initiatives, devising and planning new, effective, and interlinked ones would allow the frailest and most vulnerable of the elderly to have access to proper health services meeting and suiting their needs[9].

Ambulatory care initiatives must be taken by means of interprofessional approaches to promote health. In private healthcare systems, especially in oncology care, frail elderly patients are looked after by nurse navigators. Continuing education may help multi-professional teams offer proper care, and senior patients will experience better assistance. Consequently, patients are less likely to visit emergency care units or be hospitalized, as they are also less likely to have falls, fractures and, infections.

Ideal forms of elderly care are discussed in order to avoid unnecessary and futile hospitalizations. Since we are faced with the aforementioned demographic and epidemiologic scenarios, hospital assistance planning must be drawn up in order to offer the elderly friendly and quality assistance models. These would reduce hospitalization expenses, early re-hospitalizations, post-discharge hospitalizations, and mortality. It would provide the elderly and all those involved in the treatment with an extremely beneficial experience[13].

It is worth clarifying the concept of transitional care. It promotes patients' recovery or adequacy for a new certain health condition, and it can be delivered in patients' homes or at any specialized transitional care units. This is a current alternative method of providing frail seniors with quality care and services throughout their lives or until their passing.

PALLIATIVE CARE AND FRAILTY

Frailty Syndrome and PC are interlinked with functional loss, therapy limits, and the need for advance directives. According to WHO, PC should be required for patients with life-threatening, progressive, incurable, severe illnesses since their early identification. It focuses on chronic, degenerative, and frailty-associated diseases and patient-centered treatments. The female patient aforementioned will face clinical and functional decay, which may raise questions about appropriate PC.

This PC approach is due to the patient's gradual functional impairment. She has been diagnosed with mild hyponatremia, which may cause adynamia, fatigue, and delirium. If precipitating factors for the condition are properly treated, patients may make a full functional recovery. Although the patient in question is classified as frail and is receiving PC, her condition will not demand end-of-life care.

Some patients may be faced with bed confinement, severe cognitive decline, recurrent infections, and pressure ulcers due to gradual functional decline. Based on PC standards, the frailty syndrome criteria, and conversations with the patient's children and/or relatives (if any), end-of-life care might be delivered. Therapy limits might also be set out as long as advance directives are considered accordingly.

FINAL COMMENTS

Aging is just as real as stating it as a woman-related process alone. Lifestyle, genetics, and some other related factors make

us face frailty. Not only does it have a huge impact on patients' physical condition, but it also influences their lives as a whole. As far as assistance models are concerned (irrespective of healthcare financing models), discussing frailty in older women is essential, especially when healthcare workers do not seem to be prepared for increasing demands in this area. Therefore, we firmly believe that PC must be delivered as soon as seniors need it in order to avoid burdening families and overloading healthcare systems.

AUTHORS' CONTRIBUTIONS

CBNEOB: Conceptualization, Data curation, Formal Analysis. **IB:** Conceptualization, Data curation, Formal Analysis. **JED:** Conceptualization, Data curation, Formal Analysis. **KRSM:** Conceptualization, Data curation, Formal Analysis. **MAAML:** Conceptualization, Data curation, Formal Analysis. **POD:** Conceptualization, Data curation, Formal Analysis. **RCC:** Conceptualization, Data curation, Formal Analysis. **AF:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing.

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REVIEW ARTICLE

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Iron deficiency anemia in women: pathophysiological, diagnosis, and practical management

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EPIDEMIOLOGY AND ETIOLOGY OF ANEMIA

Anemia remains a significant global health issue, especially among children and women, regardless of socioeconomic status or geographic location. According to the World Health Organization (WHO), iron deficiency and iron deficiency anemia (ID/IDA) in the general population are the most debilitating nutritional deficiencies worldwide in the 21st century, with women being at particularly high risk[1,2]. Among 1.6 million people analyzed from 93 countries in the period between 1993 and 2005, the estimated worldwide prevalence of anemia (defined as an hemoglobin (Hb) <13 g/dL for males, <12 g/dL for nonpregnant females, and <11 g/dL for pregnant women and children) was 47.5% in children of preschool age, 25.4% in children of school age, 30.2% in nonpregnant women, and 41.8% in pregnant women[1,2]. In Brazil, the prevalence of anemia was moderate (20–39.9%) and severe (≥40%) for pregnant women and preschoolers, respectively[1,3]. ID accounts for more than 60% of anemia cases (approximately 27% of the world's population)[1,2].

ID in women has substantial health consequences with subsequent socioeconomic hazards, including impaired educational performance, decreased work capacity and productivity, and poor pregnancy outcomes. In 2017, the Global Burden of Diseases Study reported that dietary ID remains the fourth leading cause of years lived with disability in women[1,4].

ABSOLUTE IRON DEFICIENCY VERSUS FUNCTIONAL IRON DEFICIENCY

Iron plays a key role in many physiological processes, including energy production, oxygen transport by Hb in red blood cells (RBCs), DNA synthesis and oxidation-reduction reactions, myocyte function, and cell division. To meet but not exceed daily iron requirements for erythrocyte production and cellular metabolism (25 mg/day), iron is absorbed via the diet (1–2 mg/day) and salvaged from erythrocyte breakdown by macrophages (20–25 mg/day); any remaining iron requirements are met through the body's residual iron stores (a total of 3–5 g in adults)[5]. Daily iron loss (~1–2 mg/day) cannot be regulated, and thus, tight hemostatic controls exist to regulate iron absorption, recycling, and storage[5] (Figure 1).

Total body iron is distributed among Hb within erythroid precursors and mature RBCs (it represents more than two-thirds of the body's iron), myoglobin in muscles, iron-dependent proteins for cellular metabolism, and storage iron (predominantly in the liver, spleen, and bone marrow). A minority of the body's total iron is found in the circulation, where it is bound to transferrin. Iron absorption and tissue iron availability are closely regulated by hepcidin, a protein produced predominantly by hepatocytes, and it exerts control over systemic iron homeostasis by degrading ferroportin. Ferroportin is the key iron exporter expressed on macrophages and duodenal enterocytes that allows the recycling of iron from broken down/senescent erythrocytes into plasma and the absorption of iron from the gut into circulation, respectively. Hepcidin expression is increased by high body iron levels and inflammation and decreased by erythropoiesis, hypoxia, and ID[6].

In an absolute ID state, total body iron stores are reduced. Suppressed hepcidin levels lead to reduced ferroportin degradation, which in turn facilitates the absorption of iron from the gut (with help from divalent meta-transporter 1 [DMT1]) and allows iron export from macrophages and hepatocytes into the circulation. DMT1 and ferroportin are also upregulated by hypoxia-inducible factor 2a, which further facilitates

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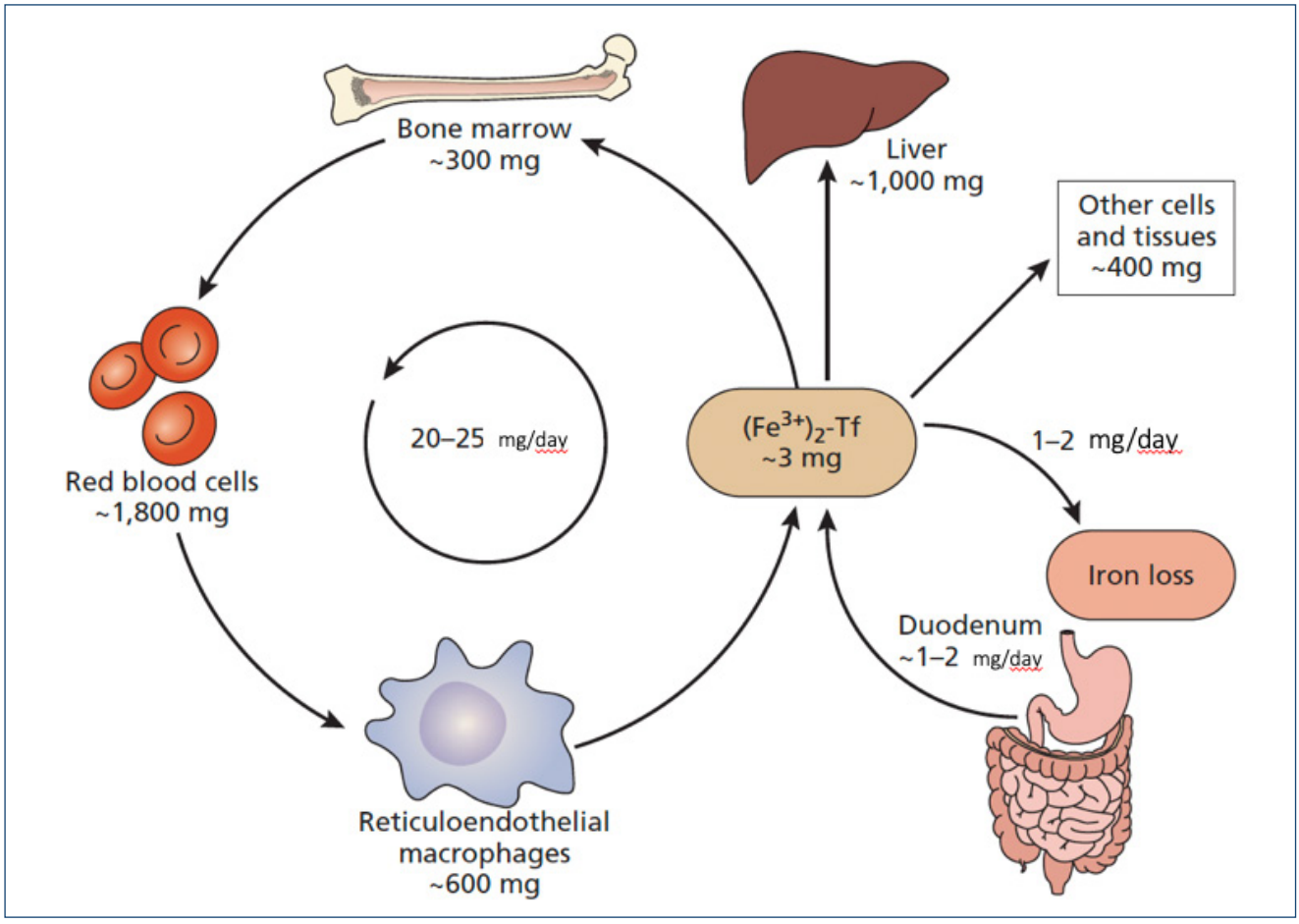

Figure 1. Body iron homeostasis. Plasma iron levels are maintained in a relatively narrow range. Iron circulates in plasma bound to transferrin, which maintains iron in a soluble form, serves as a major route of entry for iron into cells (via the transferrin receptor TfR1), and limits the generation of toxic radicals. The homeostatic system responds to signals from pathways that consume iron (e.g., erythropoiesis) and sends signals to the cells that supply iron to the blood stream. Iron is released into the circulation from duodenal enterocytes, which absorb 1–2 mg of dietary iron per day, and from macrophages, which internally recycle 20–25 mg of iron per day from senescent erythrocytes. While the body regulates processes of iron absorption, storage, and recycling, there is no process for excreting excess iron. Redrawn from Hentze et al.[5].

gastrointestinal (GI) iron absorption. Transferrin production increases in the liver and decreases the levels of iron-bound transferrin in the plasma in ID, further reducing hepcidin levels[6] (Figure 2).

Unlike absolute ID, FID is a state of imbalance between iron demand and serum iron availability, and it may occur despite adequate body iron stores. FID is most frequently observed in the setting of systemic inflammation and/or infection, in which inflammatory cytokines stimulate increased hepcidin production and thus impair iron absorption from the gut and facilitate iron trapping in macrophages by degrading ferroportin. By reducing iron bioavailability, iron-deficient erythropoiesis occurs. Cytokines may also have an impact on ferroportin production and cellular iron transport through hepcidin-independent pathways, dampen endogenous erythropoietin activity, and shorten erythrocyte life span[6] (Figure 2).

IRON DEFICIENCY/IRON DEFICIENCY ANEMIA IN WOMEN ACROSS THEIR VARIOUS STAGES OF LIFE

Unfortunately, ID and IDA are mistakenly believed to be benign conditions, unaware of IDA's significant effects on physical and cognitive functions, quality of life, morbidity, and mortality[7,8].

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN WOMEN OF REPRODUCTIVE AGE

Although ID is most common in low-income countries, recent data show that 40–50% of European nonpregnant women have low iron stores[2,4]. Women are known to have a much higher IDA prevalence compared to men of the same age; the prevalence rate is about 10 times higher than males. This difference

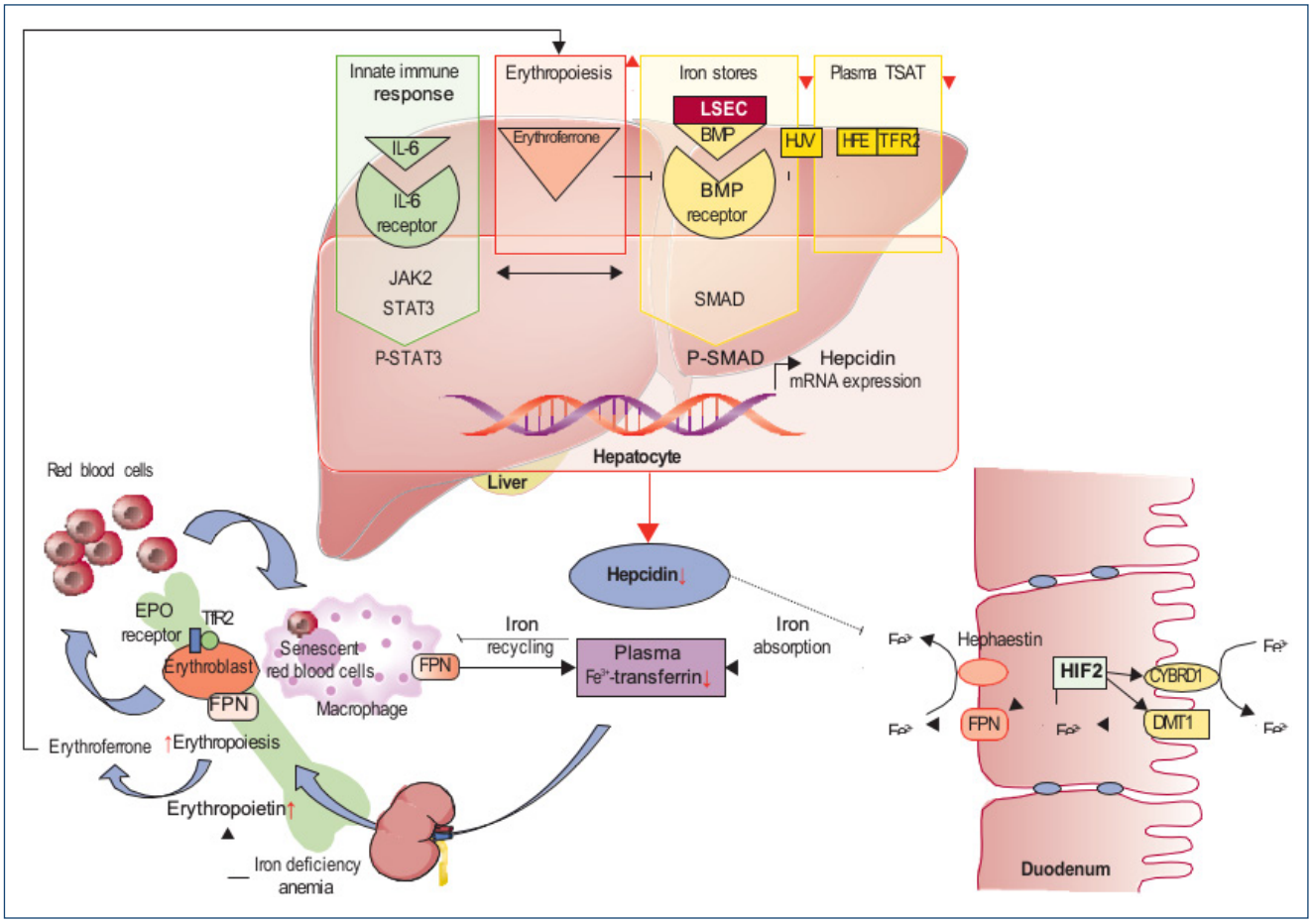

Figure 2. Coordinated homeostatic response to absolute and functional iron deficiency[6]. Modified from Pasricha et al.[6]. Red arrows refer to physiological stimuli (e.g., absolute iron deficiency or increased erythropoiesis) that suppress hepcidin expression. During absolute ID, decreased circulating transferrin saturation and liver iron storage suppress hepcidin transcription via reduced BMP-SMAD signaling (yellow pathway). As a consequence, duodenal and macrophage FPN proteins are stabilized, facilitating dietary iron absorption in duodenal enterocytes and release of iron from macrophages of the reticuloendothelial system, thereby increasing iron concentrations in the plasma. Additionally, reduced iron concentration in duodenal enterocytes is sensed by the iron-dependent prolyl hydroxylase domain enzymes that increase the stability of the transcription factor HIF-2, which regulates transcription of apical (CYBRD1 and DMT1) and basolateral (FPN) iron transport machinery. During iron deficiency, in most cell types, the IRP/IRE system stabilizes mRNAs of proteins crucial for iron uptake (e.g., TfR1 and DMT1) and suppresses the synthesis of proteins involved in the storage (ferritin), utilization (cytoplasmic and mitochondrial iron-containing proteins), and export (FPN) of iron. In functional iron deficiency, inflammation increases hepatic hepcidin expression via IL6-JAK2-STAT3 signaling (green pathway), causing reduced FPN abundance and function on cells, depriving the plasma of iron. In response to IDA, the kidney produces erythropoietin, which stimulates erythropoiesis. Erythroblast erythropoietin sensitivity can be modulated by TfR2. In absolute iron deficiency, erythroblasts, and erythrocytes donate iron through FPN-mediated iron export. Increased erythropoiesis (e.g., during recovery from anemia) causes secretion of erythroferrone, which suppresses hepatic hepcidin expression via inhibition of BMP-SMAD signaling (red pathway). LSEC, liver sinusoidal endothelial cell. P, phosphorylated. TSAT, transferrin saturation.

is mostly due to regular blood loss during menstruation, which is often associated with low iron intake. Adolescent girls are particularly vulnerable to this condition because of the elevated iron requirement for rapid growth and menstrual blood loss. Furthermore, several conditions can play a determinant role in favoring ID in women, such as chronic gynecologic bleeding due to uterine fibroids, endometriosis, adenomyosis, or endometrial hyperplasia. Moreover, intestinal malabsorption problems, frequent blood donation, and benign and malignant GI lesions are other causes of IDA in women[8-11].

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN WOMEN WITH HEAVY MENSTRUAL BLEEDING

Heavy menstrual bleeding can be defined as a total blood loss per menstrual cycle that regularly exceeds 80 mL. However, a definition requiring quantification of blood loss is only useful for research studies and accurate assessments of menstrual blood flow. The UK-based National Institute for Health and Care Excellence (NICE) has suggested that HMB should also be diagnosed when there is regularly excessive menstrual blood

loss that "affects the physical, social, emotional or material quality of life of the patient"[12].

HMB is estimated to affect approximately 18–38% of women of reproductive age and may increase in prevalence for women approaching menopause. However, there is considerable variability in the reporting of HMB, and the condition is likely to be underdiagnosed[12,13].

Prolonged blood loss, such as a menses duration of more than 7 days, or moderate blood loss in combination with an iron-deficient diet, such as often occurs in adolescents and vegans, can also contribute to the risk of ID in women. Women with HMB lose on average five to six times more iron per menstrual cycle than women with normal blood loss, resulting in totally depleted iron stores[14,15].

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN PREGNANT WOMEN

The physiological iron demand dramatically increases in pregnancy (approximately 1,000–1,200 mg with an average weight of 55 kg), despite the temporary respite from iron losses incurred during menstruation. This quantity includes almost 350 mg associated with fetal and placental growth, about 500 mg associated with expansion in red cell mass, and around 250 mg associated with blood loss at delivery. In the course of gestation, iron needs present a variation with a growing trend; in fact, there is a lower iron necessity in the first trimester (0.8 mg/day) and a much higher need in the third trimester (3.0–7.5 mg/day). At the beginning of pregnancy, approximately 40% of women show low or absent iron stores, and up to 90% of women have iron reserves of <500 mg, which represent an insufficient amount to meet the increased requirements[10,16]. Surprisingly, it is uncommon for pregnant women to be checked for ID unless anemic, and low Hb concentration alone may miss up to 55% of ID pregnant women when other iron parameters are not added to screening laboratory tests[10,16].

APPROACH TO IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

The diagnostic approach for managing ID and IDA involves a three-step approach: (1) identification, (2) investigation, and (3) iron repletion[17].

Step 1. Identification of iron deficiency/iron deficiency anemia

Although ID is by far the most common cause of anemia, laboratory evaluation is fundamental for a definitive diagnosis of ID and IDA in order to provide appropriate treatment. As the etiology of anemia includes various causes, the diagnosis cannot be based only on Hb values.

The initial laboratory tests that are essential for the etiological investigation of anemia are as follows:[6,9,10,14,17]

- Complete blood count including red cell indices.
- Reticulocyte count—to assess erythropoietic activity of the bone marrow in a case of anemia.
- Analysis of peripheral blood smear can provide important information regarding the underlying cause of anemia.
- Serum iron, total iron binding capacity, and transferrin saturation (TSAT)—result of the equation: (serum iron ÷ the total iron binding capacity) multiplied by 100.
- Serum ferritin (SF)—the most reliable initial test for diagnosing ID.

The reticulocyte count provides important information about the level of erythropoietic activity in the bone marrow and is an integral part of the screening process for every patient with anemia. In addition to the number of reticulocytes in absolute values, the Hb content of reticulocytes can provide additional information regarding impaired hemoglobinization of erythrocytes and is a valuable and early indicator of ID[5-7].

Ferritin is an intracellular iron storage protein that correlates with the body's iron stores in the absence of threshold of ferritin <30 mg/L, achieves a higher sensitivity (92%), while maintaining a high 98% specificity for the diagnosis, and is thus commonly used. Ferritin <30 mg/L and TSAT<20% have been recommended for the diagnosis of ID and, when these parameters are associated with anemia, for IDA[7,14,17].

The diagnosis of ID becomes more challenging with concomitant inflammatory conditions because ferritin is an acute-phase reactant that increases with inflammation. In these circumstances, TSAT <20% and higher ferritin thresholds (between 30 and 100 mg/L) can be used for the diagnosis of IDA[9,14,17]. An earlier marker of ID is the reticulated hemoglobin content (CHr), which is decreased (<29 pg) in ID (Table 1). The evaluation of C-reactive protein (CRP) levels may assist in obtaining the correct diagnosis, excluding infections or inflammation. If the CRP value is elevated, re-evaluation of the SF level is recommended after the normalization of CRP concentration.

Hepcidin is the main protein that controls plasma iron transit through its binding to ferroportin, the only iron-exporting protein present in the cell membrane of macrophages, enterocytes, hepatocytes, and placental syncytiotrophoblasts. After the formation of the hepcidin-ferroportin complex, it is internalized and degraded in lysosomes (Figure 2). Despite its

relevance in the differential diagnosis of ID, the measurement of hepcidin (in serum or urine) by mass spectrometry (the most reliable and reproducible method) still has a high cost, which limits its use in daily clinical practice.

Step 2. Investigation of iron deficiency/iron deficiency anemia[6-11,14,17,18]

ID and IDA are not a final diagnosis; rather, they are indicative of an underlying etiology that is decreasing iron availability and/or increasing iron needs. To effectively manage ID/IDA, the underlying etiology must be identified and, if possible, treated (Table 2).

Step 3. Iron repletion

The treatment of ID/IDA includes oral iron, IV iron, and RBC transfusions. The cause and severity of anemia, comorbidities, the time remaining until delivery, and patients' wishes are important factors that must be considered when deciding the therapeutic approach[6-11,14,17,18].

RED BLOOD CELLS TRANSFUSION

Recommendations from the American Society of Hematology and American Association of Blood Banks campaigns across jurisdictions and specialties have highlighted the importance of restrictive

Table 1. Differential diagnosis of types of iron deficiency[6-8,14,18,36].

Parameter	ID	IDA	FID	IDA+FID
Symptoms	Asymptomatic or mild symptoms of anemia	Mild-severe symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia
Hemoglobin	NI/↓	↓	↓	↓
MCV	NI/↓	↓	NI/↓	↓
TSAT	20–45%	<20%	<20%	<20%
Ferritin, ng/mL	<30	<30	NL/	NL/
Reticulated hemoglobin content	↓	↓	↓	↓
Hepcidin	NI/↓	↓		NI/↓

Table 2. Main causes of iron deficiency[6-11,14,17,18].

Increased iron requirement	Excessive loss of iron (blood loss)

• Growth*
• Menstruation**
• Pregnancy***
• Lactation
• ESA therapy
	• Gastrointestinal bleeding
	  • Esophageal: varicose veins, carcinoma, ulceration, reflux esophagitis
	  • Gastric: polyp, cancer, ulcer, gastritis, angiodysplasia, telangiectasia, antral gastric vascular ectasia, associated with the use of aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants, antiplatelet agents
	  • Small intestine: inflammatory bowel disease, duodenal ulcer, Ancylostoma duodenale and Necator americanus infection, cancer, polyp, angiodysplasia, telangiectasia, Meckel's diverticulum, associated with intense exercise, milk allergy
	  • Large intestine: cancer, polyp, diverticular disease, angiodysplasia, inflammatory bowel disease, Heyde's syndrome#
	  • Anus: Hemorrhoid
	  • Entire gastrointestinal tract: hereditary hemorrhagic telangiectasia
	• Gynecological bleeding: abnormal uterine bleeding##; uterine cancer or other cancers of the reproductive tract, intrauterine device
	• Urinary bleeding: cancer: kidney, bladder, prostate
	• Intravascular hemolysis: PNH, gait hemoglobinuria, thrombotic microangiopathy, gait hemoglobinuria, malaria
	• Respiratory bleeding: hemoptysis (cancer, infection)
	• Blood donation
	• Exercise
	• Excessive iatrogenic blood loss###

Inadequate dietary intake and/or defective absorption of iron	
• Low bioavailability of Fe diet@ • Vegetarian or vegan practice • Inflammatory bowel disease • Celiac disease • Parasitosis • Obesity • Post-gastroplasty (gastric bypass) • Post-gastrectomy • Atrophic gastritis • Helicobacter pylori infection • Medications: antacids, proton pump inhibitors, calcium, tannin • IRIDA@@	

ESA: erythropoiesis-stimulating agents; *During early childhood and adolescence; **Physiological blood loss exceeding daily iron intake; ***Additional iron requirement for each pregnancy of approximately 1,000 mg for expansion of maternal erythrocyte mass and placental and fetal development; @Resulting from poverty, especially in low-income countries, early cessation of breastfeeding, and inadequate transition diet; @@IRIDA, iron-refractory iron deficiency anemia caused by mutations in the TMPRSS6 gene; #Heyde's syndrome (severe aortic stenosis, syndrome type 2 acquired von Willebrand disease, angiodysplasia and ECD); ##Abnormal uterine bleeding usually related to uterine fibroid, adenomyosis, endometrial hyperplasia, or dysfunctional uterine hemorrhage fibroid, exacerbated by bleeding disorders (von Willebrand disease, haemophilia A or B, and platelet dysfunction); PNH: paroxysmal nocturnal hemoglobinuria; ###Excessive blood collection for diagnostic tests and iron losses during hemodialysis.

RBC transfusion and promoted the use of alternative therapeutic options to transfusion (egg, oral, or IV iron supplementation, recombinant erythropoietin) when available and appropriate, in order to avoid transfusing RBCs for IDA without hemodynamic instability. Therefore, RBC transfusion for severe IDA should be restricted for cardiovascular compromise and/or debilitating symptoms, when a rapid correction of anemia is clinically required. Unfortunately, blood transfusion for the correction of anemia is still a frequent practice observed in many centers, especially in the postpartum period[19-21].

ORAL IRON––CURRENT PRACTICAL RECOMMENDATIONS

Oral iron supplementation remains the standard first-line therapy for treating ID and IDA. Oral iron is inexpensive, easy to access, available without a prescription, and, when tolerated and taken properly, is highly effective in correcting ID[22]. Oral iron compounds vary widely according to salt type, formulation, chemical state (ferrous or ferric form), elemental iron content, bioavailability, efficacy, adverse events (AEs), and cost. The four main iron supplements commercialized in Brazil are listed in Table 3[22,23].

Historically, the recommended dose for the treatment of adult individuals with IDA has always been 100–200 mg of elemental iron per day, divided into two to three intakes, with daily doses greater than 200 mg not being recommended. In the past decade, with advances in the knowledge and importance of hepcidin in body iron homeostasis and studies with radioisotopes, and with the objective of overcoming the inhibitory action of hepcidin, reducing AEs, and improving tolerance and adherence to oral iron, new recommendations have been proposed for treatment with oral iron[24,25].

ORAL IRON PROPHYLAXIS OF IRON DEFICIENCY/IRON DEFICIENCY ANEMIA IN PREGNANCY

There is poor evidence about the effect of iron prophylaxis in pregnancy in determining a reduction in global ID prevalence and, consequently, a decrease in maternal and fetal complications. Therefore, the WHO promotes daily iron supplementation during pregnancy for women who live in areas with a high prevalence of ID because the administration of prophylactic iron to women with low iron stores represents a significant benefit. Current guidelines indicate 60–120 mg of elemental iron per day.

IV IRON

IV iron has traditionally been used for unresponsiveness to or intolerance of oral iron replacement therapy or for patients for whom rapid iron replacement (e.g., preoperative ID or symptomatic anemia, bleeding due to placenta praevia, and advanced gestational age) is desired. IV iron therapy is indicated in pregnancy from the second trimester onward[26,27].

IV iron administration bypasses the absorption difficulties associated with oral iron and represents an optimal alternative to oral iron therapy. Numerous clinical studies show a greater rise in Hb concentration and iron stores over a shorter period using IV iron when compared with oral iron[9,10,28,29]. In addition, IV iron may be useful in the treatment of AI; high single doses of IV iron may overcome the block caused by hepcidin in patients with this condition[30,31].

Despite the standard approach of using oral iron as first-line therapy for ID/IDA, the growing evidence for the greater efficacy and safety of IV preparations has convinced many experts that IV iron is frequently the preferred treatment[30,31].

The reduced number of IV iron administration needed to deliver the required total iron dose is much more convenient, potentially more cost-effective, and may be particularly suitable for the treatment of IDA, especially in the obstetrics and gynecology population when the vast majority of patients are being treated on a strictly outpatient basis, such as women with HMB and IDA, when supplemental oral iron therapy is often insufficient to keep pace with ongoing iron losses associated with recurring menses, late pregnancy, or severe anemia. IV iron has superior efficacy compared with oral iron, with significantly more women reaching target Hb levels and substantial Hb increases[30-34].

The current recommendation for the treatment of IDA with IV iron as well as the iron formulations available in Brazil (ferric saccharate, ferric carboxymaltose, and ferric derisomaltose) are summarized in Table 4[30-34].

CHRONIC IRON NEED

There are many populations who will require ongoing iron supplementation beyond initial iron repletion as a maintenance iron therapy. Such populations include those with inflammatory bowel disease and malabsorption (e.g., bariatric surgery) or ongoing GI blood loss (e.g., abnormal uterine bleeding refractory to or awaiting gynecologic intervention).

Current guidelines recommend routinely rechecking complete blood count, reticulocytes, reticulated-Hb content, and iron parameters 3–6 months after initial iron repletion to determine whether ongoing iron supplementation is required and to establish the optimal route, dose, and frequency. For some patients (e.g., women with HBM),

asymptomatic outpatients with mild ID/IDA in whom there is no inflammation and in whom oral iron is well tolerated, we are successful in maintaining normal iron stores and Hb levels using once-per-day or every-other-day oral iron. In other patients, a regimen of once per month, once every 3 months, or once every 6 months IV of iron is required, with the goal of maintaining normal iron status (ferritin >30 mg/L; TSAT >20%)[14,10,26].

Table 3. Current recommendation for the treatment of iron deficiency with oral iron[22-25,37,38].

Current recommendation for the treatment of iron deficiency with oral iron

- Single daily dose of oral iron is preferable to divided doses because divided doses twice or three times a day are physiologically ineffective.
- Ferrous salts should be taken 1 h before meals or between meals or before bedtime (time of greatest gastric acid production).
- Ferric salts can be given during or after a meal.
- The major problem with oral iron supplements is that 20–56% of patients cannot tolerate them because of GI AEs, including abdominal distress, nausea, vomiting, constipation, diarrhea, metallic taste, and dark stool; and the discontinuation of treatment is up to 20%.
- It is important for prescribers to inform patients of these potential AEs prior to commencing oral iron therapy and to encourage an open dialogue so that should negative effects occur, alternative therapies can be provided.
- The common practice of administering ferrous salts with food in an attempt to alleviate GI AEs can effectively decrease absorption by 40–66%.
- AEs rate related to oral iron are dose-dependent. It is important for the physician to be aware of the amount of elemental iron present in different medications, as this varies considerably according to the compound used or available.
- Doses up to 100 mg of elemental iron should be prescribed once a day, daily. Doses>100–200 mg of elemental iron should be prescribed on alternate-day regimen to optimize iron absorption, reduce the rate of GI AEs, and improve treatment tolerance. The rate of iron absorption is 40–50% greater on alternate days versus consecutive days for doses between >100 and 200 mg of elemental iron.
- Avoid daily dose of elemental iron>200 mg
- With consistent oral iron supplementation, reticulocytosis starts in 4–5 days, and Hb begins to improve by the second week. The main criteria for a good response to treatment are an increase of at least 2 g/dL is expected after 3–4 weeks of treatment.
- As an overarching principle, with any IDA patient, provide enough iron to not only correct the Hb deficit, but enough to provide measurable storage iron as reflected by the SF. Then, SF can be monitor for ongoing iron losses and, with appropriate administration of supplemental iron, prevent ID and IDA.
- Oral iron therapy is often required for at least 3–6 months, depending on the intensity of the ID, continuity of blood loss, occurrence of AEs, and consequently adherence to treatment. The goal of iron replacement is not only to correct the Hb deficit but also to provide enough iron to replete iron stores and normalize ferritin levels (serum ferritin>30 ng/mL and TSAT>20%).
- Periodic monitoring (SF and TSAT) and retreatment prior to the recurrence of ID are recommended among high-risk populations: pregnant women (at the first prenatal visit and in each trimester during pregnancy) and among specific groups of nonpregnant women of childbearing age.
- There are no biochemical markers to predict the likelihood of response to oral iron. In addition to the problem of AEs, impaired iron absorption such as inflammatory bowel disease and other malabsorption states, prior gastric bypass surgery, and concomitant administration of drugs can inhibit iron absorption and decrease responsiveness to oral iron.
- Intake of citrus fruits containing vitamin C (orange, lemon, and acerola) before or during a meal increases iron absorption. Multivitamins containing divalent metals (zinc, copper, and manganese) and various dietary components (phytates, polyphenols, calcium, and phosphates) reduce the absorption of ferrous salt. Therefore, it is recommended that they be administered separately from other vitamin supplements.

Comparison between the four main iron supplements marketed in Brazil

Variable	Ferrous Sulfate	Ferric salts		
		Ferripolymaltose	Aminochelated Iron	Ferrocarbonyl
Administration	Preferably with an empty stomach	During or after meal		
Efficiency	High	Intermediate to high		
Rate of Adverse events	High (35–55%)	Intermediate (15–35%) to low (10–15%)		
Treatment tolerance	Low	Intermediate to high		
Quantity of elemental iron	20%	30%	20%	33%

Definition of treatment failure with oral iron:
Hb ≤2 g/dL after 3–4 weeks of treatment with 100–200 mg of elemental iron/day.

Most frequent causes of treatment failure with oral iron:

- Continuing blood loss due to failure to identify bleeding and/or iron absorption disorder.
- Medication inappropriately used––poor adherence to treatment due to gastrointestinal AEs and/or inadequate dose and/or insufficient duration.
- Coexisting disease interfering with the response (reducing iron absorption and/or favoring bleeding) to oral iron treatment––chronic kidney disease associated with inflammatory or infectious disease.
- Diseases associated with iron absorption disorder––celiac disease, autoimmune atrophic gastritis, and Helicobacter pylori infection; incorrect diagnosis.
- Combined nutritional deficiencies.

Table 4. Current recommendation for the treatment of iron deficiency with IV iron[30-35,39-42].

Main indications for IV iron treatment

- Oral iron intolerance determined by the occurrence of AEs.
- Unsatisfactory response with oral iron due to intestinal absorption disorder associated with conditions such as: gastric bypass, gastrectomy, and chronic gastrointestinal inflammatory disease (H. pylori infection, Celiac disease, Crohn's disease, ulcerative colitis, and atrophic gastritis).
- Recurrent bleeding (gastrointestinal and gynecological) in which the amount of iron absorbed orally is not sufficient to meet the demand resulting from excessive iron loss.
- Rapid iron replacement in order to reduce transfusion requirement in patients with IDA scheduled for medium to major elective surgery, including childbirth and the puerperium.
- Faster normalization of iron stores avoiding prolonged use of oral therapy and its AEs.
- Patients with nondialytic chronic kidney disease with serum ferritin< 100 ng/mL or on hemodialysis with serum ferritin<200 ng/mL in order to ensure and optimize the response to erythropoietin administration.
- Special situations such as: pre-deposit autotransfusion programs and religious issues (Jehovah's Witness patients).

Goals of IV iron treatment

- Faster correction of anemia (an increase of 2–3 g/dL of Hb after 4 weeks of treatment) and iron stores.
- Reduce/eliminate the need for blood transfusions.
- Optimize the use of erythropoietin (cancer and chronic kidney disease).

Main practical guidelines for the use of IV ferric saccharate

- To calculate the total dose of iron (in mg) to be replaced, the Ganzoni formula can be used: body weight (kg)×(target Hb−−current Hb)×2.4+500.
- There is no need to perform a test dose before application.
- Dilute the compound only in 0.9% saline solution (SF). Do not dilute in glucose solution.
- Dilute each ampoule (5 mL, 100 mg) in at least 100 mL of saline solution.
- For each solution containing 100 mg of ferric saccharate, the infusion time should be at least 15 min. Therefore, the infusion of the solution containing 200 mL (or more) of SS and 200 mg of ferric saccharate should be done within 30–60 min.
- It is important to respect the drug infusion time.
- Respect the interval between applications, which is at least 24 h.
- Respect the maximum dose limit per application, which is 200 mg (two ampoules) and the maximum weekly dose, which is 600 mg.

Main practical guidelines for the use of IV ferric carboxymaltose

Ferric carboxymaltose (FCM) has been available for over a decade and is indicated for the treatment of IDA in various clinical situations. It is an innovative iron complex composed of a core of ferric hydroxide, surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity). After administration, FCM is phagocytosed by macrophages, especially in the bone marrow; maltose is degraded and iron molecules are released to form the intracellular pool of iron in the form of ferritin or destined for erythropoiesis via plasma transferrin. Another important advantage of this product is its convenient dosage, that is, FCM can be administered in high doses (dose of up to 1,000 mg of iron or maximum dose of 15 mg/kg per application) IV in at least 15 min and without the need for a test dose.

Hemoglobin (g/dL)	Total dose of ferric carboxymaltose	
	Body weight >35 and <70 kg	Body weight ≥70 kg
<10	1,500 mg	2,000 mg
≥10	1,000 mg	1,500 mg

- There is no need to perform a test dose before the first infusion.
- Dilute the compound only in 0.9% saline solution (SF), 50–100 and 200 mL for 500 and 1,000 mg of FCM, respectively. Do not dilute in glucose solution.
- Dilute each ampoule (10 mL, 500 mg) in at least 100 mL of saline solution.
- The recommended minimum infusion rate is 100 mg/min. Infusion time is, at least, 6 min for up to 500 mg and 15 min for doses between >500 and 1,000 mg.
- The maximum dose per application should not exceed 1,000 mg (>15 mg/kg body weight) of iron per application.
- Doses >15 mg/kg should be divided into 2 infusions 7 days apart. Do not administer more than 1,000 mg of FCM per week. Therefore, the interval between 2 and 3 applications of 1,000 mg is at least 7 days.
- FCM is for IV use only and should not be administered subcutaneously or intramuscularly.
- Ferinject® 100 mg/mL solution for infusion (5 or 10 mL vial).

Continue...

Table 4. Continuation.

Main practical guidelines for the use of IV ferric derisomaltose

Ferric derisomaltose (FD) is available in Europe and has recently been licensed in the US, Australia, and Brazil. Like FCM, it is an innovative iron complex composed of a core of ferric hydroxide surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity); it can be administered in high doses (maximum allowed dose of 20 mg of iron/kg of body weight). If the total iron dose calculated is >20 mg/kg/weight, the supplementary dose should be performed after ≥7 days.

Hemoglobin (g/dL)	Total dose of ferric derisomaltose	
	Body weight <70 kg	Body weight ≥70 kg
≥10 and<12	1,500 mg	2,000 mg
<10	1,000 mg	1,500 mg

- Whenever possible, administer the total dose in the first infusion as long as it does not exceed the maximum allowed dose (>20 mg of iron/kg of body weight).
- If total dose>20 mg/kg/weight: second dose after ≥7 days.
- Dilution ≥1 mg/mL for stability reasons. For a 500 mg dose, dilute 100 mL in saline solution and infuse the solution in at least 15 min. For doses ≥1,000 mg, dilute 200 mL in saline solution and infuse the solution over at least 30 min.
- Monofer® solution for infusion of 100 mg/mL in packaging containing 1 vial of 5 or 10 mL.

Contraindications to the use of IV iron

- Any type of anemia unrelated to iron deficiency.
- TSAT>45%.
- Serum ferritin ≥500 ng/mL, regardless of TSAT value.
- Patients with acute infection, especially in the presence of bacteremia/septicemia.
- Patients with known hypersensitivity to iron or any component of its formulation.

Warnings and recommendations with IV iron

- The use of IV iron should be done with caution in patients with asthma, eczema, or atopic allergies, especially in those with a past history of moderate-to-severe hypersensitivity reactions, including anaphylactic reactions. In these cases, the use of antiallergic drugs (IV diphenhydramine) and/or corticosteroid therapy (IV hydrocortisone) as premedication is recommended.
- Due precautions must be taken to avoid venous extravasation during drug administration, which can cause local changes such as: pain, irritation, and browning of the skin. If this occurs, administration of the product must be stopped immediately.
- The use of IV iron should be avoided in patients with severe hepatic impairment.
- The use of IV iron should be avoided in pregnant women ≤13 weeks of gestation.
- To date, FCM and FD are not recommended in children or adolescents (<18 years).
- IV oral should not be administered concomitantly with oral iron.
- Regardless of the product used, it is recommended that IV iron be applied in a hospital environment or, preferably, in clinics or infusion units with experience in IV drug administration, by duly trained nursing professionals with medical supervision.
- Observation of the patient for at least 30 min after the end of IV iron infusion is recommended.

When and how to assess response to IV iron treatment

It is recommended to carry out complete blood count, reticulocytes, serum iron, total binding capacity of iron, and ferritin after 4–6 weeks of administration of the total dose of iron calculated for the patient.

IV iron safety profile

- Minor reactions (e.g., headache, symptomatic hypotension, back pain, heartburn, chest tightness, dyspnea, nausea, tachycardia, rash, and vomiting) are due to labile free iron and consist of pressure in the chest or back or facial flushing––symptoms not seen with severe hypersensitivity. Furthermore, premedication with antihistamines can cause somnolence, diaphoresis, tachycardia, and hypotension, which may be attributed to the intravenous iron. Intervention with antihistamines or vasopressors can convert these minor reactions, which usually resolve in minutes without therapy, into hemodynamically significant AEs, ostensibly due to the intravenous iron.
- FCM has a lower risk of hypersensitivity, but a higher incidence of hypophosphatemia, which in most cases is not severe, is temporary and asymptomatic.
- Although very rare, severe hypersensitivity reaction can occur with IV iron.

MANAGEMENT OF IRON DEFICIENCY ANEMIA IN PREGNANCY

The laboratory diagnosis of ID/IDA, including Hb concentration and serum levels of biochemical markers of iron status, and the correct treatment of IDA are relevant, especially during pregnancy (Figure 3).

MANAGEMENT OF PREOPERATIVE IRON DEFICIENCY/IRON DEFICIENCY ANEMIA

Iron repletion is an important component of patient blood management (PBM), a multidisciplinary strategy that aims to conserve blood and optimize the use of blood products by

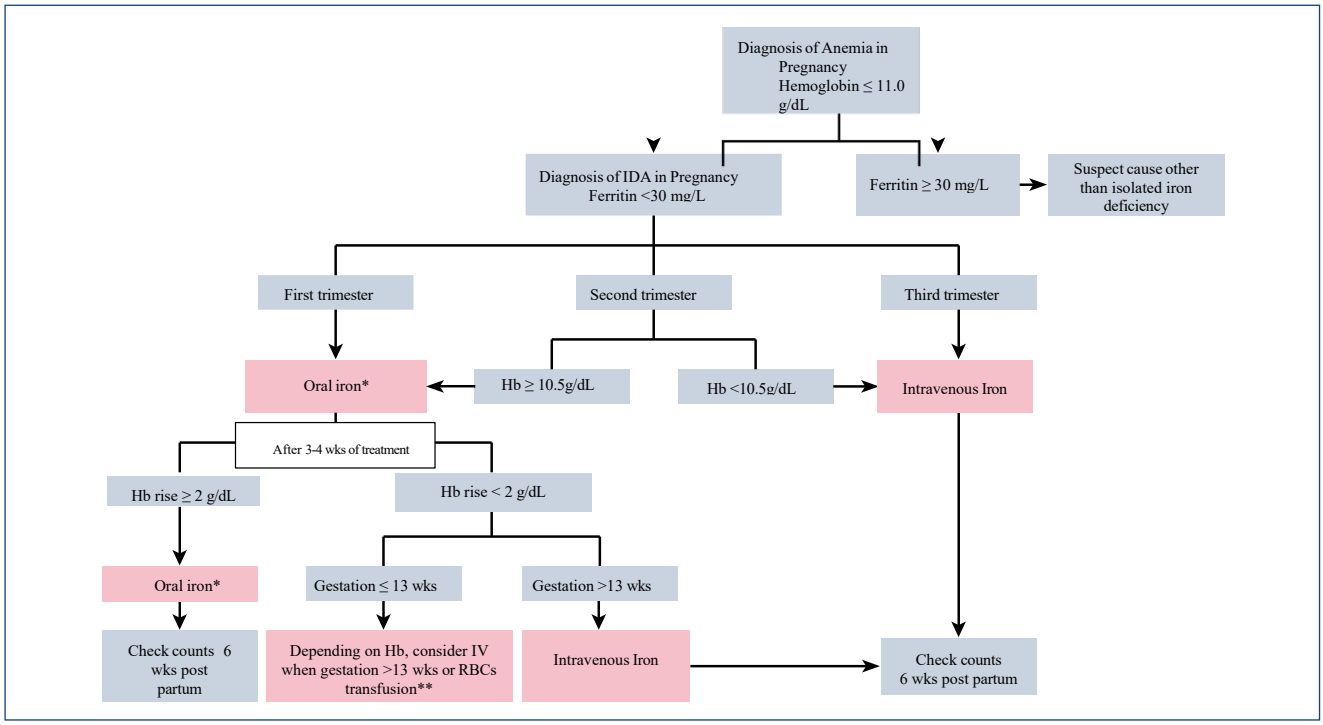

Figure 3. Algorithm of suggested approach to diagnosis and management of iron deficiency anemia in pregnancy. Modified from Achebe et al.[9] *Oral iron treatment (doses up to 100 mg of elemental iron, prescribed once a day, daily; or doses >100–200 mg of elemental iron, prescribed alternate-day regimen) should not be interrupted once hemoglobin >11 g/dL is achieved, but rather supplementation should continue to replenish iron stores (Ferritin >30 ng/mL), generally for at least 2–3 months, and until 6 weeks postpartum). **Red blood cells transfusion for severe iron deficiency anemia should be restricted for cardiovascular compromise and/or debilitating symptoms, when a rapid correction of anemia is clinically required.

optimizing and preserving the patient's own blood. Recently published recommendations from the 2018 Frankfurt Consensus Conference on PBM highlighted the importance of (1) early detection and management of preoperative anemia, given its recognized associations with poor outcomes, including mortality, and (2) use of iron supplementation in adults with IDA who are awaiting elective surgery. The care of women with HMB would involve treatment of the underlying cause of the excessive bleeding and minimize blood loss in the perioperative setting[35].

CONCLUSION

- ID and IDA are the most debilitating nutritional deficiencies worldwide in the twenty-first century, affecting almost a third of the global population, particularly among women of all ages, with potentially serious and long-lasting consequences.
- Although ID is by far the most common cause of anemia, laboratory evaluation and etiological cause investigations are fundamental for a definitive diagnosis of ID and IDA in order to provide appropriate treatment.
- Oral iron supplementation remains the first-line therapy for both prophylaxis and treatment of ID/IDA.
- IV iron administration is currently more widely used as a result of the improved safety profile and high effectiveness of last-generation compounds.

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REVIEW ARTICLE

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Homeopathy and women's health: gynecology and homeopathy

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INTRODUCTION

The repository of knowledge accumulated by Samuel Hahnemann, in the "Organon of the Art of Healing," contains the principles that underlie the homeopathic therapeutic method[1]. This medical practice, which deals with the law of similarity, has been constantly researched and improved by many followers in light of the evolution of new knowledge brought by various branches of science, such as physiology and pathophysiology, and more recently by a systemic approach to being[2].

The binomials of health and disease are different states (or, in the systemic understanding, instabilities) of the same process. The disease is dynamic and may represent different degrees of system instability that can take the form of injury, death, or a balance with cognitive gain[3].

Homeopathy, as a therapeutic capable of promoting these instabilities by similarity and aiming at cognitive gain, becomes increasingly active, either in the promotion or in the prevention of imbalances in the woman's biopsychosocial system, rescuing her self-care[4].

The prevention of women's instabilities in the various stages of their biological evolution (puberty, reproductive maturity, climacteric, and menopause) is possible through the balance (homeostasis) and maintenance of self-regulation (also called life force) of all systems involved in this process[1]. The main purpose of this study was to present to medical colleagues some updated themes of women's health, aiming at a "new approach" through more than 30 years of experience with the Homeopathy Clinic of the Hospital do Servidor Público Municipal de São Paulo (HSPM) and in private practice.

THE WOMAN AND HER COMPLEXITY

Globally, healthcare systems traditionally choose to approach women from a reproductive point of view, focusing on prenatal care, childbirth, and the puerperium, including reproductive planning. Despite the social and epidemiological relevance of this approach, comprehensive care for women and their demands and needs is still in the consolidation phase[5]. For this, knowledge on the biological and physiological processes of women, linked to the understanding of their interests and individualization of the person, is necessary, from health promotion and prevention, through screening and early detection of prevalent diseases, to the prevention of damage and unnecessary care—the quaternary prevention[6]. Understanding these processes instead of simply stimulating or blocking them is fundamental to the application of homeopathy as individual cognitive, biological, and psychic therapy and therefore integral.

The menstruation cycle is one of the most important biological markers for women. It involves endocrine, paracrine, and autocrine phenomena, as well as a complex integration of the hypothalamus-pituitary-ovary axis and other organs such as the thyroid, adrenals, liver, and kidneys, in addition to psychic balance[7].

The process of ovarian depletion begins during intrauterine life and continues until menopause. The phenomena of recruitment, selection, and follicular atresia occur continuously throughout life[8]. This inevitable loss of follicles leads to a decrease in what Hertig defined as "ovarian capital[9]." Therefore, puberty/menarche (1st menstruation) and climacteric/menopause (last menstruation) are important phases in a woman's life[7].

After the fertile period, at around 35–40 years of age, a special and long period begins, called the climacteric, where numerous physiological and physiopathological hormonal instability can occur, coinciding with multiple systemic changes, mainly in the glandular metabolism[8]. In homeopathy, this is understood as the transition between the sanguine temperament (hormonal-rhythmic) and the biliary temperament (increased catabolism)[10]. These reproductive hormones will be gradually replaced by countless others that are more adequate and adapted to the new paths of women. The previous climacteric culminates with

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menopause, the last menstruation around 48–52 years of age, a milestone between the reproductive and nonreproductive systems. The greatest clinical evidence observed in the daily practice of gynecology care with homeopathic treatment according to the model of Systemic Classical Homeopathy is the long-term demedicalization of these patients, avoiding treatments based exclusively on hormone replacement that often have abusive and non-exempt side effects, and ignoring quaternary prevention[6,11].

VIEW OF CLASSICAL SYSTEMIC HOMEOPATHY ACCORDING TO CARILLO JR'S COMPLEX SYSTEMS MODEL

Several theories have emerged based on the physiology and pathophysiology of integrated systems, for example, Pavlov's (1849–1918) conditioned reflex theory and Anokhin's (1935) functional systems theory—dynamic and self-regulating organizations. According to both the studies, the properties of the parts can only be understood within the context of the broader whole[3]. The evolution of thought by organismic biologists in the early 20th century led to the gradual transformation of the idea of function into that of organization, representing a change from the mechanistic bases of physiology to systemic ones.

The logic of the systemic conception replaces the linear understanding of cause and effect with the understanding of the effect as a result of a dynamic web of interrelated events. "The world thus appears as a complicated fabric of events, in which connections of different types alternate, overlap or combine and thereby determine the texture of the whole[12]."

The systemic thinking focuses not on basic building blocks but on basic organizing principles. Subatomic particles are not "things" but connections between things, and these in turn are interconnections between other things, and so on. In quantum theory, we never end up arriving at some "thing"; we always deal with interconnections. The perception of the living world as a network of relationships led to thinking in terms of networks. In this way, there is no prevalence of the physical structure, either at an organic or subatomic level, over the organizational pattern, since it itself is the physical embodiment of this pattern[3].

Likewise, the organizational pattern depends both on the innate memory and on the knowledge acquired through the cognitive process for building different action programs, which is the basis of the so-called vital process[1]. Therefore, the life process cannot be fixed—it has to evolve along with the structure. It is at the base of autopoiesis, cognition, and adaptation—improving as it faces health determinations, whether social or related to the physiological development of women[4]. Therefore, the best homeopathic medicine would be one that, in accordance with these assumptions, would offer women the balance (homeostasis) necessary for the development of their self-knowledge and self-care in the face of constant variations and instabilities as parts of life thus understood[3].

HOMEOPATHIC TREATMENT IN WOMEN'S HEALTH

Systemic Classical Homeopathy, according to Carillo Jr's Complex Systems Model, is based on pathogenesis, i.e., experimentation and observation of the healthy and sensitive human being[13], a true treatise on human pathophysiology; it is constantly evolving with new concepts and research developed at the Brazilian Association of Recycling and Assistance in Homeopathy (ABRAH) after the introduction of this model[14]. Such a model is fundamental for the prevention and treatment of the physiological instabilities inherent to women, leading to the balance of the entire system in a quick, smooth, and lasting way in all stages of their lives[3].

In the systemic approach to the patient, in addition to the anamnesis and thorough and investigative physical examination, where each general and particular acute and chronic symptom is exhaustively modalized, individualization also includes biotypology. The biotypological understanding corroborates the attempt to predict the tendencies of the neuropsychoimmunoendocrine axis[10]. Another aspect of individualization is the understanding of temperaments, which are nuances of the phases of biological life—lymphatic (childhood), blood (reproductive), biliary (climacteric/menopause), and atrabiliary (senility)—as well as the diagnosis of diatheses (syndromic tendencies), which are essential as personal and hereditary causalities, therefore guiding the choice of systemic treatment in this view[11].

The woman's homeopathic care flowchart is then based on anamnesis, physical examination, prioritization of instabilities, intrinsic and extrinsic, acute/chronic causes, and repertorization of the main symptoms[8], relating them to the diathesis (chronic health disorder) to be treated. The dynamic conception of the health-disease process imposes an equally dynamic model on the healing process. The dynamic character of homeopathic medicines can only be revealed through the symptoms observed in the experimentation on healthy individuals. Therefore, the reproduction capacity of the pathophysiological picture of a medicine (artificial disease) demonstrates its healing power, which is the foundation of therapy for similar conditions[1]. Therefore, the medicine capable of reproducing in healthy women, the symptoms that we intend to treat in those who are in instability, becomes the appropriate medicine

for them, so that they then start to develop means of rebalancing themselves, which is similar to the injured individuals who have benefit from physiotherapy, which does nothing more than reproduce in these individuals the same movements (in a smooth and lasting way) that caused their injury by reconditioning them. In both cases, we can state, in a comprehensive way, that the so-called cognitive gain was observed[3].

Below are examples of practical applicability of homeopathic treatment in promoting women's health.

ACUTE AND CHRONIC MUCOSAL INSTABILITIES––VULVOVAGINITIS

It is every inflammatory and/or infectious manifestation of the lower genital tract generally related to deficiency IgAs (secretory immunoglobulin A), mainly in puberty and adolescence. It can occur with secondary contamination, which corroborates the possibilities of intrinsic causality (chronic tendencies of illness—diathesis) and/or extrinsic causality (contaminations with microorganisms)[15].

In the anamnesis, it is important to search for the characterization of the secretion in terms of volume, color, odor, duration, and its relationship with the menstrual cycle; related symptoms such as burning, itching, vulvodynia, dyspareunia, dysuria, frequency, hyperthermia, and pain in the lower abdomen should also be investigated. Here are examples of homeopathic remedies that cover the main symptoms of vulvovaginitis (Table 1).

ACUTE AND CHRONIC INSTABILITIES OF THE MENSTRUAL CYCLE––MENSTRUAL DISORDERS

Whether in adolescence (menacme), where the hormonal cycle is still irregular, leading to equally irregular cycles, or in the climacteric, where the decrease in hormone secretion also generates irregularities, conditions such as anovulation, dysmenorrhea, water retention, and the premenstrual tension syndrome are commonly present[7]. Aside from the possibility of hormone replacement and stimulation of physical activity, less can be done with conventional therapy. However, such conditions find important applicability in homeopathy, in accordance with the adequate individualization of the symptoms, as shown in Tables 2 and 3.

Table 1. Main drugs in vulvovaginitis[16].

Drug	Symptoms
Hydrastis canadensis	Acts in a generalized way on the mucous membranes, altering the natural secretions. Excoriating discharge with vulvar itching.
Kali bichromicum	Irritation of the mucosa with a tendency to ulcerations.
Lamium album	Leukorrhea in girls with early menarche.
Cubeba	Inflammatory irritation of the mucous membranes, with urethritis––vaginitis
Calendula	In inflammatory processes, it eliminates pain and suppuration, favoring phagocytosis and accelerating healing, and promoting normal granulation. True homeopathic antiseptic.
Aletris farinosa	Drainer of the genital mucous membranes.
Borax	Digestive and gynecological disorders with thrush, discharge and dysmenorrhea.
Kreosotum	Cervicitis, metritis, and vaginitis. Ulceration and intense irritation; bleeding cervix injury.

Table 2. Principal medications in menacme[16].

Drug	Symptoms
Pulsatilla nigricans	Tuberculin and phosphoric girls with delayed puberty.
Actea racemosa (Cimicifuga)	Premenstrual tension syndrome (PMT) menstrual irregularity, dysmenorrhea, and characteristic headaches.
Ignatia amara	PMT, PMDD (premenstrual dysphoric disorder-DSM-V, 2013)––neurovegetative disorders of the menstrual cycle.
Magnesia phosphorica	Proiomenorrhea and pre-menstrual dysmenorrhea.
Chamomilla	Hypermenorrhagia; dysmenorrhea; PMT with hypersensitivity and irritability.
Sabina	Hypermenorrhagia and dysmenorrhea with characteristic pain.
Drymis	Emergency medicine in uterine bleeding.
Folliculinum and Oophorinum	Organotherapeutics, important in menstrual cycle disorders.

Table 3. Important medications in climacteric and menopause[16].

Drug	Symptoms and diathesis
Lachesis	Climacteric pre- and post-menopause, with gynecological, extra-gynecological, neurovegetative symptoms, and pluriendocrine and metabolic dysrhythmias.
Sulfur	Diathesis psoric––plurimetabolic syndrome. Hypertension and diabetes (type II) that worsen in the climacteric. Congested with oppression.
Actea racemosa (Cimicifuga)	Action on the nervous system (central and peripheral) related to pelvic disorders. Mental imbalance related to genitourinary disorders triggered by menstruation or its suppression.
Aurum metallicum	"Cyclothymic" psychic states, neurovegetative with cardiovascular repercussions, aggravated in climacteric and menopause.
Phosphorus	Climacteric with bleeding tendencies. Digestive and respiratory neurovegetative disorders.
Sepia	Vasomotor and hepatic neurovegetative disorders; neuropsychic disorders––hyposthenicity (dejection, sadness).
Thuya occidentalis	Neuropsychiatric hyperintensity, fixed ideas, intense anxiety, and palpitations. Tumors (fibroids, polyps).
Sulphuricum acidum	Very close to sulfur with great exhaustion due to hypermenorrhagia. Neurovegetative disorders––hot flashes with cold sweats.

CONCLUSION

When we observe, listen, and treat women systemically, we really get emotional. She was given the gift of containing a reproductive system, which is highly specialized and complex, the only one capable of exercising the sublime role of gestation. However, beyond the reproductive purposes, the systemic and complex view of this same woman points us to a break with limiting beliefs, allowing the awakening of her feminine energy to be able to promote healing, connection, and empowerment. In other words, this would be the ultimate mission of homeopathy, which, by promoting the balance of the vital force of that same woman, respecting her choices, and endowing her with reason, would allow her to fulfill the "highest ends of existence[1]".

ETHICAL ASPECTS

All the authors are, at the moment, teaching in the postgraduate and updating courses in Homeopathy of the Brazilian Association of Recycling and Assistance in Homeopathy (ABRAH), accredited school of the Brazilian Medical-Homeopathic Association (AMHB), on a voluntary basis, and declare that they have no conflict of interest with other institutions.

AUTHORS' CONTRIBUTIONS

MLHM: Conceptualization, Supervision, Writing – review and editing. **DJVC:** Conceptualization, Supervision, Writing – review and editing. **ISDT:** Conceptualization, Supervision, Writing – review and editing.

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REVIEW ARTICLE

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18F-fluoroestradiol positron emission tomography in patients with breast cancer: a systematic review and meta-analysis

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Brazilian Society of Nuclear Medicine

INTRODUCTION

Breast cancer is a neoplasm that most commonly affects women worldwide, with an estimated 1.68 million new cases per year. According to the National Cancer Institute in Brazil, 73,610 new cases of breast cancer are estimated for the 3-year period from 2023 to 2025, which is the main cause of cancer mortality in females[1]. Despite the high 5-year survival rate of up to 89.5%[2], the potential for metastasis through the bloodstream and lymphatic vessels can lead to severe consequences if not detected and treated early.

The National Comprehensive Cancer Network guidelines highlight the estrogen receptor (ER) as a crucial prognostic indicator for breast cancer patients' disease-free survival and overall mortality[2]. The presence of ERs and progesterone receptors is an important factor influencing treatment strategies and patient prognosis[3]. Furthermore, hormone receptor-positive breast cancers exhibit higher survival rates and lower recurrence rates than hormone receptor-negative tumors[4].

Testing for hormone receptors is vital for breast cancer patients to determine their prognosis and treatment options. However, the invasive nature of the biopsy limits its effectiveness, and the variations in receptor status among primary and metastatic sites make it challenging to plan treatment for patients with recurrent and/or metastatic breast cancers[5,6].

Noninvasive tests like 18F-fluoroestradiol (FES) positron emission tomography-computed tomography (PET-CT) can evaluate estrogen distribution and binding in several sites and confirm metastasis simultaneously, making it an effective tool to predict treatment response in breast cancer patients[3,5,7]. To confirm the effectiveness of 18F-FES PET-CT in predicting treatment response, we conducted a pooled analysis of its diagnostic accuracy reported to date, despite predictions of previous studies.

METHODS

Bibliographic search

A systematic review was performed in accordance with Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines[8,9].

We performed a comprehensive literature search of PubMed and the Cochrane Library without date restriction up to February 16, 2023, using the following MeSH vocabulary keywords and free text words: ((((((18F-FES) AND (PET-CT)) OR (FLUOROESTRADIOL F18)) OR (18f-FLUOROESTRADIOL)) OR (FES F18)) OR (FLUOROESTRADIOL)).

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Inclusion and exclusion criteria

Patients: Those diagnosed with breast cancer.

Index text: 18F-FES-PET.

Target condition: Diagnostic, staging, restaging.

Study design: Diagnostic accuracy cross-sectional study with prospective or retrospective recruitment.

Exclusion criteria: Case reports, animals, phantom, and radiopharmacokinetics.

No language or sample-size restrictions were used.

Reference standard

A composite standard including clinical follow-up and histopathological findings.

Outcome measures

The outcome measures included identification of predictors of 18F-FES-PET positivity, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy.

Study selection

Titles and abstracts retrieved by the bibliographic search were independently screened by two authors (M.C.S. and R.P.C.). The full text of all relevant articles was acquired, and the study was further assessed for inclusion independently by the same two authors and studies not fulfilling the inclusion criteria were excluded.

Quality assessment

Studies were independently assessed by two authors (M.C.S. and R.P.C.) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist tool[10]. The QUADAS-2 tool assesses four domains: risk of bias in patient selection, index test, reference standard, and the timing of reference test. Each paper was scored independently by two evaluators (M.C.S. and R.P.C.) and discrepancies were resolved.

Data extraction

The following information was extracted from each study: sample size, age, indication for PET (diagnosis, primary staging, or recurrent disease staging), previous therapies, initial cancer stage, 18F-FES-PET characteristics, rates of positive PET, and histopathological correlation data. When histopathological correlation data were available, the numbers of true positives, false positives, true negatives, and false negatives were collected as appropriate. Using 18F-FES-PET for both primary staging and recurrent cancer staging, the extracted data were displayed separately when available.

Extracted data were collected using Excel 2007 (Microsoft Corporation, Redmond, CA, USA), and analysis was performed using Meta-Disc 1.4[11]. The detection rates were pooled using the generic inverse variance approach in the random-effects model[12]. Heterogeneity in the meta-analysis of detection rates was assessed using the X^2 statistic in the I^2 statistic[9]. The I^2 statistic indicates the percentage of the overall variability that can be attributed to between-study (or inter-study) variability, as opposed to within-study (or intrastudy) variability. An I^2 greater than 50% is considered to indicate substantial heterogeneity[9].

We explored the variability in diagnostic accuracy across studies by plotting the estimates of the observed sensitivities and specificities in forest plots and in receiver-operating characteristic (ROC) curve space. Whenever data for computing true-positive, false-negative, true-negative, and false-positive rates were available, we performed meta-analyses using the bivariate model to produce summary sensitivities and specificities[11]. The bivariate model jointly models sensitivity and specificity, specifying their logits as random study effects; a summary of the ROC curve can be derived from the model parameters. The significance level was set at p=0.05.

RESULTS

Identification of studies

Figure 1 summarizes the process of identification and selection of studies. A total of 248 studies were identified. The electronic search was complemented by manually checking the reference lists in review papers and all included studies. Overall, we included 24 studies comprising a total of 664 patients (range: 10–90 patients per study): 23 studies on diagnostic[6,13-28] and 1 study on staging[29]. Figure 2 shows the QUADAS-2 results.

A total of seven studies were reviewed for the diagnostic accuracy, in which the sensitivity ranged between 0.700 and 0.963 and the specificity ranged between 0.500 and 0.987. The pooled sensitivity and specificity of the method were 0.824 (95% confidence interval [CI] 0.763–0.874; i^2=0.1%) and 0.938 (95%CI 0.861–0.980; i^2=42.2%), respectively (Figure 3). The pooled-positive likelihood ratio was 4.13 (95%CI 1.61–10.62; i^2=62.9%) and the negative likelihood ratio was 0.25 (95%CI 0.18–0.35; i^2=0.0%).

The statistical correlation of 18F-FES PET-CT was analyzed in 11 studies with immunohistochemical essays, and it did not correlate significantly (r=0.76; p=0.12). Similar results were revealed in two articles that correlated the examinations with the tumor size (r=0.30; p=0.32).

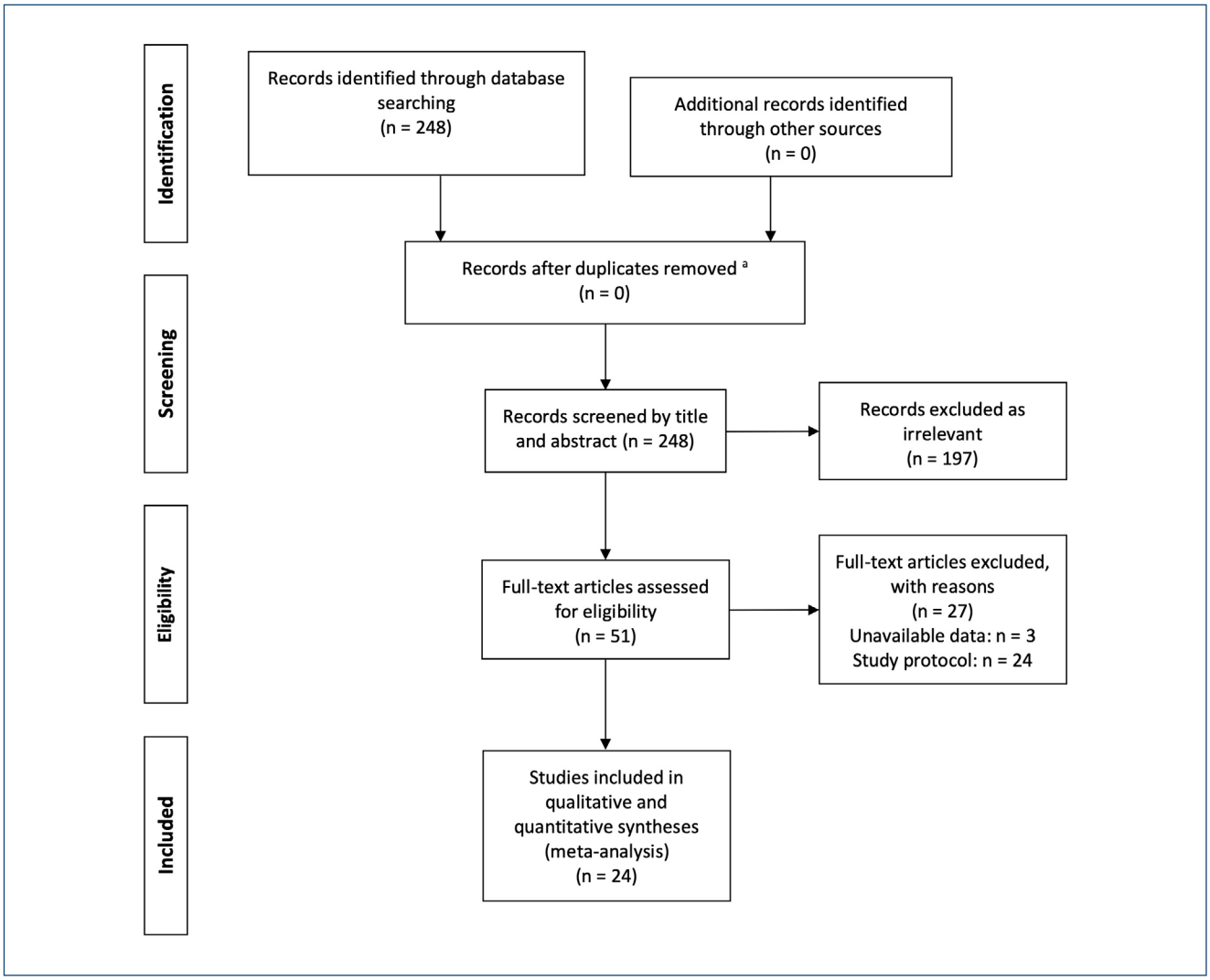

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis flowchart, demonstrating the studies selection criteria.

One article compared the sensitivity of 18F-FES PET-CT and 18F-fluorodeoxyglucose (FDG) PET-CT in the evaluation of breast cancer recurrence[30]. A total of 40 patients were ER-positive. Using a threshold for positive interpretation, the sensitivity of 18F-FES was 71.1% and that of 18F-FDG was 80%, with no significant difference between the methods (p=0.48).

Initial staging was evaluated by two studies[29,31]. Liu et al., reported a sensitivity of 90.8% for 18F-FES and 82.8% for 18F-FDG in a retrospective study with 19 patients. 18F-FES PET-CT changed patient management in 26.3% of the cases. On the contrary, Gupta et al., in a prospective study with 10 patients, reported a sensitivity of 75.32% for 18F-FES and 92.21% for 18F-FDG (p=0.0004). Excluding liver lesions, the sensitivity of 18F-FES was 85.29% and that of 18F-FDG was 91.18% (p=0.2159). Management was changed for 20% of the patients.

DISCUSSION

18F-FDG PET imaging is a well-known and established diagnostic tool for staging/restaging patients. However, some breast tumors may have low FDG uptake, such as invasive lobular carcinoma (ILC). Other molecular imaging methods may be needed for the evaluation of this malignancy. ILC is nearly always (95%) ER-positive, thus ER-targeting PET tracers such as 18F-FES may have value[5]. 18F-FES is a recently available radiotracer in Brazil that can help to noninvasively assess whole-body ER protein expression and ligand binding function across multiple metastatic

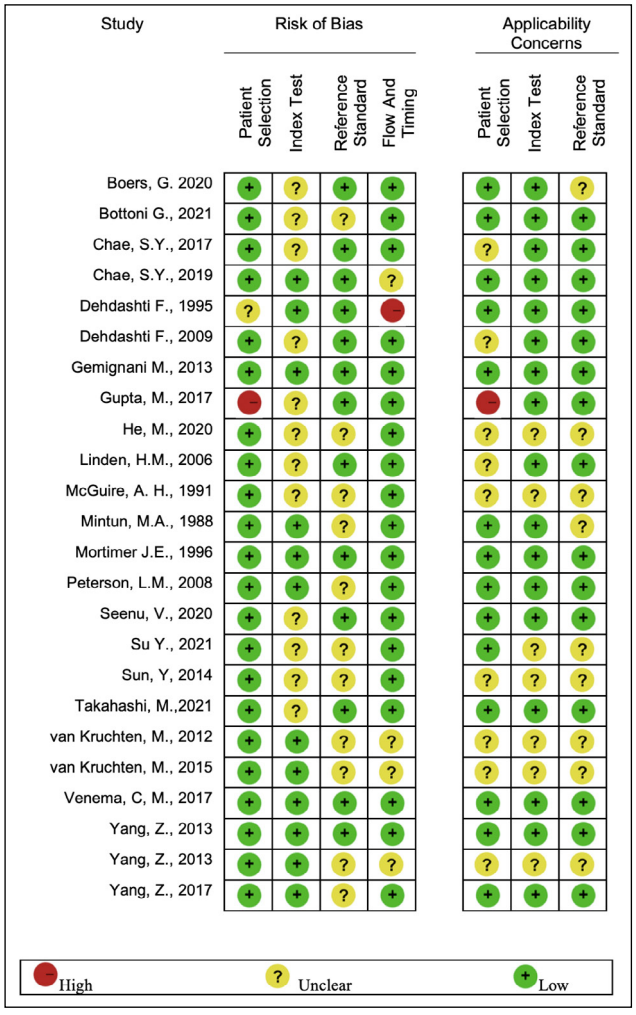

Figure 2. Quality Assessment of Diagnostic Accuracy Studies-2 results.

sites, demonstrate intertumoral and temporal heterogeneity of ER expression, quantify the pharmacodynamic effects of ER antagonist treatment, and predict endocrine therapy response.

With respect to the effectiveness of 18F-FES PET, diagnostic accuracy for the detection of lesions was evaluated in this pooled analysis, with a pooled sensitivity of 82% and a pooled specificity of 94%, resulting in a pooled AUC of 0.8899, thus demonstrating high diagnostic accuracy.

Immunohistochemistry sample analysis is the golden standard for the evaluation of ER expression. Amidst the included studies, eight perceived the correlation between the ER expression in immunohistochemistry and 18F-FES uptake, resulting in a pooled correlation of 0.76, with no significant heterogeneity, but not demonstrated statistical significance (Q=11.46, p=0.12, I^2=39%, despite a LFK index of -2.66, showing a major asymmetry).

The correlation between tumor size and 18F-FES uptake was only assessed in two studies, which differ largely in weight, with a positive correlation between size and uptake of 0.30, with no significant heterogeneity, but not demonstrated statistical significance (Q=0.95, p=0.33, I^2=0%). It is important to emphasize the small number of studies included in the analysis.

As the number of breast cancer patients seems to rise year by year, so does the drug options to treat the most variable cancer presentations[31]. For that, 18F-FES PET imaging might be a good option, allowing a correct evaluation of the ER status in vivo, noninvasively and painlessly, especially considering that the presence of metastases is one of the prognostic factors of the disease and the invasive biopsy in the bone, liver, and brain is often difficult. Furthermore, 18F-FES PET imaging can evaluate the whole body and show some heterogeneity in ER expression between the lesions (which is usually not assessed on a single lesion biopsy)[32].

A PET scan using 18F-FES may also be helpful for the interim therapy evaluation of patients under specific therapies, proving ER blockade, and then helping to choose more accurate therapies.

CONCLUSION

Current evidence suggests that 18F-FES PET for the detection of ER-positive lesions in breast cancer patients is sensible, with a pooled sensitivity of 82%, and highly specific, with a pooled specificity of 94%, demonstrating its high diagnostic accuracy, with a pooled AUC of 0.8899. This brings to light its potential to be added to the breast cancer toolbox as an imaging tool for therapy guiding and predicting the endocrine therapy response.

AUTHORS' CONTRIBUTIONS

CSM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FARFBC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **PHRC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CESS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration,

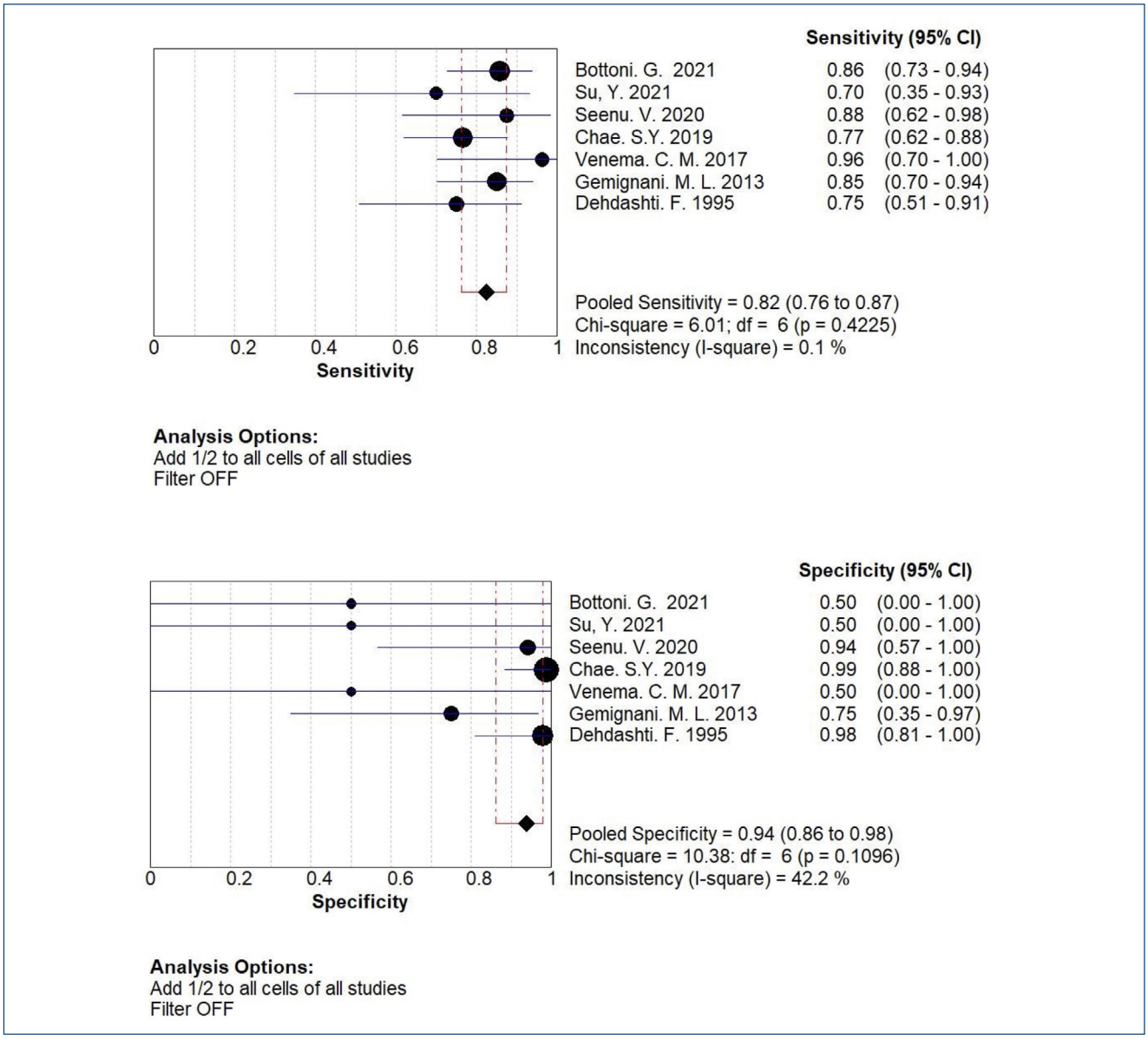

Figure 3. Pooled sensitivity and specificity.

Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DFR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DBP:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FDK:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MMS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SALS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RWL:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Kidney diseases in women: difference in risks and opportunities

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INTRODUCTION

Gender differences in access to healthcare and education persist and negatively affect women in different regions of the world. This is also true in the context of chronic kidney disease (CKD), a condition that affects approximately 10% of the adult population worldwide[1].

In this article, we will address some of the kidney diseases that predominantly affect women, the peculiarities of renal involvement during pregnancy, as well as the differences between genders observed in treatment approaches, especially in renal replacement therapy (RRT). Knowledge about such features can contribute to better planning of health care for the general population.

CHRONIC KIDNEY DISEASE

Chronic kidney disease represents a heterogeneous and frequent group of kidney diseases associated with high morbidity and mortality. In women of reproductive age, the prevalence of CKD ranges from 0.1 to 4.0%, and although relatively low, the implications of pregnancy in this context are various and can be severe. Based on the glomerular filtration rate (GFR), CKD is divided into five stages[2], and the worse the kidney function, the greater the chances of an adverse outcome in the health of the pregnant woman and the newborn. The risk is greater for women on dialysis treatment.

The hemodynamic changes observed in normal pregnant women make it difficult to identify CKD during pregnancy. Increased blood volume, decreased systemic vascular resistance, and increased cardiac output determine glomerular hyperfiltration[3], expressed by a 50% increase in GFR (serum creatinine in the normal range: 0.4–0.6 mg/dL) and a slight increase in proteinuria (the threshold for elevated proteinuria in pregnancy has been set at a higher level of 300 mg/day). Considering that the estimated GFR (eGFR) is not validated in pregnancy, the current recommendation is to assess GFR through serum creatinine.

In the context of CKD and pregnancy, the adverse clinical impact may be of pregnancy on renal function and kidney disease in pregnancy. Pregnancy potentially accelerates GFR loss and shortens the time required for RRT. The risk of deterioration of renal function is greater if the CKD is more advanced in early pregnancy, the worse is the control of blood pressure (BP) and when proteinuria >1.0 g/day. On the contrary, compared to pregnancy in the absence of kidney disease, CKD can contribute to adverse outcomes for both the pregnant woman and her newborn, the most important being preeclampsia (PE), prematurity, low birth weight, and fetal or neonatal mortality[4].

Pregnant women with CKD should be accompanied by a team composed of an experienced obstetrician and nephrologist. Every woman with CKD should receive pre-pregnancy guidance on potential risks related to the progression of kidney disease, pregnancy complications, and adverse fetal outcomes. Planned pregnancy allows women to become pregnant at the right time, take the necessary medications to treat the different causes and complications of CKD, and permit pregnancy in better health conditions without adverse outcomes.

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GLOMERULAR AND OTHER RENAL DISEASES

In the context of kidney diseases that predominate in women, lupus nephritis certainly stands out, as systemic lupus erythematosus (SLE) presents across all ages, in a female-to-male ratio that ranges between 8:1 and 15:1, being higher in childbearing age[5]. Lupus nephritis occurs in up to 60% of patients with SLE and is one of the more severe manifestations of such disease, which is particularly associated with significant morbidity and mortality[6]. In fact, 10–20% of the affected patients will progress to end-stage kidney disease (ESKD) after 10–15 years[7].

Other autoimmune diseases with renal involvement like rheumatoid arthritis and Sjögren syndrome are also more frequent in women. Rheumatoid arthritis is associated with different renal lesions, such as glomerular diseases, secondary renal amyloidosis, and acute and chronic tubulointerstitial nephritis[8]. Renal involvement in Sjögren syndrome is not uncommon, corresponding predominantly to tubulointerstitial nephritis, which may lead to renal tubular acidosis and precede other complaints.

Additional conditions that favor the development of CKD and are frequent in females are recurrent urinary tract infection in childhood that can cause renal damage, as well as recurrent adult pyelonephritis[9].

HYPERTENSION AND CARDIOVASCULAR DISEASES

Hypertension (HTN) is the most common modifiable risk factor for cardiovascular disease (CVD) and the leading cause of morbidity and mortality in women worldwide. Biological differences in HTN and CVD between men and women, a consequence of genetic, epigenetic, and sex hormone-mediated factors, are multifaceted and incompletely understood[10]. There is limited evidence on specific sex differences in HTN and CVD, despite gender-related heterogeneity, which can be proven by the absence of any differentiation in managing HTN and CVD between males and females in the Brazilian and International Guidelines[11,12].

Young women are relatively safeguarded from developing HTN and CVD by the endogenous vascular protective effects of estrogen. As estrogen goes down in premature ovarian failure, premenopausal, and after menopausal period, women develop HTN and the associated organ damage. There is a twofold increase in the risk of HTN, with a prevalence of 75–80% in postmenopausal women in the USA, and HTN rates are higher in women aged >65 years than men[13].

Hypertensive women are older and have, besides the well-known risk factors for CVD, more nontraditional variables to be considered such as autoimmune diseases, breast cancer treatment, gestational diabetes, depression, and psychological stress. Women also have singular forms of HTN such as pregnancy-related disorders, polycystic ovarian syndrome, and the use of contraceptive agents during reproductive age[14,15].

Measuring BP correctly, in office, at home (HBPM), or ambulatory (ABPM), is recommended for diagnosis, control, and treatment. Considering ABPM, women are less likely to experience nondipping patterns at younger ages, but, as they age, white and masked HTN appear, and similar findings are compared to those of men in daytime and nighttime BP.

Despite the negative impact on cardiovascular outcomes in women, BP thresholds for diagnosis and treatment, BP targets, lifestyle modifications, and antihypertensive medications for women are the same as for men, with rare exceptions because of pregnancy and sex-specific adverse effects of some antihypertensive drug classes. Thereby, renin angiotensin system blockers and mineralocorticoid receptor antagonists are contraindicated in women of reproductive potential because of the risk of fetal abnormalities; there is a greater chance in women to develop an ACEI-related cough, and more commonly they experience calcium channel block side effects[15].

Hypertension and CVD must be managed with appropriate lifestyle modifications and a personalized pharmacotherapy approach that effectively lowers BP, prevents CVD, and minimizes adverse effects. There is a need for HTN and CVD studies designed for sex-specific analysis to understand the phenotype of women at increased risk (Table 1)[14,15].

PREECLAMPSIA

Functional and anatomical adaptations during pregnancy are even more pronounced when associated with PE. It is known that the relative risk for the development of ESKD could be increased with each PE experience and its severity[16].

Women with pregnancy-induced HTN syndrome (versus normal pregnancy) show a higher incidence of obesity, metabolic syndrome and HTN, earlier onset of HTN, higher estimated vascular (Framingham Risk Score), and lower eGFR. Therefore, the history of PE should be followed later in life to reduce risks and allow early detection of CKD[17].

Despite the importance of the known association between CKD and PE, not many scientific societies emphasize the need for renal evaluation after PE or at the beginning of prenatal care, which could allow diagnosis of a previous CKD or detection of its risk factors (Table 2)[18]. The prevalence of CKD not previously

known in patients experiencing PE is about 20%[19]. Women who had PE present a higher frequency of developing microalbuminuria 5 years postpartum or persistent proteinuria 3–6 months postpartum, thus increasing their risk for CKD and renal biopsy[20].

DIALYSIS

Even though CKD is more prevalent among women, about 60% of dialysis patients in Brazil and worldwide are men. Studies suggest that the reduction of renal function usually happens faster in men. Women seem to have a healthier lifestyle and adhere more easily to the dietary restrictions needed to control CKD progression when compared to men. Furthermore, some studies suggest an antifibrotic protective effect of estrogen in the kidneys, while testosterone seems to have an opposite pro-fibrotic, pro-inflammatory effect[21]. Another important factor that must be considered is the probable overdiagnosis arising from the use of some eGFR formulas in women.

Women start dialysis with a slightly lower GFR and are, on average, 1–2 years older than men. The choice of dialysis modality does not differ between men and women, with hemodialysis being the most commonly used method worldwide[21]. The percentage of women who start dialysis using catheters is slightly higher than that of men[22].

The adequacy of dialysis is another factor that should be carefully evaluated in women. Since urea distribution volume (V) is regarded as a constant for every individual, Kt/V overestimates dialysis adequacy among women, considering that V is a replacement for lean body mass[23]. For a similar reason, women are often overtreated for anemia. Despite a general acknowledgment that women have lower hemoglobin levels than men, the guidelines for anemia in CKD patients employ the same parameters of hemoglobin to define anemia in men and women, as well as recommend the same therapeutic target[24]. This situation certainly justifies a tendency of women needing higher doses of erythropoietin when compared to men.

Finally, women on dialysis have more frequent and severe symptoms and also need more time for post-dialysis recovery than men[25]. Men on RRT have greater family support than women—situation explained by socially determined gender roles; therefore, it is more frequent to find men cared for by their wives and relatives than the other way around[26].

Table 1. Women and cardiovascular disease.

Sex-specific risk factors under-recognized	Traditional risk factors poorly considered	Lifestyle modification early on: Life's simple 7 must be done!
Prematurity	Hypertension	Blood pressure management
Age at menarche (≤10 years)	Hypercholesterolemia	Lipids control
Polycystic ovarian syndrome	Metabolic syndrome	Control weight (normal body mass index)
Contraceptive use (type, duration)	Diabetes	Reduce blood sugar
Gestational diabetes	Smoke	Stop smoking
Premature ovarian failure/menopause		Become and remaining active. Exercise 150 min/day
Gestational hypertension, especially pre-eclampsia		Healthy diet
Delivery small for gestational age infant	**Key points** • Cardiovascular disease is poorly diagnosed • False perception that women are at low-risk population: reduced awareness and there is a need for reconsideration this bias of recognition • Knowledge barriers: lack of specific evidenced-based data • Risk calculation maybe different for men and women in a more personalized way • Consider lifestyle modifications and treatment early on when sex-specific risk factors are present	
Pre-term delivery (<37 weeks)		
Recurrent miscarriage		
Breast cancer treatment		
Inflammatory diseases		
Depression and stress		

Table 2. Key points in the relationship between chronic kidney disease and pre-eclampsia.

- PE can increase the risk of CKD and CVD later in life.
- PE is an early stress test for CKD diagnosis.
- The history of PE should be an early detection indicator of CKD.
- PE is associated with long-term microalbuminuria and persistent proteinuria.
- Women who had PE have higher incidence of obesity, metabolic syndrome, and hypertension later in life.
- Renal evaluation at the beginning of prenatal care could diagnose previously CKD.

PE: pre-eclampsia; CKD: chronic kidney disease; CVD: cardiovascular disease.

KIDNEY TRANSPLANTATION

As for the whole population, kidney transplantation (KT) is considered the best RRT for women. Compared to the other RRTs, KT promotes increased survival, a better quality of life, and lower costs[27]. However, there are some disparity issues to be highlighted. Women are more frequently living donors than men, for parents or husbands. The potential explanations are the higher level of empathy or the economic dependence because fathers and husbands are often family providers[28]. Conversely, men account for more deceased donors because traumatic death is more frequent in this group[29].

Women have less access to the waiting list and are less transplanted after being listed[29]. Factors reported as potential causes are the lower probability of KT offered as RRT, difficulties in completing the pre-KT evaluation, and more frequent concerns about KT. Due to previous pregnancies, women are more prone to develop antibodies against the human leukocyte antigens and subsequently against the potential donors, limiting to find a compatible graft. Some effects have also been attributed to the hormonal profile, with women producing more vigorous immune reactions because of the immune-stimulating effect of estrogen and the diminished immune-suppressing effect of testosterone[30].

After KT, graft survival is lower in women, even after adjusting for other factors. Recently, more robust evidence showed that these results are seen when women received a graft from male donors. An exacerbated immune response in female recipients against the HY antigen (present in all male tissues) may explain these outcomes[31].

Infertility is common among women in dialysis therapy, which is associated with the effects of uremia on the hypothalamic-pituitary-gonadal axis. However, a restoration to normal hormone levels occurs around 6 months after KT, and fertility increases. Pregnancy counseling after KT is crucial because of the risk of immunosuppression on the fetus, the risk of worsening kidney allograft function, and other maternal or fetus complications, such as pre-eclampsia, premature delivery, small for gestational age, and intrauterine growth restriction[32].

CONCLUSION

As described, women have unique risks for kidney diseases that should be recognized to increase the opportunities for timely diagnosis and equitable access to health education, health care, and prevention. We also highlight that pregnancy may be a special opportunity for an early diagnosis of CKD. The deleterious effects of PE may result in cardiometabolic and renal overload that may be associated with the development of CVD and CKD later in life. Finally, it is still necessary to evaluate several aspects of RRT for better treating women (dialysis adequacy, treatment of anemia, opportunities in transplantation, and others).

AUTHORS' CONTRIBUTIONS

GMK: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **AFM:** Writing – original draft, Writing – review & editing. **CISR:** Writing – original draft, Writing – review & editing. **HSP:** Writing – original draft, Writing – review & editing. **JAMN:** Conceptualization, Writing – original draft, Writing – review & editing. **JM:** Writing – original draft, Writing – review & editing. **LRRM:** Conceptualization, Writing – original draft, Writing – review & editing. **MGB:** Writing – original draft, Writing – review & editing. **TAF:** Writing – original draft, Writing – review & editing. **APS:** Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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An update on intraductal and intralobular proliferative lesions of the breast

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INTRODUCTION

Intraductal and intralobular proliferative lesions or epithelial hyperplasias of the breast comprise a heterogeneous spectrum of proliferations that generally originate in the terminal duct-lobular units (TDLUs) of the breast and are confined to the ductal-lobular system[1]. Such lesions are subdivided into two major categories based on cytological and architectural criteria: ductal and lobular. The magnitude of the risk of subsequent breast cancer varies widely, and part of these proliferations represent risk indicators, whereas others act as true precursors of invasive breast carcinomas (IBCs)[1-5].

Since 2012, the classification of breast tumors according to the World Health Organization (WHO) has adopted the traditional nomenclature of "intraductal and intralobular proliferative lesions" (Tables 1 and 2), and previous terminologies like "breast intraductal neoplasia" and "lobular intraepithelial neoplasia" proposed by Tavassoli have been withdrawn[1].

INTRADUCTAL PROLIFERATIVE LESIONS

Intraductal proliferative lesions are grouped into three classes based on cytological and architectural criteria: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS)[1]. Moreover, there is the

Table 2. Histopathological classification of precursor lesions of the breast.

Precursor lesions
Atypical ductal hyperplasia
Flat epithelial atypia
Ductal carcinoma in situ
Noninvasive lobular neoplasia
Atypical lobular hyperplasia
Lobular carcinoma in situ
Classic lobular carcinoma in situ
Pleomorphic lobular carcinoma in situ
Florid lobular carcinoma in situ

WHO classification of breast tumors (5th edition, 2019).

Dupont and Page (1985)	Tavassoli (1998)	WHO (2012 and 2019)
Mild ductal hyperplasia	Usual ductal hyperplasia	Usual ductal hyperplasia
Moderate ductal hyperplasia without atypia		
	Ductal intraepithelial neoplasia grade 1A (DIN 1A)	Columnar cell lesion - Columnar cell change - Columnar cell hyperplasia - Flat epithelial atypia
Atypical ductal hyperplasia	Ductal intraepithelial neoplasia grade 1B (DIN 1B)	Atypical ductal hyperplasia
Low-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 1C (DIN 1C)	Low-grade ductal carcinoma in situ
Intermediate-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 2 (DIN 2)	Intermediate-grade ductal carcinoma in situ
High-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade (DIN 3)	High-grade ductal carcinoma in situ

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group of columnar cell lesions (CCLs)[1], which will be discussed separately.

Usual ductal hyperplasia

In general, UDH represents an incidental finding in breast biopsies that is morphologically composed of a polymorphic population of benign epithelial cells displayed in a haphazard orientation, regularly forming secondary lumina and fenestrations, in a slit-like fashion (Figure 1). The proliferations may show a solid, streaming, or micropapillary pattern. UDH cells have indistinct borders and are irregularly organized, with variably sized nuclei, frequently exhibiting intranuclear cytoplasmic inclusions and grooves. Immunohistochemistry demonstrates a mixed phenotype of UDH cells, with heterogeneous positivity for high-molecular-weight cytokeratins (CK 5/6, CK14, and 34βE12) and estrogen receptor (ER)[1].

Long-term follow-up studies have determined that women diagnosed with UDH have a slight increase in the risk for subsequent breast cancer (1.5- to 2-fold relative risk [RR])[3-5].

Atypical ductal hyperplasia

Atypical ductal hyperplasia is a clonal, epithelial proliferative lesion with cytological architectural characteristics analogous to those of low-grade DCIS, although with partial involvement of ductal spaces and/or a limited extent[1,6]. Clinically, lesions are often detected by screening mammography due to the association with microcalcifications, accounting for 2–14% of diagnoses in breast biopsies in the context of screened populations[6].

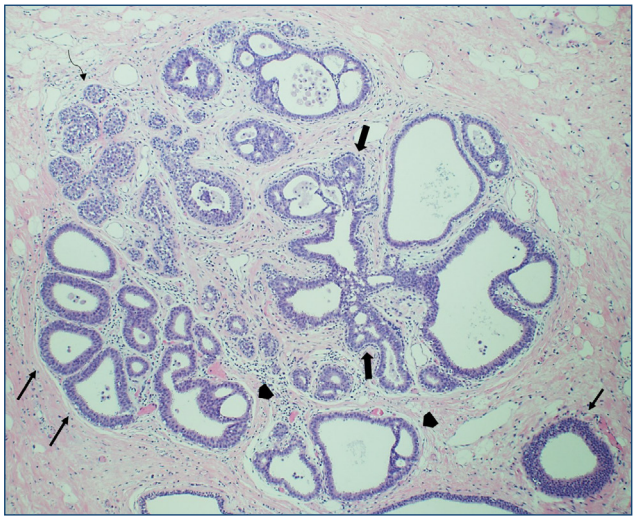

Figure 1. A histological section stained with H&E showing multiple epithelial proliferative lesions of the breast: usual ductal hyperplasia (thick arrows); atypical ductal hyperplasia (arrowheads); flat epithelial atypia (thin arrows); and classic noninvasive lobular neoplasia (curved arrow).

For the distinction from low-grade DCIS, Page et al. proposed a cutoff value of ≤2 mm in the contiguous dimension or less than two completely involved spaces. ADH cells are monomorphic, with round nuclei and dense chromatin. They are evenly spaced and are disposed in rigid bridges, arcades, and bars, forming bulbous micropapillae or well-developed secondary spaces in a cribriform pattern (Figure 1). Unlike UDH, ADH cells typically demonstrate diffuse and strong expression of ER and lack staining for CK5/6, with an immunophenotype that parallels other lesions in the low-grade breast neoplasia pathway (CCL, low-grade DCIS, and classic noninvasive lobular neoplasia [n-LN]). The main differential diagnoses of ADH include low-grade DCIS, collagenous spherulosis, and micropapillary UDH (gynecomastoid hyperplasia)[1,3,6].

The RR associated with ADH for the development of IBC is 3- to 5-fold, while the absolute risk is 1% per year in 25 years[3-5]. Antiestrogen chemoprevention significantly decreases the risk of future breast cancer. For ADH detected on core needle biopsy (CNB), according to contemporary series with imaging-pathological correlation, the upgrade rate to DCIS or IBC ranges from 10 to 20%. Therefore, current guidelines recommend surgical excision for patients with this CNB diagnosis[6-9].

Ductal carcinoma in situ

Clinical presentation and epidemiology

Before the advent of imaging screening programs, DCIS represented only 2–3% of palpable breast cancers. Afterward, the incidence has increased, and nowadays it comprises 20–25% of newly diagnosed breast cancers in the United States[1,10,11]. The mean age at diagnosis varies from 50 to 59 years, and 80–85% of DCIS is detected by mammography that typically shows unilateral calcifications. On magnetic resonance imaging (MRI), a non-mass-like enhancement may be seen. Occasionally, DCIS may present as a palpable nodule, nipple discharge, or Paget disease[1,10,11].

Definition and morphological features

Ductal carcinoma in situ encompasses a morphologically, biologically, genetically, and clinically heterogeneous group of lesions defined as a noninvasive, epithelial neoplastic proliferation confined to the mammary ductal-lobular system and that represents a nonobligate precursor of IBC[1].

Histologically, DCIS is a unifocal disease categorized as being of low (grade I), intermediate (grade II), or high (grade III) nuclear grade, based on cytonuclear morphology. Low-grade lesions measure more than 2 mm and are constituted by small, monotonous cells with uniform nuclei, regular chromatin, and

inconspicuous nucleoli, which show polarization around the involved spaces. Nuclei size is 1.5–2 times that of a red blood cell, and mitotic figures are sparse. Necrosis is also rare. In contrast, high-grade DCIS is composed of large, atypical cells with big, pleomorphic nuclei (>2.5 times the size of a red blood cell), coarse chromatin, and prominent nucleoli. Mitoses are frequent, as well as comedonecrosis and calcifications. DCIS of intermediate nuclear grade displays cells with a moderate variation in size, shape, and polarization. Necrosis may be found, both punctate and comedo types[1].

Architectural patterns include comedo, solid, cribriform, micropapillary, and papillary. Paget disease is one of the presentations of high-grade DCIS, which extends to the epidermis of the nipple[1].

In addition to the nuclear grade, pathological reports have to mention architectural patterns, presence and type of necrosis, presence and site of microcalcifications, size of the lesion, status, and distance to surgical margins[1].

Differential diagnoses comprise UDH, ADH, lobular carcinoma in situ, invasive cribriform carcinoma, and adenoid cystic carcinoma.

Immunohistochemical and molecular findings

Estrogen receptor expression in DCIS is observed in 75% of cases, whereas HER2 (epidermal growth factor receptor family member 2) overexpression is found in 40%. Currently, ER is the only predictive marker recommended in guidelines for routine clinical use in DCIS in order to select patients for anti-estrogen therapy. PR testing is optional[1].

Non-high-grade DCIS is generally ER+/HER2- and has fewer copy number alterations than high-grade DCIS. Many aberrations are recurrent in the latter, including alterations in known cancer genes such as *MYC* (gain at 8q22–24), *CCND1* (gain at 11q13), and *ERBB2* (gain at 17q12). Most driver mutations observed in DCIS are also found in IBCs, with the most common mutated genes being *PIK3CA* and *TP53*[12-15].

Prognosis and follow-up

If untreated, patients diagnosed with DCIS have a 10-fold risk of developing ipsilateral IBC. However, the breast cancer-specific risk associated with DCIS is extremely favorable. Data on its natural history are limited, and about 50% of recurrences after breast-conserving surgery (BCS) occur as IBC. Several factors have been described in association with a higher relapse risk: younger age, large lesion size, high nuclear grade, comedonecrosis, and positive margins. In patients who underwent breast radiation therapy, outcome analyses have consistently demonstrated a 50% reduction in local ipsilateral recurrence. Similarly, adjuvant hormone therapy decreases the risk of relapse, even though this benefit is restricted to ER-positive disease. Currently, the standard of care for DCIS patients is either BCS with clear margins (ideally ≥2 mm) and radiotherapy with or without hormone therapy or mastectomy[1,9,13,15-17].

INTRALOBULAR PROLIFERATIVE LESIONS: NONINVASIVE LOBULAR NEOPLASIA

Non-invasive lobular neoplasia refers to the spectrum of atypical epithelial proliferative lesions characterized by cell dyshesion consequent to the functional alteration or loss of E-cadherin-mediated cell adhesion[1]. According to the definition by the World Health Organization (WHO) Classification of Tumors of the Breast, 5th ed., this designation comprises atypical lobular hyperplasia (ALH) and classic lobular carcinoma in situ (C-LCIS), as well as two LCIS variants, specifically florid LCIS (F-LCIS) and pleomorphic LCIS (P-LCIS)[1]. ALH and C-LCIS can be denoted together as classic lobular neoplasia (c-LN) (Figure 1).

Clinical presentation and epidemiology

The estimation of the real incidence of n-LN is challenging, but it is projected to vary from 0.5 to 4% of benign breast biopsies[1,2,18].

Clinically, c-LN predominantly affects premenopausal women, and the median age at diagnosis is 50–55 years, while LCIS variants tend to occur in older patients with a median age of 59–61 years[1,19]. C-LCIS is described as multicentric in up to 85% of cases and bilateral in 30–67%. Of interest, c-LN is asymptomatic and usually represents an incidental finding in breast specimens obtained to assess other lesions. Although mammographically silent, it can be identified by an MRI examination[20]. Conversely, F-LCIS and P-LCIS tend to have unifocal and continuous distribution and are regularly detected mammographically due to the presence of pleomorphic calcifications, architectural distortion, and mass lesions with or without associated calcifications. In addition, both variants of LCIS are generally diagnosed in association with invasive lobular carcinoma (ILC)[21,22].

Definition and morphological features

Classic LCIS, as defined by Foote and Stewart, is characterized by the proliferation of noncohesive, nonpolarized, uniform, and round cells with low nuclear grade, which fill and distend more than 50% of the acini of the TDLUs[1,23]. Intracytoplasmic mucin vacuoles are often found, while mitotic figures are rare.

Two population cell types can be encountered, alone or in combination: type A and type B cells. Type A cells are small and exhibit a scant cytoplasm, with monotonous nuclei and dense chromatin; type B cells are rather larger, have more cytoplasm, and display slightly bigger nuclei with inconspicuous nucleoli[1].

The differential diagnosis includes ALH, low-grade DCIS with a predominantly solid architectural pattern, myoepithelial hyperplasia, and clear cell change of the epithelium of the TDLUs[1].

ALH consists of cells morphologically identical to those of C-LCIS. However, the extent is limited, and the lesion involves less than 50% of the acini of the TDLUs, with minimal expansion[1].

Both lesions commonly coexist and may demonstrate ductal pagetoid involvement[1].

Florid LCIS was first described by Fadare et al., and it was initially referred to as "LCIS with comedonecrosis"[24]. This lesion is composed of type A and/or type B cells analogous to those of classic LCIS, but they fill multiple TDLUs with massive acinar distension and little to no intervening stroma, frequently forming nodular aggregates, with an architecture that differs from C-LCIS. Central comedonecrosis and calcifications may be found, although their presence is not required for the diagnosis. The main distinction is with solid DCIS with low-to-intermediate nuclear grade[1,21,24].

Pleomorphic LCIS is constituted by big discohesive cells with marked nuclear atypia, large nuclei (four times larger than the size of a lymphocyte), coarse chromatin, and prominent nucleoli. Neoplastic cells usually have more cytoplasm and mitoses. Central necrosis with calcifications is frequently seen. The key differential diagnosis is with high-grade DCIS[1]. This variant was first recognized by Sneige et al.,[25] and since then, the number of reported cases of P-LCIS not associated with invasive carcinoma remains limited. Moreover, a subset of P-LCIS is composed of ovoid to plasmacytoid cells with large nucleoli and abundant eosinophilic, granular cytoplasm which is called apocrine P-LCIS[1,21,22,25].

Immunohistochemical and molecular findings

The dysfunction of E-cadherin represents the hallmark feature that defines all lobular lesions. It is a transmembrane glycoprotein encoded by the *CDH1* gene (16q22.1), which plays a critical role in cell-to-cell adhesion and forms a complex with β-catenin, α-catenin, and p120-catenin. Therefore, n-LN is characteristically distinguished by the loss of membranous expression of E-cadherin and β-catenin is on immunohistochemistry, as well as the cytoplasmic distribution of p120 catenin[1,25,26]. However, 15% of all subtypes of lobular neoplasia show cytoplasmic staining or retain some membrane reactivity for E-cadherin ("aberrant" expression), though with a reduced intensity/fragmented pattern. In contrast, benign ductal cells and DCIS cells show strong, uniform membrane positivity for E-cadherin, β-catenin, and p120 catenin[1].

Typically, ALH, C-LCIS, and F-LCIS demonstrate strong and diffuse positivity for ER and PR and lack HER2 overexpression[1,20,23]. Even though P-LCIS is regularly ER-positive/HER2-negative, approximately 13–30% of cases exhibit negativity for ER and HER2 overexpression, particularly in apocrine P-LCIS[1,22,25].

Molecular studies have demonstrated that LCIS is a clonal proliferation that harbors recurrent chromosomal loss at 16q and gain at 1q. Furthermore, F-LCIS and P-LCIS present greater genomic instability than C-LCIS, showing increased copy-number aberrations and gene amplifications. The most commonly mutated genes include *CDH1* (81% of cases), *PIK3CA* (41%), and *CBFB* (12%). Interestingly, previous reports have uncovered that LCIS and ILC can be clonally related and share molecular alterations. These observations support that n-LN is not only a high-risk lesion but also a nonobligate precursor of ILC[1,26-28].

Prognosis and follow-up

Lobular carcinoma in situ represents a risk factor as well as a nonobligate precursor, IBC, either lobular or no special type/ductal. For patients diagnosed with C-LCIS, the RR for the development of subsequent breast cancer varies from 8 to 10 times the risk expected in women without this lesion, and the absolute risk is 1–2% per year, leading to a cumulative rate of more than 20% at 20 years. For women with C-LCIS, the 20-year breast cancer-specific survival rate is superior to 90%[1,2,19,29]. Among patients with ALH, the RR is 4–6 times the risk in the general population, whereas the absolute risk is about 1% per year[1,30].

Given this background, active surveillance of patients with c-LN and no suspicious clinical/imaging findings is currently favored over surgical management, and antiestrogen chemoprevention lowers the risk of subsequent breast cancer[31]. The surgical management of c-LN detected at CNB has remained arguable. If LCIS is not the radiological target lesion and once cases with radiological-pathological discordance are excluded, excisional upgrade rates of incidental c-LN decrease to 1–4%[1,8,32,33]. Hence, guidelines by the American Society of Breast Surgeons recommend follow-up over surgery for women diagnosed with only c-LN in CNB and imaging-histological concordant findings. Of note, reporting of margin status for ALH and C-LCIS is not required[9].

Regarding LCIS variants, the natural history remains poorly understood, and optimal treatment is unclear. As many as 87% of cases are associated with invasive carcinomas at diagnosis. Moreover, around 25–60% of cases of F-LCIS and P-LCIS documented on CNB are upgraded to carcinoma upon excision[1,8,32,33]. Consequently, surgical resection is mandatory after the detection of these LCIS variants in CNB. Recurrence rates of P-LCIS treated with BCS range from 0 to 57%. The potential benefit of adjuvant radiation therapy and the prognostic impact of a positive margin status are not well established, although data from follow-up studies support that surgical excision should try to achieve clear margins, and pathologists thus need to report margin status for both P-LCIS and F-LCIS[1,21,22].

Finally, both classic and nonclassic LCIS are no longer staged as pTis according to the eighth edition of the American Joint Committee on Cancer TNM classification[1].

COLUMNAR CELL LESIONS

Columnar cell lesions of the breast include columnar cell change (CCC), columnar cell hyperplasia (CCH), and flat epithelial atypia (FEA). They represent clonal alterations of the TDLU and are marked by the presence of unevenly enlarged and dilated acini lined by columnar epithelial cells. These lesions are frequently detected on mammography as a result of the association with calcifications[1].

Lesions in which the epithelial cell lining of TDLUs is only 1–2 cell layers thick are classified as CCC, while CCH is designated for those with>2 cell layers. Cellular stratification and tufting are common, and cytological atypia is absent. FEA is characterized by low-grade cytological atypia, and the acini of involved TDLUs are lined by one to several layers of monotonous cuboidal to columnar cells (Figure 1), regularly with prominent apical snouts[1]. Complex architectural proliferations are not encountered. Furthermore, FEA is frequently associated with ADH, low-grade DCIS, n-LN, and low-grade IBCs, sharing molecular alterations with these lesions[34].

The risk of progression to IBC seems to be very low, and surgical excision upon a CNB diagnosis of FAE is controversial. Radiological-pathological correlation is mandatory for guiding further management, and patients may be spared resection if a postbiopsy mammogram documents that all calcifications have been removed[1,8,35,36].

CONCLUSION

Knowledge of diagnostic criteria is essential for the accurate recognition and classification of epithelial proliferative lesions of the breast, which will define management and help estimate the risk for the development of subsequent IBC.

AUTHORS' CONTRIBUTIONS

RFA: Writing – original draft. **HG:** Writing – review & editing. **MDB:** Conceptualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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What does a doctor need to know about breastfeeding and adolescent health and pregnancy?

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INTRODUCTION

For the World Health Organization (WHO), breastfeeding (BF) should start in the delivery room in the first hour of life, should be maintained in the form of exclusive breastfeeding (EBF) for the first 6 months of life, and after that period, along with healthy complementary feeding, should be maintained for at least 2 years of age[1].

Among the different medical specialties, traditionally, it is pediatricians, obstetricians, and family and community physicians who act more directly in supporting and helping women during the lactation period, acting as educators and protagonists in interventions during pregnancy, in the immediate puerperium and in the childcare consultations[2-5]. However, it is imperative that every physician, regardless of specialty, has knowledge about BF, as many specialties will require longitudinal follow-up of their patients, allowing the physician to play a fundamental role in planning and supporting BF, such as, for example, support that the general practitioner or occupational physician can offer to working women in the transition between maternity leave and returning to work, one of the critical periods in which lack of guidance can lead to interruption of BF[5].

This article aimed to address the most current scientific evidence on the benefits of BF on women's health, as well as specific situations that may arise in women's health that contraindicate BF, the few drugs whose use is prohibited during BF and ends by addressing attention integral to adolescent health and pregnancy.

BREASTFEEDING

Short-term benefit

Although gestational diabetes mellitus (GDM) tends to resolve after childbirth, in most women, another portion ends up progressing in a few months or years to the onset of type 2 diabetes mellitus (DM2)[6]. In this context, in women with a history of GDM, studies associate BF with improvement in the functioning of maternal pancreatic beta cells in the postpartum period, generating lower glycemic, total, and LDL cholesterol levels and higher HDL cholesterol levels[7-9]. Shub et al. found that among women, with or without GDM during pregnancy, EBF was associated with lower fasting blood glucose concentrations at 6–10 weeks postpartum, after adjusting for possible confounding biases[7]. Tarrant et al. conducted a systematic review involving 13 articles that studied the influence of BF on postpartum glycemic status and eight that compared mean blood glucose values between BF and non-BF participants. Of the 13 studies that compared postpartum glycemic status, nine found that BF reduced rates of glucose intolerance. In eight of the studies, there were mean blood glucose values, and in six of the studies, the fasting plasma glucose was lower in participants who breastfed, with reductions ranging from 3.7 to 7.4 mg/dL[8].

A recent randomized clinical trial tested whether BF during the oral glucose tolerance test affects glucose and insulin results. For this, 20 women with previous GDM were recruited; each woman performed two OGTTs in the first 3 months after

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delivery, BF the child in one and avoiding BF in the other. Glucose and insulin were measured in four moments. In BF OGTTs, higher values were observed for global glucose and insulin concentrations, glucose and insulin peaks, and individual glucose (at 0, 30, and 60 min) and insulin (at 0 and 60 min) points, but without differences at 120 min[9].

The act of sucking the nipple-areola region is the most important stimulus for the secretion of oxytocin, which also causes uterine contraction, so that BF accelerates the return of the uterus to its normal size, reducing the occurrence of postpartum hemorrhage, and consequently anemia. In addition, high levels of oxytocin can increase the pain threshold, reducing maternal discomfort and thus contributing to an increase in the mother-infant bond[10].

The oxytocin released during BF also has lipolytic and anorexigenic effects. Based on this, there will be faster weight loss and a return to pre-pregnancy conditions, with an average monthly reduction of 450 g in maternal weight during BF[11]. A study conducted with 314 Mexican mothers revealed that those who exclusively breastfed for at least 3 months had a weight reduction of 4.1 kg compared to those who did not breastfeed[12].

As long as there is the lactation period, the high levels of prolactin lead to the inhibition of the hormone gonadotropin, estrogen, and progesterone, leading to the interruption of ovulation and amenorrhea. As long as a woman breastfeeds exclusively on demand, at least eight times a day, and has not menstruated, her protection against pregnancy can reach 96% during the first 6 months. After the return of menstrual cycles, the probability of conception can decrease by 7.4% for each additional month of BF[13].

Long-term benefits

Some studies suggest that the benefit of BF on maternal insulin sensitivity may persist over time. Among them, Ley et al. evaluated 4,372 American women with DM2 and a history of GDM and observed an inverse association between the duration of lactation throughout life and the risk of developing DM2. Compared with not BF, adjusted hazard ratios (HRs) were significantly lower depending on duration with a ratio of 0.73 (95%CI 0.57–0.93) for a cumulative duration of BF greater than 24 months[14].

There appears to be an inverse dose-response relationship between the duration of BF and the risk of developing cardiovascular disease. In a prospective study, 139,681 women who reported a lifetime history of more than 12 months of lactation were less likely to have various postmenopausal conditions, including hypertension (odds ratio [OR] 0.88, p<0.001), hyperlipidemia (OR 0.81, p<0.001), and cardiovascular disease (OR 0.91, p=0.008) than women who never breastfed but were not likely to be less obese. When adjusted for BMI, similar relationships were observed. During an average of 7.9 years of study participation, women with a single live birth who breastfed for 7–12 months were significantly less likely to develop cardiovascular disease (HR 0.72, 95%CI 0.53–0, 97) than women who never breastfed[15].

Studies have shown an association between the duration of BF and the consequent protective effect against the risk of breast cancer, probably due to the following mechanisms: lower levels of estrogen during the lactation period reduce the rates of cell proliferation and differentiation, and epithelial apoptosis at the end of the nursing period assists in the destruction of damaged DNA cells. . It is estimated that the risk of breast cancer can be reduced by more than 4% for each year of BF[16].

Compared with never BF, women who breastfed for any length of time were associated with a 22% reduced risk of breast cancer (OR 0.78; 95%CI, 0.74–0.82) and also had a 30% less risk of ovarian carcinoma (OR 0.70; 95%CI, 0.64–0.77)[17]. BF is also associated with a significant reduction in the risk of endometrial cancer (relative risk (RR): 0.77; 95%CI, 0.62–0.96), and each month of BF has been associated with a reduction of 2% RR for endometrial cancer (RR 0.98; 95%CI, 0.97–0.99)[18].

According to Farland et al., the duration of full and EBF was significantly associated with decreased risk of endometriosis, as for every 3 additional months of full BF per pregnancy, women had an 8% lower risk of endometriosis (HR 0.92; 95%CI 0.90–0.94), 14% lower risk for every 3 additional months of EBF per pregnancy (HR=0.86; 0.81–0.90), and women who breastfed for 3 years or more in total over their reproductive lifetime had a 40% risk lower incidence of endometriosis compared to women who never breastfed (HR=0.60; 0.50–0.72)[19].

Meta-analysis with six studies, conducted by Chen et al., demonstrated that BF is associated with a lower risk of developing rheumatoid arthritis among women who breastfeed for between 1 month and 1 year (OR 0.783, 95%CI 0.641–0.957, p=0.015) and for more than 12 months (OR 0.579, 95%CI 0.462–0.726, p<0.0005)[20].

The biological and psychosocial effects of BF, such as better stress regulation, may exert long-term benefits for the mother's brain health. A convenience sample of Californian women over 50 years old was recruited through two clinical trials and found that BF women performed better on several cognitive tests in the domains of learning, delayed recall, executive functioning, and processing speed in comparison with women who did not breastfeed, suggesting that BF may have a protective effect for Alzheimer's disease, possibly due to the hormonal effects of estrogens on brain receptors and the insulin sensitivity provided by BF[21].

Women who breastfed for 15 months or more had a reduced risk of multiple sclerosis compared with those who breastfed for 4 months or less[22].

Maternal contraindications to breastfeeding

There are few maternal health conditions in which there is a formal contraindication to BF. Mothers who have infectious diseases such as infection by HIV (human immunodeficiency virus), infection by HTLV (human T-lymphotropic virus), infection by herpes simplex (in the presence of active lesions in the breast), chickenpox (mothers who develop the disease within 5 days before up to 2 days after delivery), and cytomegalovirus (provided the neonate is extremely premature, that is, gestational age at birth <30 weeks or birth weight <1,000 g) should not be breastfed, due to the risk of direct transmission to the child, or in the case of cytomegalovirus and chickenpox, the antibodies that would prevent infection in children are not present[23].

Mothers who regularly use illicit drugs (marijuana, cocaine, crack, amphetamine, ecstasy, and others) should not breastfeed their children[24].

In some specific situations such as debilitating infection for the mother, maternal leprosy, invasive systemic maternal infection by *Staphylococcus aureus* or group B Streptococcus, acute phase of maternal dengue infection, occasional consumption of alcohol or illicit drugs, yellow fever vaccine in mothers of children under 6 months of age, or who are undergoing an examination with radiopharmaceuticals, temporary interruption of BF is recommended, and the time that the woman should not breastfeed varies according to each situation[25].

Breastfeeding and medication

The number of women who interrupt their children's BF to use medication is still frequent. This may occur because the prescribing physician is unaware of the issue of safety in the use of medications during BF, because the content of medication inserts often recommends not using them in pregnant and lactating women, and the fear that mothers have that a certain medication could harm their child. Nowadays, only a minority of drugs actually contraindicate lactation. In 2010, the Ministry of Health (MS) published the second edition of the manual "Breastfeeding and the use of medicines and other substances," now updated in 2022[26].

Medications are classified into compatible, judicious, and contraindicated use. It is important that the physician, when prescribing a drug to a nursing mother or if asked about the compatibility or otherwise of a drug, can consult such support material to provide accurate information

COMPREHENSIVE HEALTH CARE FOR ADOLESCENTS AND PREGNANCY

Comprehensive adolescent health care (AISA) should offer periodic routine and occasional care, when the situation requires it, in order to work on issues related to the prevention of injuries and health promotion, recognizing risk behaviors and/or signs/symptoms that may denote the onset of some disease. The actions of this service should be aimed at reducing vulnerability and risks to physical and emotional health; promoting relationships of trust and self-care; preventing injury and manifesting diseases in adults, but with early onset, diseases related to unprotected sexual activity; and questioning about work, school, citizenship, technology, digital addiction, environment, nutritional aspects, and violence[27,28].

The AISA should be extended to the entire population aged between 10 and 20 years, with longitudinal and distinct follow-up between the different stages, to be carried out through individualized outpatient care, home visits, and participation in educational groups with the following objectives general: monitor physical growth and development; expand vaccination coverage; promote sexual and reproductive health; promote food and nutrition education; promote safety and accident prevention; promote the prevention of intentional injuries in the home, school, and interpersonal environment; encourage health promotion and prevention of the most common diseases in this age group; promote physical and mental hygiene and the practice of leisure activities appropriate to each phase; and provide socialization, cultural stimulation, and adaptation of adolescents. In this age group, pregnancy is still considered a social and public health problem 28-31 in their social environment, promoting oral health[27-30].

In Brazil, the pregnancy rate is above the Latin American average in adolescents aged 15–19 years, with this number being 68.4/1,000 adolescents in Brazil, 65.5/1,000 in Latin America, and an average of 46/1,000 in the world. In 10 years, the number of births in children under 19 years in Brazil has decreased by about 40%, but the teenage pregnancy rate is still high, with more than 400,000 pregnant women per year. Only 2% of teenagers who became pregnant continued their studies[27-30].

For the teenage mother, complications and severity will be greater or lesser according to age, parity, adherence to prenatal care, weight gain, and socioeconomic and cultural factors. The physical consequences are hypertension; anemia, resulting from situations of poverty, malnutrition, chronic malnutrition, and inadequate diet to avoid gaining weight; higher rate of cesareans; urinary and genital infections; maternal mortality (risk increases the lower the chronological age and with successive pregnancies at short intervals); spontaneous and clandestine abortions; toxemia; and dystocia, sexually transmitted infections (STIs)[27-30].

As psychosocial consequences, there is emotional tension, family rejection that increases the probability of developing physical and mental problems; loss of autonomy; partner abandonment; low schooling, associated with low socioeconomic status, being the cause of higher absenteeism in prenatal care; difficulty in returning to school after childbirth due to the fragile support network; and dreams interrupted by the lack of preparation for work, as many drop out of school when they become pregnant and, therefore, lose the opportunity to acquire knowledge and enter the job market[27-30].

As for the son of a teenage mother, the consequences are prematurity, abandonment, low weight at birth, increase in the infant mortality rate in the first year of life, higher number of hospitalizations, violence, and even BF can be affected. BF should be encouraged for adolescent mothers, making them aware of the benefits for both the child and her (all the same benefits of BF as adult mothers) and the importance of BF to the child exclusively for the first 6 months of life, continuing up to 2 years[30].

The prevention of untimely pregnancy takes place through sex education, through frank, open, and sincere dialogue with parents, health professionals, and teachers, in addition to contraceptive methods[27-31].

Ethical-legal aspects of contraception in adolescence

Contraception can and should be indicated for adolescents, respecting the medical eligibility criteria of the WHO for the use of contraceptives, including for children under 14 years of age, and its prescription is based on technical standards of the MoH and Code of Medical Ethics. However, it turns into a dilemma when deals with adolescents under 14 years of age. If the law is on the one hand, the issue of sexual and reproductive rights is on the other[32-34].

From a legal point of view, in 2009, article 217 was inserted in the Brazilian Penal Code, which establishes the crime of rape of a vulnerable person, "having carnal intercourse or performing another libidinous act with someone under 14 years of age," with mandatory notification to the Tutelary Council or the Public Ministry. Therefore, the notification must be made even in cases where the relationship is consensual, the parents are aware of it or even when it is a pregnancy desired by the adolescent and her family, not discriminating the age difference between the partners nor the degree of affectivity of the partner couple[32-34].

Scientific societies have promoted meetings with professionals from the social, health, and justice areas, with the aim of finding possibilities to guarantee adequate assistance in sexual and reproductive health, without failing to propose a reflection on the beginning of sexual life and on the conscious possibility of consider postponing the act.

Special emphasis is given to the importance of the right to information and prevention of pregnancy and STIs, both for those who already have sexual activity and for those who have not yet started it[32-34].

Recognizing the adolescent as a subject with rights and respecting her as such is essential in order to advance in the challenge of providing comprehensive health care for this population.

AUTHORS' CONTRIBUTIONS

RSP: Conceptualization, Writing – original draft, Writing – review & editing. **LMDL:** Conceptualization, Writing – original draft. **AEBIA:** Conceptualization, Writing – original draft, Writing – review & editing. **DVSB:** Conceptualization, Writing – original draft. **LMN:** Conceptualization, Writing – original draft, Writing – review & editing. **IMDL:** Conceptualization, Writing – original draft.

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REVIEW ARTICLE

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Puerperal psychosis: an update

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INTRODUCTION

Mental illnesses contribute to the total number of sick people in the world. Between 2000 and 2012, the World Health Organization (WHO) estimated that 64 million worldwide disability-adjusted life years (DALYs) were lost due to mental and behavioral problems among women of reproductive age (15–49 years)[1]. For women, the proportioc. cn of DALYs lost is greatest during their prime reproductive years. These results emphasize the need to consider perinatal (i.e., prenatal and postnatal) mental illnesses[2].

Depressive and anxiety disorders are the most frequent psychiatric problems in pregnant and postpartum women, with a prevalence of approximately 10 and 13%, respectively[2]. In low- and high-income countries (LMICs), the prevalence is higher, with prenatal rates of nearly 16% and postnatal rates of about 20%[2].

Perinatal mental morbidity can have severe repercussions for everyone involved. Perinatal mental illnesses may be related to maternal difficulties and an increased risk of poor neonatal and developmental outcomes. Also, an increase in pregnancy-related comorbidities is worrisome, which can lead to more severe outcomes[2].

In the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)[3], they are not recognized as a distinct clinical diagnostic entity. In *DSM-5*, postpartum psychosis is categorized as a "short psychotic illness"[3]. The *International Classification of Diseases 11th Revision* (*ICD-11*) classifies postpartum psychosis as one of the syndromes associated with pregnancy or the puerperium (beginning approximately 6 weeks after delivery) that involves significant mental and behavioral characteristics, such as delusions, hallucinations, or other psychotic symptoms[4]. Mood symptoms, including depression and/or mania, are almost always present as well. If the patient's symptoms are consistent with the diagnostic criteria for a certain mental condition, then that disorder must also be ascribed (*ICD-11*)[4].

The prevalence of prenatal psychosis was reported by one study to be 5 in 1,000 newborns, whereas the incidence of perinatal psychosis ranged from 0.89 to 2.6 in 1,000 women throughout the investigations[2,5].

In this update, the objective is to present the differential diagnosis and treatment of postpartum psychosis.

METHODS

A search was carried out to create this update using PubMed and SciELO. Two reviewers were involved. Postpartum was picked as the keyword in articles of all language types that were published in the most recent 5 years. Systematic reviews, meta-analyses, controlled trials, cohort studies, and case-control studies were the categories of articles that were included. When necessary, different kinds of items were substituted in their place. Four writers carried out the study and the comprehensive review.

RISK FACTORS AND ETIOLOGY

Postpartum psychosis is one of the few mental illnesses for which it is possible to identify a particular etiological event as the cause. Other mental conditions include schizophrenia and bipolar disorder. Even though having a child might trigger postpartum psychosis, there are still several significant questions concerning the pathophysiology of this condition that have not been answered.

Primiparity is a major predictor; consequently, a woman's probability of developing postpartum psychosis following a later birth is significantly reduced if she did not experience any complications related to postpartum psychosis during her first delivery[6,7].

Clinical factors like first-time motherhood, puerperal hormone shifts, lack of sleep, and disruption of circadian rhythms are taken into consideration[7]. Other factors that are considered risk factors for PP are high environmental stress, perinatal

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mortality after birth, and congenital deformity[7,8]. Acute mania, psychosis, anxiety, and depression are all possible side effects of postpartum immune activation[7].

Primiparity is universally recognized as a significant variable in modeling risk factors. On the contrary, delivery problems are not always present as a PP risk all of the time[8].

The most significant risk factors for postpartum psychosis are a previous history of psychotic episodes or a bipolar condition. It is recognized that a person has a 40–80% chance of developing bipolar illness after experiencing a fresh beginning of postpartum affective psychosis[8]. According to several research findings, people with PP are at an increased risk of developing a schizoaffective disorder or bipolar illness, and 12% of these patients acquire schizophrenia[8].

Pregnancy and postpartum, far from being protective factors against mental disorders, can aggravate pre-existing or trigger new psychiatric disorders. During pregnancy, approximately 1 in 13 women may suffer the start of a severe depressive episode for the first time, and approximately 1 in 7 will have an episode during the peripartum period[9].

In contrast to postpartum depression, which is unipolar, the development of postpartum psychosis does not include the effects of stressful life events or interactions with other individuals[9].

Additional possible risk factors include a history of bipolar disorder in the patient's family, particular genetic variants of the serotonin transporter gene (5-HTT), and a genome-wide significant linkage signal at chromosome 16p13 in patients with a history of both bipolar disorder and postpartum psychosis[7].

Postpartum psychosis hormonal studies were mostly done 20 years ago. Pregnancy raises estrogen, progesterone, and other hormones. After 35 weeks, corticotropin-releasing hormone (CRH)-binding protein decreases, increasing CRH and ACTH levels before birth. After delivery, estrogen and progesterone levels decrease considerably and recover to normal within 3 weeks. This multiple-fold reproductive hormone shift may induce postpartum psychosis. After birth, estrogen, which modulates hypothalamic dopaminergic tone, increases, causing affective psychosis[7].

Hormonal, immunological, and circadian rhythm disruptions in genetically susceptible women induce postpartum psychosis. Postpartum psychosis may have several causes or a unifying factor[7].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Among women who had postpartum psychosis, irritability (73%), aberrant thinking content (72%), and anxiety (71%) were the most common symptoms. Approximately one-fifth (19%) of patients also had thoughts of suicide, and approximately 8% also considered killing a newborn as a solution[10]. The feelings associated with delusions and hallucinations were often unpleasant. Manic (34%), depressed (41%), and atypical (25% of the sample) symptom profiles were identified using latent class analysis[10]. Manic symptoms and agitation indicate the manic profile, whereas depressed and anxious symptoms describe the depressive profile, and disturbances of consciousness and disorientation define the atypical profile[10].

Within the first 6 weeks after giving birth, a new recurrence of the following symptoms within postpartum psychosis is classified[1]. Manic or mixed episodes that may or may not be accompanied by psychotic symptoms[2]. Depression is characterized by psychotic symptoms[3]. Psychosis that is not accompanied by any mood symptoms. Due to the significant influence that this variable has on the patient's prognosis, the treating clinician has to determine if the patient is experiencing the first episode of psychosis in her lifetime or whether she has a history of depression, hypomania, or mania[3,4,7]. This needs a tough investigation since there are likely many women who have had experiences in the past that were not recognized[3,4,7].

Women who experience postpartum psychosis for the first time typically have one of two disease courses: isolated postpartum psychosis (vulnerability to affective psychosis only after birth) or postpartum psychosis as an expression of bipolar mood disorder with non-perinatal episodes. Both disease courses are possible in women who have experienced first-time postpartum psychosis[5,7,8].

Examining the patient's physical state as well as brain state is essential. Request a tough metabolic profile, urine, complete blood count, TSH, free T4, TPO antibodies, and ammonia levels. Screening for drugs of abuse that may present with psychotic symptoms as a secondary effect of intoxication or withdrawal is an essential consideration that should not be overlooked. Imaging of the brain, study of cerebrospinal fluid, testing for limbic encephalitis, and antibody screening should all be considered when neurological symptoms are presented[5,7,8].

Treatment

It is important to begin by managing psychiatric emergencies such as psychomotor agitation, suicidal behavior, substance use disorder, and clinical emergencies. Specific protocols for agitation and suicidal behavior can be found in specific guidelines[9,11-16].

In most cases, a woman who has been diagnosed with postpartum psychosis will need inpatient psychiatric therapy to undergo diagnostic examination, safety evaluation, and

treatment commencement. The woman's significant others are identified and involved in her therapy and rehabilitation so that they can be an ally to her[9,11-16].

During the acute period of the disease, the medication of first choice is lithium, unless it is contraindicated for the patient (e.g., due to impaired renal function or serious side effects during prior treatment)[9,11-16]. On the contrary, this indication is appropriate if there is a suspicion of either psychotic depression or bipolar illness. ECT can be used for schizophrenia and related disorders, bipolar disorder, depression, or induced psychosis[9,11-16].

When possible, antipsychotic medication should be used, although its use has risks. Acute treatment of severe manic or psychotic symptoms may benefit from additional medicines, such as benzodiazepines[9,11-16]. Patients with severe catatonic characteristics and depression with psychotic elements may benefit from ECT since the median length of their episodes is much greater than that of postpartum mania[9,11-16].

Antidepressants should only be used to immediately treat postpartum depression with psychotic characteristics. The administration of a mood stabilizer or antipsychotic should always accompany the antidepressants[9,11-16].

Prognosis

There is a significantly higher risk of postpartum depression. New-onset affective psychosis is also rare during pregnancy and postpartum. For women with mental illness, the postpartum period increases the chance of recurrence and first-onset affective psychosis[5,8,17]. Bipolar women are more likely to need puerperal psychiatric hospitalization. If they stop taking their medication, bipolar women may have episodes during pregnancy[9,11-16].

Symptoms typically occur days or weeks before mental health institution admission. Insomnia, mood fluctuations, and irritability precede mania, depression, or a mixed state in postpartum psychosis[5,8,17]. Despite fast mood swings, postpartum psychosis symptoms are generally different from those of bipolar disease. Mood-incongruent birth fantasies are common. Disorganized behavior and obsessive thoughts about the child are also common[9,11-16].

Postpartum psychosis increases infanticide and suicide. Shorter acute postpartum psychosis episodes had a better prognosis[9,11-16]. First-onset PP had a better outcome than non-postpartum affective psychosis. Some women have severe, lasting mental disorders following PP. After postpartum affective psychosis, which affects 20–50% of women[9,11-16], she has a 50–80% chance of another significant mental episode, frequently a bipolar one.

Prevention

An individualized postpartum relapse prevention plan should be developed in collaboration with the patient, their family, and obstetrical and pediatric care professionals. This plan should include the following components: a description of medication prophylaxis (during pregnancy and/or after delivery) based on a previous diagnosis; progressive intervention strategies to be implemented, beginning with the earliest signs of prodromal symptoms of relapse; coordination of the patient's pregnancy, labor, and pain management plan with the obstetrician[5,16,17].

For women who have had a single episode of postpartum psychosis, a risk-benefit analysis should be performed, and they should consider continuing their preventive medication while breastfeeding[5,16,17].

The medication prescribed to the patient will be determined by her previous reactions to medications. Nonetheless, lithium is the treatment with the most scientific backing. There is a lack of information available about the preventive effects of lamotrigine, olanzapine, quetiapine, and risperidone[5,16,17].

Health and safety of patients and children

One of the most difficult problems for obstetricians and psychiatrists is determining whether perinatal patients pose a danger to themselves or their children. It is crucial to do a risk assessment, and it is important to remember that it is always advisable to err on the side of caution; this is because the rates of both infanticide and suicide are high in severe cases[5,9,16,17].

Women who struggle with mental illnesses can become wonderful moms, and in most instances, they are[5,9,16,17]. When they are going through acute episodes of their illness and have impaired insight and volition, they may be at risk of causing harm to their children, either intentionally or through negligence brought on by the mental illness[5,9,16,17]. This can happen either because of the mother's lack of awareness of the risk she poses to her children or due to the mental illness itself[5,9,16,17].

When dealing with a female patient of reproductive age, the physician must always consider the possibility of the patient becoming pregnant as well as the woman's desire to breastfeed her child[5,9,16,17]. To be more precise, the following mental symptoms provide the greatest risk to her throughout the postpartum period, and as a consequence, women who exhibit any of these symptoms may be aggressively questioned: thoughts of having an abortion, the possibility of killing an infant, mental problems and signs associated to the pregnancy itself (e.g., an intense dread of giving birth; tokophobia) and the puerperium (e.g., an acute anxiety of being unable to continue with the mother's routine); ideas or attitudes that are antagonistic against the fetus and the infant (e.g., an aggressive behavior

displayed by the pregnant woman toward her abdominal area); erroneous beliefs about the health of the mother and the postpartum period[5,9,16,17].

CONCLUSION

It is not only psychiatry that has trouble with mental crises during pregnancy and the peripartum period but obstetrics and other fields of medicine also encounter the same challenge.

One of the most urgent situations is postpartum psychosis, which may have serious consequences for the patient and be challenging to treat. Even though there are still many unanswered questions, current knowledge may be utilized in clinical practice.

AUTHORS' CONTRIBUTIONS

LB: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **VSL:** Data curation, Formal Analysis, Methodology, Writing – original draft. **ALST:** Visualization, Writing – review & editing. **AGS:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE

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History of radiotherapy in the treatment of uterine cervix cancer: an overview

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INTRODUCTION

Since the very first beginning of the use of radiation in cancer treatment, cervical cancer has been one of the most suitable diseases for this application because it has a topography that is easy to assess for both diagnosis and the new emergent technology.

This manuscript will present a brief overview of the evolution of radiotherapy in the treatment of cervical cancer, with the main achievements and perspectives in the field.

HISTORICAL NOTES

The first treatment of cervical cancer using radium alone was performed by Robert Abbe, an American surgeon, in 1904[1]. In 1912, Forsell reported clinical healing in several cases of inoperable cervical carcinoma with radium application in Stockholm[2]. However, most part of the method was developed in France, where in 1913, Dominici, Cheron, and Rubens-Duval reported 158 cases[1]. Soon, there was a worldwide recognition of the value of the new element, and its use was adopted in most countries[1]. Those implants paved the way to what is now described as brachytherapy.

After 1916, roentgen rays started to be more efficient for the treatment of deeper parts of the body with the possibility of delivering large doses to the uterus. Roentgen rays alone or in combination with radium implants were then used for the treatment of cervical cancer[1]. In the early 1930s, the reported cure rate for all stages of cervical cancer was around 22% using this strategy[1].

In the decade of 1950–1960, randomized trials founded many principles of radiotherapy for cervical cancer. It was established that for stages I and II, two insertions of radium alone within a period of 10 days would be the treatment of choice. For stage III (or II, with infiltration of the parametrium), x-ray therapy should be combined with the radium implants for an overall treatment course of 5–6 weeks. For stage IV, megavoltage x-ray therapy of the pelvis with an additional low-dose radium contribution or a single palliative radium insertion was recommended[3].

As an outstanding treatment for cervical cancer, irradiation presented increasing rates of cure and long-term survival for those patients. Radiotherapy was used either in association with surgery, or alone, in locally advanced disease. Standard treatment consisted of external beam irradiation and intracavitary/interstitial brachytherapy, as it is used until today.

ASSOCIATION OF RADIOTHERAPY WITH SURGERY

Historically, the association of irradiation with surgery has always been attempted. Results varied according to disease stage and treatment indications. Since the association could elevate the complication rates, better patient selection and treatment strategy definitions were warranted.

For stages I and IIA tumors, the results of surgery or radiotherapy alone are equivalent with survival rates of 70–90%. The modalities, however, differ in the associated morbidity and types of complications. Several prospective, randomized studies reported comparable survival outcomes with radiotherapy or radical hysterectomy for stages IB and IIA. The most remarkable one was from Landoni et al.[4] who observed no significant differences in overall 5-year survival (83%), disease-free interval (74%), or relapses (25%), with twice the morbidity in the surgery arm. Even for bulky tumors (4 cm or more), the Gynecologic Oncology Group (GOG) trial 71[5] demonstrated the lack of benefit of the association of adjuvant surgery after irradiation in these patients with a 60–65% 5-year survival rate.

In the adjuvant scenario, postoperative radiotherapy is currently indicated based on the criteria defined by GOG 92 study ("Sedlis criteria") for the definition of high- and intermediate-risk

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disease. Lymph node involvement, parametrial invasion, and positive/close margins (3–5 mm) are considered high-risk factors with an indication for post-operative pelvic irradiation. Lymphovascular invasion, depth of stromal invasion, tumor size, and histological type are considered intermediate- or low-risk factors and should be evaluated individually for an indication of postoperative irradiation[6,7].

Currently, it is wise to choose the treatment strategy based on an evaluation of the risk factors. If an indication of adjuvant irradiation is a possibility, then radiotherapy should be the preferred treatment, as historically proposed by Landoni, a surgeon, in his landmark publication.

RADIOTHERAPY ALONE OR COMBINED WITH CHEMOTHERAPY?

After the establishment of radiotherapy as the standard of care for locally advanced cervical cancer (LACC), the expected overall 5-year survival remained stable, around 40–60%, including all stages. Thus, new treatment strategies emerged over the years.

In 1999–2000, the publication of five randomized trials[8-12] that evaluated radiation alone versus chemoradiation made the National Cancer Institute of the United States of America release an announcement: all patients with high-risk invasive cervical cancer should be treated with the combination of radiotherapy and chemotherapy. The combined treatment presented an absolute benefit of 10–13% with an improvement in overall and progression-free survival and a reduction of local and systemic relapses[13].

Later (2008), a more consistent 6% benefit in survival (from 60 to 66%) favoring the chemotherapy groups was demonstrated[14] with an increase in acute toxicity. Of note, platinum-based chemotherapy should be used.

In most of those studies, patients with stage III tumors were underrepresented. A phase III Brazilian study[15,16], including only patients with stage IIIB squamous cell carcinoma, demonstrated a significant benefit in disease-free and overall survival in favor of the combined regimen. Thus, concomitant chemoradiation proved to be beneficial for all patients with LACC.

Studies evaluating neoadjuvant chemotherapy, with different drug combinations, followed by irradiation alone or concomitant with chemotherapy, failed to demonstrate any benefit, with even a detrimental effect of the neoadjuvant strategy in some[17,18].

The same occurred with adjuvant chemotherapy after chemoradiation, where the evidence of the use of this strategy is not yet encouraging[19].

Therefore, the current standard of care for LACC is concomitant radiochemotherapy. Whenever chemotherapy is not possible to deliver, the historical regimen of radiotherapy alone remains the standard of care.

TECHNOLOGICAL DEVELOPMENTS AND ACHIEVEMENTS

Technological developments in radiotherapy, allied with the computing sciences and imaging evolution, diversification, and availability, allowed the improvement of treatment delivery. From an era of bidimensional (2D) techniques based only on surface anatomy and radiographs, generation of tridimensional (3D) image reconstructions of patient's and tumor's anatomy from computed tomography scans became possible. A range of possibilities emerged with the increased use of 3D conformal radiotherapy, followed by intensity-modulated radiotherapy and more advanced techniques that are available nowadays (volumetric modulated arc therapy [VMAT], image-guided radiotherapy [IGRT], radiosurgery, and stereotactic radiotherapy, among others). A better definition of tumor anatomy and topography could improve results by preventing eventual geographic misses[20], and intensity-modulated techniques that have the property of better conform the target have been demonstrated to be less toxic[21-23] (Figure 1).

Brachytherapy followed the same path, evolving from a simple insertion of radium capsules in the uterine cavity by visual and hand-guidance only to 2D treatments using radiographs and 3D image-guided techniques, based on volumetric images of magnetic resonance imaging and/or computed tomography scans. The development of different radioactive sources (Cesium-136, Cobalt-60, and Iridium-192), applicators, afterloading systems, and high dose-rate brachytherapy made the treatment safer for both the patient and the staff. The simple fact of better defining the tumor volume and dose delivery with the image-guided approach increased local control and survival, with lower toxicity[24-27] (Figure 2).

Approaches with proton therapy and stereotactic body therapy may present dosimetric advantages over the other techniques. For cervical cancer, attempts have been made to replace brachytherapy by these techniques or to use them as a boost for patients where brachytherapy is not feasible. However, neither technique has yet proven to be superior[28,29].

The historical and basic concepts of cervical cancer treatment are keeping the same over the years, but the technologies are still evolving and are promising in the oncological treatment scenario. New drug combinations, associations with immune and targeted therapies, and more precise radiation delivery possibilities are on the way[30].

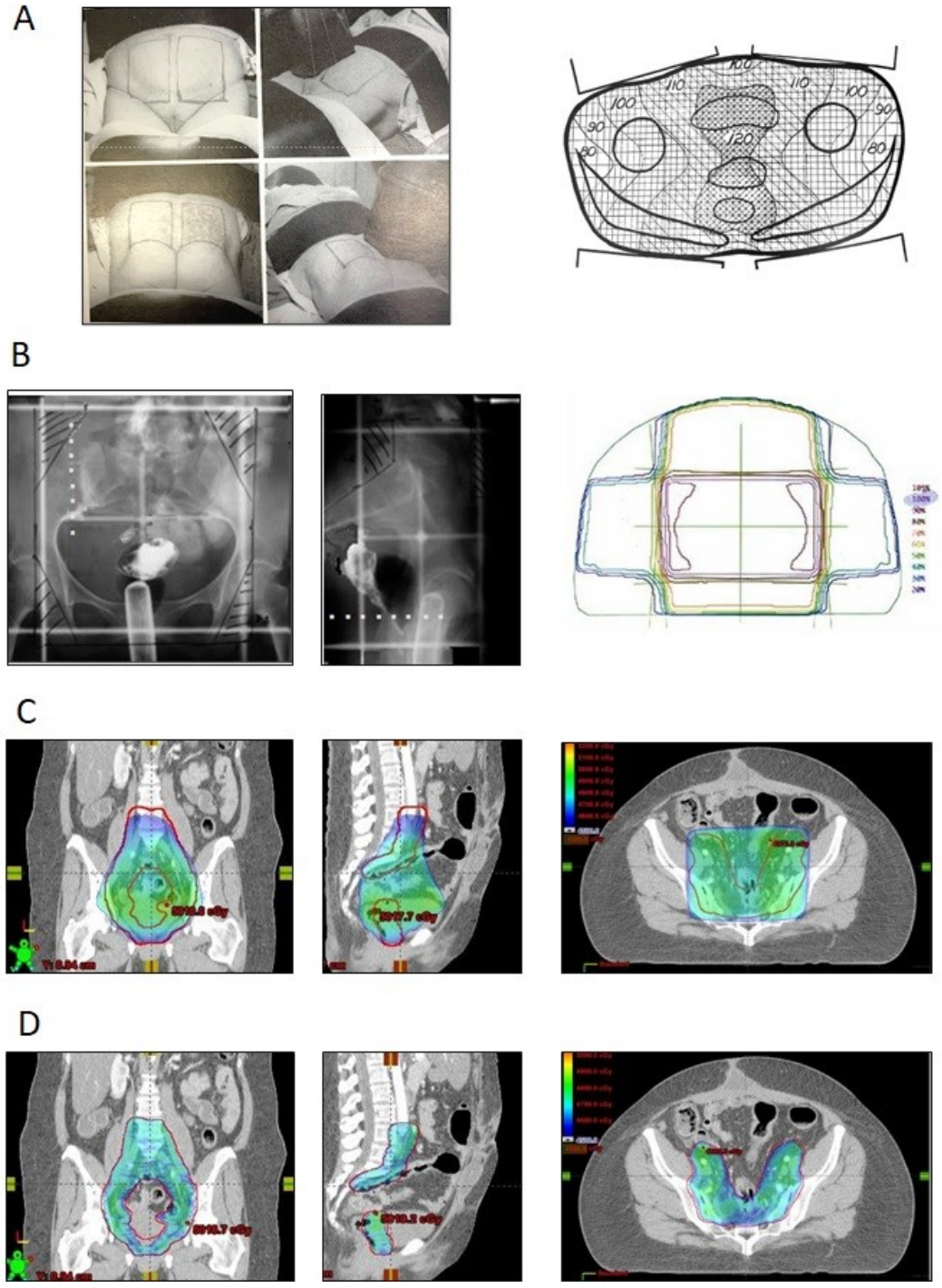

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Figure 1. Evolution of radiotherapy for cervical cancer over the years. External beam irradiation. (A) Bidimensional (2D) technology, beginning with surface anatomy only and roentgen therapy, followed by panel (B) orthogonal x-rays for fields definition, and the correspondent dose distribution below. (C) Three-dimensional (3D) technology based on computed tomography scans with volumetric image reconstruction and the respective dose distribution. (D) Intensity-modulated radiotherapy (IMRT) dose distribution. Comparing panel (C) with panel (D), target coverage is the same, but IMRT provides better normal tissue sparing.

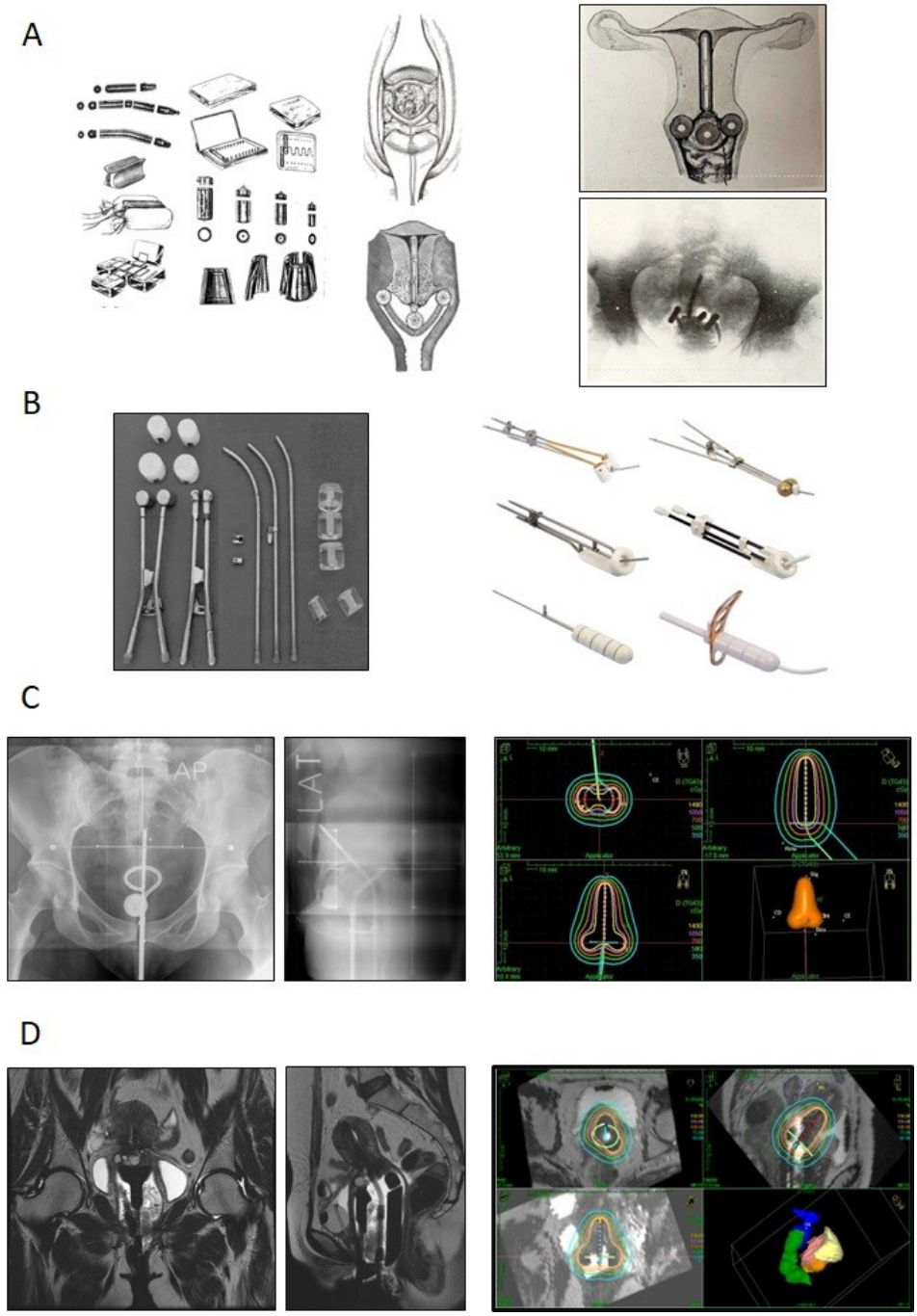

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Figure 2. Evolution of radiotherapy for cervical cancer over the years. (Brachytherapy). (A) Diagrams of among the first brachytherapy pre-loaded applicators and their positioning with available imaging in the right. (B) Low dose-rate (left) and high dose-rate (right) brachytherapy gynecological applicators, both for afterloading systems. (C) Radiographs and dose distribution of high dose-rate intracavitary brachytherapy based on dose points (bidimensional). (D) Magnetic resonance images of image-guided gynecological brachytherapy, with the applicator in place and the correspondent volumetric dose distribution.

REMARKS AND CONCLUSION

Cervical cancer is the fourth-most frequently diagnosed and the fourth-leading cause of cancer death in women worldwide. In low- and middle-income countries, it occupies the first place, both in incidence and mortality[31,32]. It affects mainly young women with a higher number of childbirth, and the most important risk factor is the herpes papilloma virus (HPV) infection[31]. Therefore, it is imperative to study and understand the disease for better prevention, treatment, and control.

Since the beginning of the 20th century until today, the combined treatment of external beam irradiation with brachytherapy has become the standard of care for advanced cervical cancer. The irradiation techniques have evolved, combined treatments have improved the results, and complications are being reduced and better controlled over time. Nevertheless, the cure for invasive cervical cancer still relies on the combination of treatment with radiotherapy.

In 2018, the World Health Organization (WHO) launched a global call for action toward the elimination of cervical cancer in the world[33]. "Each country should meet the 90-70-90 targets by 2030 to get on the path to eliminate cervical cancer within the next century.

- Vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15;
- Screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45;
- Treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed."

The management of invasive cervical cancer was addressed[34], and several other linked initiatives around the world were taken.

We hope that, not so far in the future, this disease will no longer exist. Until then, radiation will remain as one of the cornerstones in the treatment of this disease.

AUTHORS' CONTRIBUTIONS

HAC: Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **GPM:** Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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The challenge of tobacco and nicotine use among women

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INTRODUCTION

There is growing concern about smoking among women, considering the trend toward reducing the gender gap in some WHO regions. In high-income countries, female smoking is declining but is increasingly concentrated among disadvantaged women[1]. In low-/middle-income countries, the pattern is more complex[1]. Women began smoking after men, lagging behind around 20–30 years[2]. Over time, the increasing female smoking trend narrowed the gender gap, and even more so among youth[1]. This gender gap is narrowest in high- and upper-middle-income countries; in the region of the Americas and Europe, where 1 in 3 tobacco users are female[3]. In contrast, in most low- and low-middle-income countries, particularly in Africa, the Eastern Mediterranean, and the Western Pacific regions, female smoking remains under 5% and is expected to decline[3].

All WHO regions are on track to decrease female prevalence by at least 30% by 2025, with the exception of Europe, which remains the region with the highest tobacco use among females[3].

Female prevalence is lower than males in most countries. According to WHO estimates, in 2020, worldwide prevalence of tobacco use among people aged ≥15 years was 22.3% in both sexes (male: 36.7%; female: 7.8%)[3]. Furthermore, tobacco use will continue to decrease, reaching 20.4% in 2025 (male: 34.3%; female: 6.6%)[3]. Nevertheless, female smoking-attributable mortality is estimated to increase, following the tobacco-epidemic model[2].

Women who smoke have a relatively greater risk of smoking-related diseases than men, such as heart disease, stroke, decreased lung function, COPD, and LC in earlier ages[4]. Remarkably, women face unique problems linked to tobacco and their biological/reproductive life-cycle: female-specific cancers (cancer of the cervix); coronary heart disease, stroke, and thromboembolism (increased risk with oral contraceptives); menstruation (irregular cycles and dysmenorrhea); early menopause; osteoporosis; and impact on fertility/pregnancy and fetus/child development, including the damaging effects of nicotine on brain development. Furthermore, women tend to face more difficulty to quit smoking[4] and are more exposed to SHS[5].

The tobacco companies have targeted women by marketing light, mild, and menthol cigarettes, tailoring their advertisements to women. The greatest health challenge is to avert the increase in smoking among disadvantaged women, which fosters health inequalities[1]. Moreover, the launch of novel nicotine/tobacco products may menace the decreasing worldwide

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trend of cigarette consumption. Remarkably worrying is the narrower gender gap on e-cigarette use[3].

Female smoking trends are influenced by age, psychological, socioeconomic, demographic, and cultural factors, as well as the tobacco industry's underhanded marketing and promotion strategies[6]. Women are targeted using the same themes as tobacco companies have for decades: their use is tied to independence, stylishness, sophistication, and power[6].

A comprehensive tobacco control program requires coordinated efforts by state and community partners to provide public education and support for policies that work to reduce disparities. There is overwhelming evidence that the tobacco industry understands, exploits, and shapes gender norms. Strikingly, the design and delivery of tobacco control policies/programs remain mostly gender-blind and gender-unresponsive, failing a key determinant not only of risk but also of effective interventions[6].

WOMEN'S HEALTH AND PREGNANCY

Tobacco/nicotine use during pregnancy is the leading preventable cause of maternal and fetal health hazards, and the epigenetic changes caused may be transmitted transgenerationally[7]. TS exposure affects all stages of human reproduction[8]. TS contains thousands of compounds with known toxic effects on reproductive health, such as carbon monoxide, nicotine, and heavy metals, including lead, mercury, and cadmium[9]. Smoking reduces fertility in women, with an apparent conception delay for first-time pregnancies. Smoking women require twice as many *in vitro* fertilization attempts and are more likely to enter menopause earlier than non-smokers[9]. Findings from studies evaluating the effects of in-utero exposure to maternal smoking on later fertility/fecundability are mixed[9].

Conception delays reflect a range of possible adverse effects on reproduction: interference with gametogenesis/fertilization, difficulty on implanting the fertilized egg, or subclinical loss after implantation. Animal studies suggest that tobacco compounds interfere with all early pregnancy events[10,11]. Furthermore, female mice exposed to benzopyrene, a cigarette component, have impaired fertility, potentially related to primary oocyte destruction[12].

Maternal smoking has also been associated with increased risk of ectopic pregnancy, premature membrane rupture, abruptio/previa placentae, and miscarriage; stillbirth, preterm birth, low birth weight, and gestational age small size; and congenital anomalies (such as cleft lip, cardiac septal defects, pulmonary, tricuspid valve and great arteries malformations, pyloric stenosis, and clubfoot) and multiple malformations[8,12,13].

Smoking during pregnancy is responsible for 20% of low-birth-weight babies, 8% of premature births, and 5% of all perinatal deaths[14]. Economic estimates indicate that the costs of perinatal complications are 66% higher for smoking mothers than for non-smokers[15]. Although the most significant benefits for fetal development occur with early smoking cessation, abstinence at any stage of pregnancy or in the postnatal period remarkably improves family health.

Uteroplacental insufficiency is the primary mechanism for fetal growth retardation in pregnant smokers. Nicotine causes uterine/placental vasoconstriction, reducing blood flow, oxygen, and nutrients for fetal delivery.

Smoking also contributes to several causes of premature membrane rupture and miscarriage. Tobacco toxicity decreases macrophage phagocytic capacity, alters mucous membrane immunoglobin A levels, and interferes with local infection control mechanisms. Additionally, it reduces ascorbic acid concentration in amniotic fluid and amino acid transport through the placenta, influencing amniochorionic membrane development[16,17].

Decreased placental synthesis of nitric oxide, a potent myometrial relaxant, increases spontaneous abortion risk. Moreover, decreased platelet activating factor can cause uterine contractions and premature birth since it is involved in initiating/maintaining labor through prostaglandin synthesis[16,17].

SECONDHAND TOBACCO SMOKE HAZARDS IN PREGNANT WOMEN AND FETUS

Secondhand tobacco smoke (SHS) results from the burning of a tobacco product (side stream) and the smoke exhaled by smokers (mainstream). It is estimated that 85% of SHS in an enclosed smoking environment arrives from the tip of a lit cigarette[18]. Cigarettes, pipes, cigars, and hookahs generate SHS. TS contains more than 7,000 toxic chemicals[18]. Exposure to secondhand aerosol from electronic cigarettes also poses harmful effects to bystanders[19].

Despite smoking bans in public places, pregnant women may be exposed to SHS in the home, especially in subpopulations with higher smoking prevalence[15].

Little is known about SHS exposure during pregnancy. SHS surveys in pregnant women in low-/middle-income countries found that daily exposure ranged from 6 to 73%, which was higher than mother smoking in all countries[20]. Being wealthier, having a mother's job, having a higher education, and living in an urban area were associated with lower SHS exposure[20].

The association between social determinants and SHS during pregnancy varies according to the type of exposure[21]. Women at risk of any exposure to smoke during pregnancy include unmarried women who allow indoor smoking[7]. Those most exposed include the younger ones and in early pregnancy[7].

Maternal smoking during pregnancy and SHS exposure are associated with mother/child health hazards, such as infant stillbirth, congenital and respiratory illnesses, neonate lower mean birth weight, length, and head circumference[7,15,20].

A study found that non-smoking women exposed to SHS had an increased risk of stillbirth (23%) and congenital malformations (13%), but not spontaneous abortions[7].

There was a greater risk of discontinuing breastfeeding before 6 months among women exposed to SHS during pregnancy[15]. Postnatal maternal smoking doubled lower respiratory infection risk compared to prenatal smoking[15]. The risk of orofacial clefts was accentuated by 200% when pregnant mothers were exposed to SHS[7], similar to active smoking risk[7].

Women exposed to SHS have a 20% greater risk of giving birth prematurely[15]. SHS exposure in pregnant women may be linked to a 70% increase in mental health disorder risk (depression and suicide ideation)[15].

SMOKING AND CARDIOVASCULAR DISEASE IN WOMEN

Among women, CVDs are the leading cause of death[22]. While tobacco and hypertension are the most preventable CVD risk factors, smoking also increases the risk of arterial hypertension, diabetes, and dyslipidemia, reinforcing CVD risk. Worryingly, tobacco is the main cardiocerebrovascular risk factor in young women, especially if associated with oral contraception, increasing the risk by 30 times compared to non-smoking women without it[23].

The association of smoking with CVD occurs through several mechanisms: endothelial damage/dysfunction, oxidative stress, changes in hemostatic factors, fibrinolysis, inflammation, lipid changes, and vasomotor function; directly influencing pathways related to atherogenesis and thrombosis. Smoking activates the sympathetic nervous system, increasing heart rate and blood pressure and leading to cardiac hypoxia; its effects are more pronounced in women[22].

Women have an increased gender-related risk for CVD. A large sample cohort demonstrated a 25% greater risk for coronary heart disease in female smokers than in male smokers[24]. Female smoking is associated with an increased risk of premature myocardial infarction (<66 years) and higher stroke risk, increasing with higher consumption[25]. A review on hormonal contraception among e-cigarette users has identified no evidence on cardiovascular outcomes, but further research is needed[25]. E-cigarettes expose users to high levels of ultrafine particles that penetrate deep into the lungs[26], triggering inflammatory mechanisms and causing CVD and acute cardiovascular events[26].

Vigitel 2021 showed that 6.4% of adult Brazilian women were exposed to SHS in their homes. SHS exposure is significantly associated with cardiovascular risk; exposed women have a 24% increased risk for CVD, 24% for coronary disease, and 21% for stroke[28].

Smoking cessation has a direct and rapid effect on CVD risk, fostering reductions in inflammatory markers and hypercoagulability, rapid changes in HDL levels, and possibly improving endothelial function. Moreover, a study following 104,519 nurses (1980–2004) showed that women who continued to smoke had higher mortality from coronary and cerebrovascular disease than those who quit less than 5 years ago[28].

The dose–response relationship between smoking and SHS exposure and cardiovascular mortality is nonlinear: light/intermittent smoking, frequent among women, poses similar CVD-risk as daily or higher cigarette consumption; reducing consumption does not warrant cardiovascular health benefits[23].

There is overwhelming evidence supporting smoking cessation and smoke-free environments as key interventions in the prevention and management of CVD[22,27]. Smoking cessation is the single most effective intervention for improving prognosis after a cardiac event, resulting in larger reductions in CVD mortality when compared with secondary prevention[22,29]. Nonetheless, smoking cessation remains neglected in CVD clinical practice[29].

RESPIRATORY HEALTH EFFECTS

The inhalation of harmful substances (such as cigarette smoke and environmental pollutants) is associated with an increased airway inflammatory activity[30].

Tobacco stands as the main and greatest preventable cause of respiratory diseases. The "big five" respiratory diseases (such as asthma, COPD, lung cancer, tuberculosis, and pneumonia/acute lower respiratory tract infections), as well as ILDs, are caused or aggravated by tobacco use or exposure to SHS[30].

ENDS aerosol is not harmless "water vapor"; it contains nearly 2,000 chemicals, mostly ignored[31], including heavy metals, ultrafine particulates, and cancer-causing agents[31].

LUNG CANCER

Tobacco causes 55% of lung cancer deaths in women. Although past research had suggested that women were more likely to

develop cancer at a younger age and with lower smoking rates, recent epidemiologic studies failed to demonstrate this[33]. Remarkably, the tobacco epidemic is not yet fully mature in women, eventually underestimating lung cancer risk in women.

Since 1987, lung cancer has overtaken breast cancer as the leading cause of cancer death among women in the United States and other 28 industrialized countries, due to increased[32] smoking in women. Although LC mortality has reduced over time, it is still higher than deaths from breast, prostate, and colon cancers combined[33].

Nevertheless, studies suggest that sex hormones play an important role in tobacco-induced LC[34] and that disease is not the same in both sexes, especially in terms of modifiable/non-modifiable biological risk factors of carcinogenesis[34].

There is a higher LC incidence in non-smoking young females (female: 15–20%; male: 7–9%)[35]. Adenocarcinoma is the most common histological pattern in women. Finally, women have better five-year survival, regardless of age, staging, and treatment.

TUBERCULOSIS

Smoking is a risk factor for both active and latent TB. Several epidemiological studies have shown that, even after adjusting for sex, age, and educational level, TB is more common in smokers than in nonsmokers[36]. Additionally, smokers with TB tend to have a more severe disease course and worse treatment response and relapse. This association occurs for several reasons, including the reduction in mucociliary clearance and ciliary dysfunction caused by smoking. Furthermore, smoking negatively impacts the function of neutrophils, dendritic cells, and T lymphocytes, which are responsible for controlling the dissemination of tuberculosis[36].

INTERSTITIAL LUNG DISEASES

ILDs are a heterogeneous group of lung disorders; several may lead to progressive pulmonary fibrosis[37]. There is a higher ILD prevalence in women related to connective tissue diseases and hypersensitivity pneumonitis (HP); home environmental antigens are mostly responsible for this gender-difference. Because they can have extremely aggressive behavior, treatable traits for ILDs have been proposed[37]. Smoking is definitely one of them, being linked to more severe HP, worse survival in idiopathic pulmonary fibrosis, and other progressive ILDs. Furthermore, there are some ILDs that are closely smoking-related, such as Langerhans cell histiocytosis, respiratory bronchiolitis, desquamative pneumonitis, and combined pulmonary fibrosis and emphysema.

ASTHMA

In adults, asthma is more frequent in females, and smokers have increased asthma prevalence and incidence. In addition, ENDS use increases symptoms, self-reported diagnoses, and asthma exacerbations. Smoking during pregnancy increases the risk of developing asthma in childhood[38]. Asthma is characterized by airway inflammation and BHR. BHR is higher in smokers compared to nonsmokers and in women than in men[38].

Smoking and SHS exposure significantly impact asthma, worsening disease severity, and control. In asthmatics, smoking accelerates lung function loss, decreases the response to inhaled and systemic corticosteroids, and increases exacerbation risk, hospitalizations, and mortality. Importantly, smoking cessation improves asthma control, reduces inflammation and exacerbations, and improves lung function[38].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is diagnosed in the presence of respiratory symptoms, identification of a risk factor, and confirmation of airflow obstruction by spirometry. Smoking is the main COPD risk factor in Brazil, with other factors being SHS, occupational exposure to particulate matter or gases, environmental pollution, alpha-1-antitrypsin deficiency, and low lung growth[39].

A lower lung growth rate was recorded in female adolescent smokers compared to males. Non-smokers lose about 20–25 mL/year of forced expiratory volume in 1 s after the age of 25 years, due to the aging process. In smokers at risk for developing COPD, loss of lung function is more accelerated. Women may be more susceptible to smoking than men, with more symptoms and exacerbations, greater loss of lung function, and more small airway disease with the same smoking history[39].

Quitting smoking improves symptoms such as cough and sputum, reduces exacerbations, and accelerates lung function loss. While early cessation prevents COPD, later cessation increases survival in established disease[39].

GENDER-SPECIFIC TOBACCO/NICOTINE USE CESSATION TREATMENT

TNU is a chronic, relapsing disorder. Treatment combines pharmacological therapy to overcome withdrawal symptoms and behavioral counseling to deal with smoking triggers and behavioral aspects[40].

Women often visit health services due to their biological/reproductive life-cycle and also being caregivers for their children/relatives. This is a golden opportunity to systematically

ask and advise about TNU and SHS exposure and offer support to quit whenever women contact healthcare, even if it is not tobacco-related. Importantly, healthcare providers should record both TNU and the counseling intervention in the clinical files so that they can be followed at a later visit[23,40].

Pregnancy is commonly seen as a unique window of opportunity since women are more motivated to quit and smoking cessation at any pregnancy time results in health benefits. Early smoking cessation during the first trimester obtains the greatest benefits and should be strongly encouraged[16].

Smoking cessation counseling during pregnancy is effective[41]. It should ideally be offered while planning pregnancy to maximize maternal-fetal health benefits, and when pharmacological therapy may be used without restrictions[7]. Behavioral counseling, pregnancy-specific self-materials reinforcing benefits, and psychosocial support are first-line treatment[7,16]. The woman's family, environment, and partner should be approached and involved[7,23]. Regarding the efficacy and safety of cessation pharmacotherapy when used during pregnancy, the evidence is inconclusive. In some countries, nicotine replacement therapy (NRT) is recommended for women who do not succeed in quitting without pharmacotherapy[16].

There are recent literature reviews and smoking cessation guidelines for intervening in pregnancy[7,16,41,42].

The greatest challenge is how to engage and promote smoking cessation among socially disadvantaged women who are more likely to smoke during pregnancy, perceive a less negative attitude toward their smoking, are more tempted in habit-related situations, and profit less from valuable empirical processes of change[43].

Although women smoke fewer cigarettes and with lower nicotine content than men, they have a higher dependence risk, reporting greater physical and emotional dependence on smoking[4]. Particularly, women may be less receptive to nicotine reinforcement effects but more sensitive to non-nicotine conditioned-smoking cues and sensory aspects. Furthermore, women may be less likely to report readiness to quit and less confident in quitting success, usually reporting more difficulty to cope with stress and withdrawal symptoms, especially anxiety and negative mood[23,44].

Women face gender-related barriers and more difficulty to quit: weight gain concerns; menstrual/hormonal cycles influencing withdrawal and metabolization of nicotine/NRT; greater likelihood of depression and mood variability; lack of social support; family work; and caregiver burden. These barriers require tailored behavior interventions[4,23,40,44]. Treatment programs should use a patient-centered approach, focusing on gender-specific barriers, individual concerns, and beliefs; consider the complexity of variables influencing smoking behavior in women; and include intensive multicomponent interventions, i.e., motivational interviewing, problem-solving skills strategies, and cognitive behavior therapy addressing smoking cues, negative mood, weight management, and social support. Group therapy may enhance motivation, self-efficacy, and social support[23].

Women respond less to NRT than men, requiring more intensive behavior counseling[4]. Nevertheless, NRT in women is effective and should be used in combination therapy with other NRT or non-nicotine medications[4,23,40].

Bupropion and varenicline clinical trials demonstrate no treatment-gender interaction, benefiting both sexes equally, indicating that these drugs may be more effective in female patients. Non-nicotine medication reduces craving and desire to smoke and may help weaken smoking-conditioned cues[23]. While varenicline is more effective than bupropion[45], bupropion helps to delay weight gain, as does oral NRT[40]. For women with weight concerns, bupropion and oral NRT are pharmacotherapy options. Additionally, regular, moderate exercise and a healthy diet should be encouraged.

Research addressing gender and pregnancy-specific smoking cessation interventions, developing tailored behavior change strategies, and targeting socially disadvantaged women is much needed.

COGNITIVE BEHAVIOR TREATMENT AND RELAPSE PREVENTION

"When you want to see me again
You'll find me redone, believe me
Eye to eye, I want to see what are you gonna do
When I feel that without you I'm doing too well"
(Chico Buarque, Olhos nos olhos)

Smoking Cessation Outpatient Clinic of the State University of Rio de Janeiro (UERJ) is a multidisciplinary team. All patients undergo individual consultations; participation in group sessions, made up of 10 patients of both sexes and different ages, is optional. Meetings occur every Wednesday. In the first month, there are four weekly meetings of 90 min each, and then a monthly meeting until completing 1 year of follow-up.

Since January 2022, 130 patients have attended UERJ, mostly women (71%), with an average age of 59.7 years. They have been prescribed NRT (patch and/or gum) and Bupropion, available at the Brazilian Public Health Service. Giving voice to these women reveals a rich and challenging universe. They

know why they are there and that they should not smoke; they want to stop but still continue to, i.e., ambivalence.

In the first meeting, tobacco-related diseases are discussed. It is emphasized what is gained by quitting. Addiction is debated without prejudice; the "belief system" is presented, and beliefs that hinder decision-making are discussed, such as "it's too hard and I won't make it". Patients are engaged in choosing the quit method and the treatment plan, reducing drop-out, and strengthening the patient–physician relationship. This shared decision-making builds autonomy and commitment.

Relapse prevention is a cognitive-behavioral intervention designed to prevent or manage relapse. The goal is to teach individuals how to anticipate and cope with high-risk relapse situations. Once relapse has occurred, UERJ's team identifies *when, with whom, where, and what you were feeling when you smoked*.

Patients with psychiatric comorbidities are referred for specialized care; they report fear of failing and a lack of social/family support. Many have low self-efficacy. It is not uncommon to hear: "*I was so nervous that my family ended up buying me cigarettes.*" Many men arrive with their wife or mother. Women come alone.

Post-smoking cessation weight gain (PSCWG) is a concern in both sexes and an independent predictor of quitting failure, mainly among teenage girls and women[4]. A real-world prospective cohort study conducted at the Outpatient Smoking Cessation Clinic of São Lucas Hospital (Porto Alegre, Brazil) between 2010 and 2016 found that 64.6% of the patients who achieved biochemically confirmed continuous abstinence maintained their weight or changed no more than 5% in relation to their baseline weight[46]. PSCWG is not reported by UERJ's patients as a barrier to quitting; many of them lost weight while suffering from COPD or cancer, considering it positive.

Justifying cessation benefits from our point of view does not work. It is their own reasons that will motivate them to quit: whether it is getting fragrant, saving money, using clear nail polish, improving health, or "*I want to hold my grandson*". Treatment should be individualized. The patient-centered approach and active listening with reflection of feelings, among other techniques, elicit the smoker to seek internal motivation to change, i.e., eye to eye. Any doctor can do this, and it is based on the therapeutic doctor–patient relationship.

Cigarettes steal their youth, health, and freedom, and they ask "*How am I going to live without smoking? I smoked all my life*!" In front of us, reality is imitating fiction: "*Do I want to die healthy after being sick all my life?*" Yet, they seek comfort in their tormentors.

Some received brief counseling, mostly guilt-generating or not "supportive": "T*he doctor said I had to stop smoking, but didn't explain how to do it*". When doctors omit advising on tobacco hazards, smoking is allowed. Doctors often fail due to negligence, or poor knowledge.

Group sessions allow participants to understand the behavior change process, create complicity, and foster engagement. They need to learn to live and face daily challenges without cigarettes. Sessions' content includes strategies to manage craving, enhance self-esteem, and make choices. We recognize each person's strengths and celebrate baby steps. Patients associate relapse with a relative's death or illness, divorce, unemployment, stress, and negative mood.

Partnership, compassion, and evocation are also part of our daily lives. Helping them to achieve long-term abstinence is our biggest challenge. They move on with their lives.

"Despite of you, tomorrow will be another day" (Chico Buarque, Apesar de você).

ABBREVIATIONS

BHR: bronchial hyperreactivity; COPD: chronic obstructive pulmonary disease; ENDS: electronic nicotine delivery systems; ILDs: Interstitial lung diseases; LC: lung cancer; SHS: secondhand smoke; TB: tuberculosis; TNU: tobacco and nicotine use; TS: tobacco smoke; WHO: World Health Organization.

WARNING SIGN

This review results from a collaboration between the tobacco control committee of the Brazilian Respiratory Society (SBPT) and the Portuguese Respiratory Society (SPP), with the International Network of Women Against Tobacco (INWAT), Europe.

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