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Editorial

Embracing a Sustainable Approach in Gynecology and Obstetrics: The Surgeon's Duty to Safeguard both Patient and Environment

Adotando uma abordagem sustentável em ginecologia e obstetrícia: o dever do cirurgião de proteger o paciente e o meio ambiente

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The detrimental effects of climate change on global health and wellbeing have become increasingly apparent and concerning. According to the World Health Organization (WHO),[1] climate change is projected to cause an additional 250,000 deaths per year between 2030 and 2050, due to malnutrition, malaria, diarrhea, and heat stress. Unfortunately, the healthcare sector also contributes to the problem, as it is a major source of greenhouse gas emissions, accounting for 4.6% of total emissions in 2017.[2] The operating theater is one of the most energy-intensive areas within healthcare facilities, with energy consumption rates three to six times higher than those of other hospital areas.[3,4] Medical waste production and the emission of harmful anesthetic agents during surgical procedures further exacerbate the environmental impact of healthcare.[5]

To address these environmental issues, the concept of "green surgery" has emerged as a promising solution. Green surgery involves incorporating environmentally friendly materials and practices that conserve energy, reduce waste, and minimize greenhouse gas emissions, while still ensuring high-quality patient care.[4,5] In this editorial, we aim to provide a comprehensive examination of the importance of green surgery, with a specific focus on its application in gynecological and obstetric surgeries. We will explore the benefits, strategies, and challenges of incorporating green surgery into surgical practices, and provide insights into its potential to reduce the environmental impact of surgical procedures and promote sustainability in healthcare.

Sustainability in health systems, as defined by the WHO, is a comprehensive approach that balances health outcomes with minimizing environmental harm. This approach recognizes the interconnectedness of health and the environment and stresses the importance of considering both when delivering healthcare services.[3] To achieve this goal, it is crucial to educate healthcare professionals about metrics related to greenhouse gas emissions, life cycle analysis, and strategies for reducing environmental impact in healthcare. The 5Rs rule—reduce, reuse, recycle, rethink, and research—can be effectively applied in medical practice, particularly in the operating room, to promote eco-friendly practices.[6] Adopting green surgery practices, which include minimizing waste, reducing energy and water consumption, implementing sustainable supply chain management, and prioritizing the use of renewable energy systems, is a crucial aspect of promoting sustainable healthcare (►**Fig. 1**). These efforts not only increase the sustainability of healthcare facilities but also align with the principles of environmental responsibility in the healthcare sector. By reducing their carbon footprint, medical facilities demonstrate their commitment to creating a more sustainable future for the planet.[5]

The incorporation of green surgery presents a significant challenge due to the high costs associated with the use of green energy. Hospitals need to alter their processes and structures to achieve sustainability goals, which involves the entire chain of patient care. For instance, hospitals need to adopt new sterilization devices that emit fewer pollutants, consume less water, and deliver the same level of quality as disposable devices. The entire surgical team needs to be sensitized to the need to change the way it behaves in the use of resources, from proper handling of contaminated materials to energy savings. Additionally, surgical blocks should be equipped with modern LED devices to reduce

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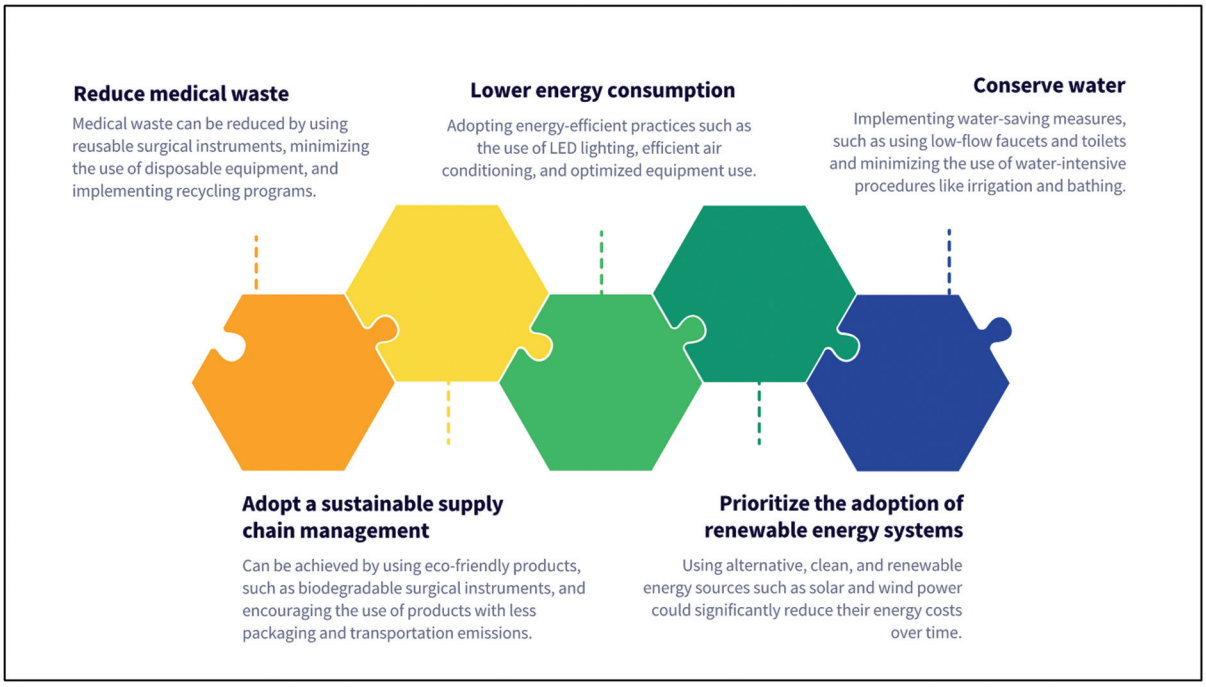

Fig. 1 Greening Gynecology and Obstetrics: Key Strategies for Implementing Sustainable and Environmentally Friendly Practices.

energy consumption and automatic faucets to control water usage.[7,8] Unfortunately, such efforts may require a significant financial investment, particularly in underdeveloped countries. To overcome this challenge, it is essential for surgeons and anesthesiologists to lead the way in developing an ecological mindset. This involves acquiring greater knowledge of recyclable or reusable materials, rational consumption of greenhouse gases used in inhalational anesthesia, and energy-saving practices.[9–11]

The Royal College of Surgeons of England has devised a comprehensive list of recommendations aimed at reducing the environmental impact of operating theaters. This list has been compiled based on an exhaustive review of all relevant guidance and published evidence and is available in the Compendium.[12]

In the healthcare setting, sustainability efforts must go beyond the facility walls and begin from the preadmission stage. This involves the development of health promotion strategies and encouraging the use of eco-friendly transportation modes for patients, healthcare professionals, and medical supplies. Within the hospital, the implementation of renewable energy sources, optimization of energy systems, and reduction of disposable materials can significantly lower the carbon footprint and contribute to sustainability efforts. The use of intravenous and local anesthesia instead of anesthetic gases during surgical procedures is another environmentally friendly option. Implementing recycling programs and utilizing telemedicine can also play a crucial role in reducing waste production and supporting sustainability goals.[3,5,6]

Hospitals in developed countries play a significant role in the generation of solid waste and greenhouse gas (GHG) emissions, accounting for 1% of the former and 2.1% of the latter on an annual basis. A considerable portion of these emissions is attributed to the operating room (OR) due to the usage of energy-intensive equipment and the emission of anesthetic gases. Additionally, the transportation and incineration of waste also contribute substantially to GHG emissions. It is estimated that the incineration of 1 kg of clinical waste generates 3 kg of carbon dioxide. Despite these facts, the WHO reports that a substantial amount of hospital and OR waste, ~ 85% and 90%, respectively, is non-hazardous and similar to domestic waste, providing opportunities for recycling and reducing emissions.[6] Furthermore, gynecological surgeries can exacerbate this situation by producing a significant amount of waste, including disposable surgical instruments, gowns, drapes, and other single-use items, which can have a negative impact on the environment if not properly managed.

To mitigate this impact, green surgery focuses on reducing waste through the use of reusable surgical instruments and reducing single-use plastics. Reusable surgical linens and instruments are an eco-friendlier alternative as they result in lower waste generation and decreased expenses for landfill and incineration. A comprehensive evaluation of the production-to-sterilization process showed that the carbon footprint of reusables is more favorable compared with that of disposable options. For instance, the use of reusable surgical devices in laparoscopic procedures can save an estimated 122 kg of waste per case.[13] The use of reusable gowns can also significantly reduce waste output by up to 70%.[3]

Minimally invasive surgery (MIS) is known for its benefits, but it also generates a significant amount of waste due to the reliance on disposable surgical instruments. To address this issue, healthcare providers need to adopt a comprehensive approach that includes minimizing material usage, transitioning to eco-friendly anesthetic gases, maximizing instrument

reuse, and reducing energy consumption during off-hours in the operating room. The combined efforts of these measures can reduce the carbon footprint of an average laparoscopic hysterectomy by up to 80%.[14] A systematic review on the environmental sustainability of robotic and laparoscopic surgery has shown that the clinical benefits of robotic surgery may not justify its increased environmental impact. However, the review suggests several measures that could help reduce GHG emissions and waste in surgical practice. These include the use of alternative surgical approaches, reusable equipment, repackaging, surgeon preference cards, and staff awareness on open and unused equipment, as well as avoidance of desflurane. Implementing these changes could contribute to a more sustainable healthcare system.[15]

In addition to considering changes in general medical procedures, it is crucial to incorporate sustainable practices in obstetric care as well. Maternity services should focus on developing and disseminating green and sustainable practices, which can be implemented quickly.[16] One area of particular concern is the OR and labor-delivery waste, which accounts for $\sim$ 70% of hospital waste.[17] Targeted solutions should be explored to address sustainability in this area. It is important for healthcare providers to prioritize environmental sustainability in obstetric care to minimize the impact of healthcare services on the environment.

Green surgery aims to minimize energy consumption through the implementation of energy-efficient technologies and practices, such as LED lighting and low-flow anesthesia machines, thereby reducing OR costs and enhancing the overall sustainability of healthcare facilities.[4,5] In addition, water conservation is a crucial aspect of green surgery, which can be achieved through the use of water-saving devices in the OR and minimizing water-intensive procedures.[3] Simple measures, such as avoiding repetitive water scrubbing and implementing automatic or pedal-controlled water taps, can effectively reduce water and energy consumption.

Sustainable supply chain management is a crucial aspect of green surgery, with the aim of minimizing the environmental impact of the production, transportation, and disposal of surgical supplies and equipment. A significant portion of carbon emissions produced by healthcare facilities arises from the procurement of drugs and medical devices, including the production methods, packaging, transportation to the hospital, and the energy and materials required for drug delivery.[6] In gynecologic and obstetric surgery, this objective can be achieved through the adoption of eco-friendly products, such as biodegradable surgical instruments, and the promotion of products with minimal packaging and transportation costs.[3]

Optimizing efficiency, reducing waste generation, and conserving energy not only positively impacts the environment but also results in cost savings. A systematic review conducted by Sullivan et al. (2023)[5] evaluated the environmental and financial impact of quality-improvement initiatives in ORs. The review found that 90.9% of the 10 studies analyzed reported annual savings, ranging from $6,572 to $322,405 per year. Out of these, 45.5% reported savings per procedure, with cost reductions mainly attributed to reduced instrument processing or sterilization (54.5%). A few studies reported cost reductions from decreased supplies per case (27.3%) or less frequent use of individual instruments/supplies (27.3%). One study (9.1%) also included cost savings from labor, utilities, and instrument depreciation. In terms of patient outcomes, two studies (18.2%) reported positive results. One study found that changes in elective hand surgery procedures, including reducing disposables and modifying anesthetic approaches, resulted in a 96% satisfaction rate among patients. The implementation of a surgeon-specific scorecard with direct cost feedback and supply usage also led to reduced waste and had no negative effect on procedure times, length of stay, or complications.

Hospitals are significant consumers of energy, using more than 10% of the energy consumed for commercial purposes.[18] This high demand for energy presents an opportunity to explore alternative, clean, and renewable energy sources such as solar and wind power. By transitioning to these forms of energy, hospitals could significantly reduce their energy costs over time. Moreover, renewable energy systems are less vulnerable to disruptions than traditional fossil fuel systems in the event of accidents or natural disasters, making them a reliable and sustainable option for hospitals in Brazil. These technologies can help hospitals to operate efficiently and reduce their environmental impact while providing critical healthcare services to the population.[19]

While there are numerous benefits to implementing green surgery, significant challenges must be addressed to effectively adopt this approach. These challenges include the lack of standardized guidelines and protocols, high costs associated with green technologies, and limited resources for their acquisition. Furthermore, insufficient knowledge among healthcare providers and inadequate training on how to utilize related technologies hinder the adoption of sustainable approaches in healthcare. Economic and financial challenges, including limited access to funding for implementing climate action, also pose significant barriers. Additionally, challenges related to policy, leadership, conflicting interests, and the lack of global awareness and advice on green surgery further impede progress. Finally, social and cultural challenges, such as the influence of adaptation and decision-making, as well as technological and infrastructure challenges and limited adaptive capacity due to a lack of human resources must also be addressed.[3]

In conclusion, green surgery is an important concept in gynecology and obstetrics, with potential benefits in reducing the carbon footprint of surgical procedures, improving patient outcomes, and reducing healthcare costs. The implementation of green surgical practices, such as the use of reusable instruments, biodegradable materials, and energy-efficient electrosurgical generators, can have a significant impact in reducing the environmental impact of surgical procedures, as well as improving patient outcomes and reducing healthcare costs. However, there are still several barriers to the widespread implementation of green surgery, including the high cost of green technologies and the limited resources available for their purchase, as well as a lack of awareness and training among healthcare providers.

Conflict of Interests
The authors have no conflict of interests to declare.

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The Effect of SARS-CoV-2 İnfection on Perinatal Outcomes in Hypertensive Disorders of Pregnancy

O efeito da infecção por SARS-CoV-2 no perinatal resultados em distúrbios hipertensivos de gravidez

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Abstract

Objective To evaluate the fetal and maternal effects of the severe acute respiratory syndrome virus 2 (SARS-CoV-2) infection in women with hypertensive disorders of pregnancy.

Methods Patients with hypertensive disorders of pregnancy and SARS-CoV-2 polymerase chain reaction (PCR) positivity ($n = 55$) were compared with cases with similar characteristics and PCR negativity ($n = 53$). The study group was further divided into two groups as severe ($n = 11$) and nonsevere ($n = 44$) coronavirus disease 2019 (COVID-19). The groups were compared in terms of clinical characteristics and perinatal outcomes.

Results The study and control groups were similar in terms of maternal age, parity, gestational age at diagnosis, type of hypertensive disorders, magnesium sulfate administration rate, gestational age at birth, birth weight, Apgar scores, and maternal complications. However, all cases of fetal loss ($n = 6$) were observed in the SARS-CoV-2 positive group ($p = 0.027$). From the 6 cases, there were 5 in the nonsevere group and 1 patient in the severe SARS-CoV-2 positive group. Moreover, higher rates of maternal complications, lower oxygen saturation values, and intensive care unit admissions were observed in the severe COVID-19 group.

Conclusion Physicians should be cautious about the management of hypertensive disorders of pregnancy cases with SARS-CoV-2 positivity. Fetal loss seems to be more common in cases with SARS-CoV-2 positivity and severe COVID-19 seems to be associated with higher rates of maternal complications. Close follow-up for fetal wellbeing and active management of severe cases in terms of maternal complications seem to be favorable.

Keywords
- COVID-19
- hypertensive disorders of pregnancy
- perinatal outcomes
- SARS-CoV-2
- preeclampsia

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Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[1] The primary effect of SARS-CoV-2 is on the lungs, followed by liver damage, thrombocytopenia, hypertension, and kidney damage.[2] The reason why the virus can cause disease in many organs is believed to be due to the angiotensin-converting enzyme-2 (ACE-2) receptor. The virus binds to the ACE-2 receptor, causing endothelial dysfunction, vasoconstriction, and increased vascular resistance.[3] It is known that SARS-CoV-2 infection directly causes endothelial damage and leads to vascular damage, together with diffuse thrombosis and microangiopathy.[4]

Hypertensive disorders of pregnancy (HDP) occur in 6 to 8% of pregnant women and cause significant maternal or fetal morbidity and mortality.[5] These disorders are considered to cause the widespread activation and dysfunction of the maternal vascular endothelium, resulting in increased sensitivity to angiotensin II.[6] The increased expression of adhesion molecules on the activated endothelium intensifies the inflammation process and results in further endothelial damage.[7]

During pregnancy, COVID-19 causes specific vascular pathology and inflammation similar to preeclampsia, gestational hypertension, and essential hypertension.[8] Considering this similar pathophysiology, we aimed to evaluate the fetal and maternal effects of SARS-CoV-2 infection in women with HDP. We also aimed to compare severe and nonsevere COVID-19 cases in the same patient group.

Methods

Patients who presented to the hospital over a 2-year period from April 15, 2020, through April 15, 2022, were retrospectively analyzed. All pregnant women admitted to our hospital, regardless of symptoms, were tested for COVID-19 as a requirement of universal screening. The study group consisted of 55 patients aged 18 to 49 years, with a single pregnancy at 20 to 40 gestational weeks, who were diagnosed with HDP, tested positive for SARS-CoV-2 in the polymerase chain reaction (PCR) test, and did not have a history of COVID-19 vaccination. The control group comprised 53 patients diagnosed with HDP, who did not have COVID-19 during pregnancy, did not have a history of COVID-19 vaccination, and had a negative result in the COVID-19 PCR test. The control group was selected from cases with similar demographic features who were hospitalized for HDP and tested negative for SARS-CoV-2. We further divided the study group into two, with severe ($n = 11$) and non-severe ($n = 44$) cases according to the course of COVID-19. Patients with chronic liver and kidney diseases, history of malignancy, and known lung and heart diseases were excluded from the study.

Informed consent was obtained from all individuals included in this study. Approval for the study was obtained from the local ethics committee and the Turkish Ministry of Health.

The participants' demographic data, symptoms, vital signs, laboratory results, obstetric histories, pregnancy outcomes, obstetric and maternal complications, and the COVID-19 disease course were examined and recorded in the case report form. Intrauterine growth restriction, oligohydramnios, fetal tachycardia, placental abruption, and intrauterine fetal death were assessed for the obstetric complications. Maternal complications included wound infection, hemorrhage, relaparotomy requirement, hemolysis elevated liver enzymes low platelets (HELLP), pulmonary edema, intracranial complication, dialysis requirement, and death.

The diagnosis of COVID-19 was made based on a positive test result in the PCR analysis of combined nasopharyngeal and oropharyngeal swab samples.[9] Severe COVID-19 was defined as the presence of dyspnea, respiratory rate of 30 or greater per minute, oxygen saturation of 93% or less in room air, or findings consistent with pneumonia, while patients with a positive PCR test for SARS-CoV-2 without severe symptoms of the disease were evaluated to have the nonsevere disease.[10]

The HDP were divided into the following four categories, according to the criteria recommended by the American College of Obstetricians and Gynecologists: preeclampsia/eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension. Gestational hypertension was defined as hypertension that occurred for the first time after the 20th week of pregnancy in the absence of proteinuria and continued for 6 weeks after pregnancy. Chronic hypertension as a blood pressure equal to or higher than 140/90 mm Hg before pregnancy or before the 20th week of pregnancy. Preeclampsia as a blood pressure of 140/90 mm Hg or greater and proteinuria or accompanied by significant end-organ dysfunction without proteinuria that developed after 20 weeks. Superimposed preeclampsia is the addition of new-onset proteinuria or other preeclampsia findings to new-onset or progressing hypertension in pregnant women with documented chronic hypertension. Finally, eclampsia is the convulsive form of preeclampsia.[11]

The Statistical Package Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was conducted to determine whether the data with continuous values fit the normal distribution. The Student *t*-test was used to evaluate normally distributed (parametric) variables between the two groups. The chi-square test was performed to compare categorical variables. The statistical significance level was set as $p < 0.05$.

Results

During the study period, 108 patients diagnosed with HDP were included in the study. Of these patients, 55 constituted the SARS-COV-2-positive study group and 53 constituted the negative control group. The patients in the positive study

group were further divided into two groups as nonsevere ($n = 44$) and severe ($n = 11$) COVID-19 cases.

Demographic characteristics such as age, gravida, parity, gestational age at diagnosis, and body mass index (BMI) were similar in the study and control groups. The systolic and diastolic blood pressure values at the time of hospitalization were statistically significantly higher in the control group. Concerning the laboratory data, the alanine aminotransferase (ALT) value was significantly higher in the study group, and the creatinine level was significantly higher in the control group ($p < 0.05$). There were no significant differences between the two groups in relation to the aspartate aminotransferase (AST), platelet, and lactate dehydrogenase (LDH) values (►**Table 1**).

The oxygen saturation was higher in the study group than in the control group. The two groups were statistically similar in terms of delivery method, newborn weight, APGAR 1st- and 5th-minute scores, length of hospital stay, intensive care requirement.

The rate of maternal complications was 20% (11/55) in the study group and 9.4% (5/53) in the control group, with no statistically significant difference. Wound infection was the most common maternal complication in both groups.

Obstetric complications were found at a statistically similar rate—27.2% (15/55) in the study group and 22.6% (12/53) in the control group. When the obstetric complications were examined individually, intrauterine fetal death (IFD) was observed in 6 patients in the study group and no patient in the control group, which was a statistically significant difference ($p = 0.027$) (►**Table 2**).

There were 6 cases of IFD between 24 and 33 weeks. The weeks of cases are 24 (2 cases), 25, 29, 30, and 33 weeks. Intrauterine fetal death was observed 2 to 14 days after SARS-CoV-2 positivity (2,3,4,7,9, and 14 days). Placental abruption was observed in one patient. Furthermore, one of them was found to have intrauterine growth restriction. An IFD case was found to have severe SARS-CoV-2 and preterm premature rupture of membranes (PPROM). In another, her blood pressure was 160/110 mm Hg at the time of admission to the hospital, and she was diagnosed with severe preeclampsia. One case was diagnosed with HELLP. In one patient, no additional pathology was observed other than COVID-19 and gestational hypertension. Thus, at least one severe obstetric complication was present in 5 of the 6 cases with IFD. Placental specimen evaluation was performed in all cases. The main findings were placental infarction, intervillous hemorrhage, focal necrosis, and increased inflammation.

When we divided the study group into two subgroups according to the severity of the disease (severe and

Table 1 Comparison of demographic data and laboratory results of the groups

	SARS-CoV-2 positive ($n = 55$)	SARS-CoV-2 negative ($n = 53$)	*p*-value
Maternal age (years)	31 ± 6.5	29.5 ± 6.1	0.313
BMI (kg/m^2)	29.2 ± 4	30.3 ± 4.1	0.166
Gravida	2.9 ± 1.8	2.3 ± 1.3	0.126
Parity, n (%)			0.125
Primiparous	18 (32.7)	25 (47.2)	
Multiparous	37 (67.3)	28 (52.8)	
Hypertensive disorders, n (%)			0.244
Chronic hypertension	2 (3.6)	2 (3.8)	
Superimposed preeclampsia	4 (7.2)	6 (11.3)	
Gestational hypertension	13 (23.6)	11 (20.8)	
Preeclampsia	35 (63.6)	34 (64.2)	
Eclampsia	1 (1.8)	0	
Gestational age at diagnosis (weeks)	32.1 ± 4.7	33.3 ± 3.7	0.144
Systolic blood pressure (mmHg)*	138.9 ± 25	149.7 ± 13.4	0.002
Diastolic blood pressure (mmHg)*	82.1 ± 14	94.6 ± 8.7	<0.001
AST (U/L)	45.4 ± 52.6	22.2 ± 15.5	0.080
ALT (U/L)	42.2 ± 54.9	16.8 ± 11.9	0.023
Platelets/μL	235.4 ± 96.3	233.9 ± 60.5	0.907
LDH (U/L)	303 ± 107.8	266.2 ± 87.1	0.098
Creatinine (mg/dL)	0.6 ± 0.3	0.6 ± 0.1	0.036

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. **Notes:** Values are expressed as mean ± standard deviation or number (percentage). *The blood pressures of the patients were measured during hospitalization. Other laboratory parameters are the values at the time of admission to the hospital.

Table 2 Comparison of obstetric complications, maternal complications, and perinatal outcomes between the groups

	SARS-CoV-2 positive ($n = 55$)	SARS-CoV-2 negative ($n = 53$)	*p*-value
Delivery week, n (%)			0.217
<34 weeks	14 (25.5)	9 (17.0)	
34–37 weeks	21 (38.2)	16 (30.2)	
>37 weeks	20 (36.4)	28 (52.8)	
Delivery method, n (%)			0.616
Cesarean section	44 (80)	45 (84.9)	
Vaginal delivery	11 (20)	8 (15.1)	
Newborn weight (g)	2,304.8 ± 848.2	2,553.9 ± 824.3	0.103
1-minute Apgar score <7, n (%)	11 (22.4)	14 (26.4)	0.642
5-minute Apgar score <7, n (%)	5 (10.2)	3 (5.7)	0.394
Admission to neonatal intensive care unit, n (%)	14 (28.6)	19 (35.8)	0.432
Hospitalization (day)	5.1 ± 4.8	3.6 ± 1.7	0.216
Admission to intensive care unit, n (%)	7 (12.7)	3 (5.7)	0.205
Oxygen saturation	95.1 ± 2.6	96.3 ± 1.2	0.010
Magnesium sulfate therapy, n (%)			0.482
Yes	22 (40)	25 (47.2)	
No	33 (60)	28 (52.8)	
Maternal complications, n (%)			0.632
Wound infection	4 (7.3)	2 (3.8)	
Hemorrhage	0	1 (1.9)	
Relaparotomy requirement	1 (1.8)	1 (1.9)	
HELLP	2 (3.6)	1 (1.9)	
Pulmonary edema	1 (1.8)	0	
Intracranial complication	1 (1.8)	0	
Dialysis requirement [a]	1 (1.8)	0	
Death	1 (1.8)	0	
Obstetric complications, n (%)			0.250
Intrauterine growth restriction	3 (5.5)	4 (7.6)	
Oligohydramnios	3 (5.5)	5 (9.4)	
Fetal tachycardia	1 (1.8)	1 (1.9)	
Placental abruption	2 (3.6)	2 (3.8)	
Intrauterine fetal death [b]	6 (10.9)	0	0.027

Abbreviation: HELLP, Hemolysis elevated liver enzymes low platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. **Notes:** [a] Lupus nephritis was detected as a result of examinations and kidney biopsy (diffuse proliferative glomeruloneritis). The patient started to receive dialysis for the first time in the postpartum period. [b] When the obstetric complications were examined individually, a difference was observed between the groups in terms of the number of intrauterine fetal deaths. Values are expressed as mean ± standard deviation or number (percentage).

nonsevere COVID-19), we determined that the demographic data and laboratory results of these groups were similar (►**Table 3**).

Initial symptoms at hospitalization were similar in both groups. Perinatal outcomes were similar between these two groups. While intensive care requirement was higher in those with severe disease, the saturation value was lower. The rates of antihypertensive use and magnesium prophylaxis treatment were similar between the two groups. Hospital stay was longer in the severe group ($p = 0.033$). Maternal complications were seen in 15.9% (7/44) of the patients in the nonsevere group and in 36.3% (4/11) of those in the severe group, indicating a statistically significant difference ($p = 0.011$). Obstetric complications occurred at a rate of 29.5% (13/44) in the nonsevere group and 18.1% (2/11) in the severe group, which was not statistically significant (►**Table 4**).

Discussion

In this study, we compared the SARS-CoV-2-positive (study group) and negative (control) patients with HDP. The study and control groups were similar in terms of perinatal outcomes, maternal complications, and obstetric complications.

Table 3 Comparison of the demographic data and laboratory results of the study group according to the severity of the disease

	Non-severe SARS-CoV-2 ($n = 44$)	Severe SARS-CoV-2 ($n = 11$)	*p*-value
Maternal age (years)	31.2 ± 6	30.5 ± 8.5	0.643
BMI (kg/m^2)	29.2 ± 4.1	29.1 ± 3.7	0.929
Gravida	2.9 ± 1.9	2.6 ± 1.6	0.763
Parity, n (%)			0.774
Primiparous	14 (31.8)	4 (36.4)	
Multiparous	30 (68.2)	7 (63.6)	
Hypertensive disorders, n (%)			0.101
Chronic hypertension	2 (4.5)	1 (9.1)	
Superimposed preeclampsia	3 (6.8)	0	
Gestational hypertension	12 (27.3)	1 (9.1)	
Preeclampsia	27 (61.4)	8 (72.7)	
Eclampsia	0	1 (9.1)	
Gestational age at diagnosis (week)	32 ± 4.6	32.5 ± 5.4	0.598
Systolic blood pressure (mmHg)*	140.9 ± 24.6	130.9 ± 25.7	0.335
Diastolic blood pressure (mmHg)*	82 ± 14.1	82.5 ± 14.6	0.940
AST (U/L)	45.8 ± 55.7	43.6 ± 40.5	0.792
ALT (U/L)	43.1 ± 59.7	38.2 ± 30.6	0.406
Platelets/μL	226.4 ± 94.6	271.6 ± 99.2	0.230
LDH (U/L)	299.7 ± 107.3	316 ± 114.1	0.570
Creatinine (mg/dL)	0.5 ± 0.2	0.7 ± 0.5	0.643

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. **Notes:** Values are expressed as mean ± standard deviation or number (percentage). *The blood pressure of the patients was measured during hospitalization. Other laboratory parameters are the values at the time of admission to the hospital.

Table 4 Comparison of the obstetric complications, maternal complications, and perinatal outcomes of the study group according to the severity of the disease

	Non-severe SARS-CoV-2 ($n = 44$)	Severe SARS-CoV-2 ($n = 11$)	*p*-value
Delivery week, n (%)			0.617
<34 weeks	10 (22.7)	4 (36.4)	
34–37 weeks	17 (38.6)	4 (36.4)	
>37 weeks	17 (38.6)	3 (27.3)	
Delivery method, n (%)			0.866
Cesarean section	35 (79.5)	9 (81.8)	
Vaginal delivery	9 (20.5)	2 (18.2)	
Newborn weight (g)	2,320.9 ± 875.1	2,240.5 ± 766	0.760
1-minute Apgar score <7, n (%)	8 (20.5)	3 (30)	0.521
5-minute Apgar score <7, n (%)	4 (10.3)	1 (10)	0.981
Admission to neonatal intensive care unit, n (%)	11 (28.2)	3 (30)	0.911
Hospitalization (day)	3.8 ± 1.6	10.3 ± 8.7	0.033
Admission to intensive care unit, n (%)	2 (4.5)	5 (45.5)	<0.001
Oxygen saturation	96.1 ± 0.9	90.7 ± 2.6	<0.001

(*Continued*)

Table 4 (*Continued*)

	Non-severe SARS-CoV-2 ($n = 44$)	Severe SARS-CoV-2 ($n = 11$)	*p*-value
Initial symptoms, n (%)			0.106
Asymptomatic	24 (54.5)	3 (27.3)	
Symptomatic	20 (45.5)	8 (72.7)	
Cough	6 (13.6)	3 (27.3)	
Dyspnea	7 (15.9)	1 (9.1)	
Fever	2 (4.6)	1 (9.1)	
Headache	4 (9.1)	1 (9.1)	
Sore throat	1 (2.3)	1 (9.1)	
Chest pain	0	1 (9.1)	
Antihypertensive therapy, n (%)			0.291
Yes	16 (36.4)	5 (45.5)	
No	28 (63.6)	6 (54.5)	
Magnesium sulfate therapy, n (%)			0.783
Yes	18 (40.9)	4 (36.4)	
No	26 (59.1)	7 (63.6)	
Maternal complications, n (%)			0.011
Wound infection	4 (9)	0	
Hemorrhage	0	0	
Relaparotomy requirement	1 (2.3)	0	
HELLP	2 (4.6)	0	
Pulmonary edema	0	1 (9)	
Intracranial complication	0	1 (9)	
Dialysis requirement	0	1 (9)	
Maternal death	0	1 (9)	
Obstetric complications (n)			0.845
Intrauterine growth restriction	3 (6.8)	0	
Oligohydramnios	2 (4.6)	1 (9)	
Fetal tachycardia	1 (2.3)	0	
Placental abruption	2 (4.6)	0	
Intrauterine fetal death	5 (11.4)	1 (9)	

Abbreviation: HELLP, hemolysis elevated liver enzymes low platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. **Notes:** Values are expressed as mean ± standard deviation or number (percentage).

We further divided the study group in two subgroups according to the course of the disease as severe and non-severe. These two subgroups were similar in terms of perinatal outcomes and obstetric complications, but maternal complications were more common in the severe COVID-19 group.

It is important to point out that HDP is an umbrella term covering a series of conditions, namely preeclampsia/eclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia.[5] Maternal and fetal complications increase in pregnant women with HDP. Premature birth (spontaneous/iatrogenic), intrauterine growth restriction, placental abruption, and stillbirth are the most common fetal complications of HDP.[12] Intracranial complications, pulmonary edema, postpartum hemorrhage, acute renal failure, and maternal death can be listed as maternal complications.[13] Approximately 25% of maternal deaths in the United States of America have been associated with HDP.[14]

Furthermore, it is known that SARS-CoV-2 infection increases the risk of preeclampsia, stillbirth, preterm birth, and neonatal intensive care requirement, and severe COVID-19 during pregnancy is a risk factor for unfavorable maternal, fetal, and neonatal outcomes.[15] It has been shown that COVID-19 during pregnancy increases severe maternal morbidity and mortality, especially respiratory dysfunction

requiring invasive mechanical ventilation or admission to the intensive care unit.[16]

The combination of nasopharyngeal and oropharyngeal swab that we use in every pregnant woman hospitalized in our hospital is one of the most frequently used test samples for the diagnosis of COVID-19.[17] According to the results of a report including a metanalysis, 43.5 to 92% of cases were asymptomatic at hospital admission. Fever was the most common clinical findings reported in the infected pregnant women. In one study, fever was observed less frequently in pregnant women than in nonpregnant women.[18] While fever was 5.6% in our study, the most common symptoms were cough and dyspnea, and asymptomatic patients were 49.1%. When we examined the gestational week at the time of diagnosis, 30.6 ± 9.5 weeks were observed in the WAPM study.[19] In our study, it was observed as 32.1 ± 4.7.

Studies have shown that COVID-19 modulates the expression of placental ACE-2, which may be related to the development of HDP.[20] This receptor is a new component of the renin-angiotensin aldosterone mechanism (RAAM) identified in 2000.[21] The infection with SARS-CoV-2 exhibits its effects through the ACE-2 receptor, causing vasoconstriction resulting from renin-angiotensin system dysfunction.[22] In mothers with gestational hypertension and preeclampsia, there is a marked progressive dysfunction in RAAM activity starting from early placentation.[23] The systematic endothelial dysfunction caused by HDP may share a common pathway with SARS-CoV-2 infection.[15]

In the current study, in which we examined the effects of SARS-CoV-2 positivity on maternal, fetal, and obstetric outcomes in patients with HDP, we found similar results between the two groups. Although the obstetric complications were similar, when each complication was analyzed separately, we determined that the rate of IFD cases was significantly higher in the SARS-CoV-2-positive group, which may have resulted from sudden hypertensive attacks caused by the placental vascular malperfusion and ACE2/RAAM dysfunction observed in SARS-CoV-2 positive patients.[24,25]

Previous studies suggest that maternal and fetal complications are more common in severe SARS-CoV-2 cases.[25,26] In one of these studies, while the rate of preterm delivery was 31.9% in severe cases, it was 13.1% in the nonsevere group.[26] In our study, the rate of preterm birth was over 70% in the severe COVID-19 group, which was statistically similar to the rate detected in the nonsevere group. The reason for the higher rate of preterm birth in our sample was due to our patients being also hypertensive. In a metanalysis, it was shown that the rate of admission to the neonatal intensive care unit was higher in severe COVID-19 cases.[4] In our study, we did not observe a significant difference between the severe and nonsevere COVID-19 group in relation to neonatal intensive care requirement.

The two main mechanisms implicated in the pathophysiology of HDP are placental dysfunction and systemic inflammation.[6] Similarly, SARS-CoV-2 infection not only impairs placental function but also causes an uncontrolled inflammatory response in the host through increased inflammation and thrombotic tendency mechanisms.[3] Thus, the clinical course and pregnancy outcomes of hypertensive SARS-CoV-2 positive cases remain a matter of curiosity. Currently, there are no adequate and satisfactory studies on this subject in the literature. Therefore, the current study is one of the first in this area and has the potential to guide further similar studies that can be conducted in future. However, we found no significant difference between the groups regarding the majority of perinatal outcomes. This can be attributed to the relatively small sample size and the limited number of severe COVID-19 cases.

The most significant findings obtained from the present study were the higher rate of IFD cases in the SARS-CoV-2 positive group. Additionally, nearly all cases had at least one accompanying severe obstetric complication and placental pathologic assessment indicated vascular pathologies together with increased inflammation. In our opinion, the potential adverse impact of SARS-CoV-2 on the growing conception material might lead to IFD. However, more data are necessary to confirm these results. Furthermore, the increased rate of maternal complications in the severe COVID-19 group was also an important finding. As HDP was associated with vascular dysfunction and increased inflammation, additional infectious agents like SARS-CoV-2 might lead to adverse outcomes. Thus, optimal care should be provided in the management of these complicated cases.

The strengths of the study are the multiplicity of investigated parameters and its unique design. However, it also had certain limitations, including its retrospective design and the relatively low number of patients in the sample.

Conclusion

Physicians should be cautious about the management of hypertensive disorders of pregnancy cases with SARS-CoV-2 positivity. Close follow-up for fetal wellbeing and active management of severe cases in terms of maternal complications seem to be favorable.

Contributions

All authors have read and approved the final article. All authors contributed to the following sections of the article and fulfilled the conditions for being an article writer. Tanaçan: Data analysis, Manuscript writing, Study concept, design. Sakcak: Data collection, Study concept, design. Şahin: Manuscript editing, Study concept, design. Farisoğulları: Manuscript writing, Data collection, Project development, Study concept, design. Kara: Data analysis, Project development, Study concept, design. Denizli: Manuscript writing, Study concept, design.

Conflict of Interests

The authors have no conflict of interests to declare.

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Comparison Between the Effect of the Information–Motivation–Behavioral (IMB) Model and Psychoeducational Counseling on Sexual Satisfaction and Contraception Method Used Under the Coercion of the Spouse in Iranian Women: A Randomized, Clinical Trial

Comparação entre o efeito do modelo Informação-Motivação-Comportamental (IMB) e o aconselhamento psicoeducacional sobre a satisfação sexual e o método contraceptivo usado sob coerção do cônjuge em mulheres iranianas: um ensaio clínico randomizado

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Abstract

Objective Women play an essential role in maintaining the family's health, and family planning is part of women's and families' health. The couple's mutual understanding of family planning methods is essential in selecting contraception. Acceptance of and satisfaction with different contraception methods can impact sexual satisfaction. The present study aimed to compare the effect of the information-motivation-behavioral (IMB) model and psychoeducational counseling on sexual satisfaction and contraception methods of women referring to health centers in Kerman.

Methods This trial was conducted on 81 women aged 18 to 45, in Kerman health centers, from 2021 to 2022. Participants were randomly divided into 3 groups of 27 people (control, psychoeducational counseling, and IMB method). Three online counseling sessions were held for the psychoeducational group, and four were held for the IMB group. The control group received routine care. The IBM SPSS Statistics for Windows, version 22 (IBM Corp. Armonk, NY, USA) was used for data analysis using nonparametric Friedman and Kruskal-Wallis tests.

Results The mean age of participants was 32.59 ± 7.04, and the majority of them had university degrees and were homemakers. The mean sexual satisfaction score significantly increased immediately after the intervention and 1 month later in the 2

Keywords
- psychoeducational counseling
- information–motivation–behavioral model
- sexual satisfaction
- contraception violence

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interventional groups ($p < 0.0$). Changes in contraception methods after intervention were significant in the psychoeducational group ($p = 0.0$)

Conclusion The results indicate the positive impact of psychological counseling on women's sexual satisfaction and contraception method. The IMB method also impacted men's sexual satisfaction but did not lead to any changes in the contraceptive method.

Resumo

Objetivo A mulher desempenha um papel essencial na manutenção da saúde da família, e o planejamento familiar faz parte da saúde da mulher e da família. A compreensão mútua do casal sobre os métodos de planejamento familiar é essencial na seleção da contracepção. A aceitação e a satisfação com os diferentes métodos contraceptivos podem afetar a satisfação sexual. O presente estudo teve como objetivo comparar o efeito do modelo informação-motivação-comportamental (IMB) e aconselhamento psicoeducacional sobre a satisfação sexual e métodos contraceptivos de mulheres encaminhadas para centros de saúde em Kerman.

Métodos Este estudo foi realizado em 81 mulheres de 18 a 45 anos, nos centros de saúde de Kerman, de 2021 a 2022. As participantes foram divididas aleatoriamente em 3 grupos de 27 pessoas (controle, aconselhamento psicoeducacional e método IMB). Foram realizadas três sessões de aconselhamento online para o grupo psicoeducativo e quatro para o grupo IMB. O grupo de controle recebeu cuidados de rotina. O *IBM SPSS Statistics for Windows*, versão 22 (IBM Corp. Armonk, NY, EUA) foi utilizado para a análise dos dados por meio dos testes não paramétricos de Friedman e Kruskal-Wallis.

Resultados A média de idade das participantes foi de $32{,}59 \pm 7{,}04$, sendo que a maioria delas possuía nível superior e eram donas de casa. A pontuação média de satisfação sexual aumentou significativamente imediatamente após a intervenção e 1 mês depois nos 2 grupos de intervenção ($p < 0{,}0$). As mudanças nos métodos contraceptivos após a intervenção foram significativas no grupo psicoeducativo ($p = 0{,}0$)

Conclusão Os resultados indicam o impacto positivo do acompanhamento psicológico na satisfação sexual das mulheres e no método contraceptivo. O método IMB também impactou a satisfação sexual dos homens, mas não levou a nenhuma mudança no método contraceptivo.

Palavras-chave
- aconselhamento psicoeducativo
- modelo de informação-motivação-comportamental
- satisfação sexual
- violência contraceptiva

Clinical trial registration: https://fa.irct.ir/ Iranian Registry of Clinical Trial (IRCT20151103024866N16).

Introduction

Women play an essential role in family maintenance, which, ultimately, has a a direct impact in the community's health; therefore, the community's health is affected when there is a threat to a woman's health.[1] Family planning is a part of comprehensive reproductive health and one of the most basic and essential healthcare system programs.[2] Contraception methods are essential in preventing unintended pregnancies, achieving the desired number of children and the proper spacing between pregnancies, and preventing high-risk pregnancies, unsafe abortions, maternal and neonatal mortality, and sexually-transmitted infections.[3] The diversity of contraceptive options for women, the limited methods available for men, and the existence of misconceptions, including gender attitudes, which consider family planning to be solely the responsibility of women, have led men to participate less in family planning programs.[4] The lack of couples' shared participation in using contraceptive methods is one of the areas of violence in reproductive health. Reproductive coercion is a behavior that interferes with the independent decision-making of a woman concerning reproductive health. It may take the form of pregnancy coercion, controlling the outcome of pregnancy, birth control sabotage, non-use of contraceptive methods, and forced use of a specific prevention method. The choice, acceptance, and satisfaction of women with different contraceptive methods affect their quality of life and sexual function, and different contraceptive methods have different effects on women's sexual satisfaction.[5] Sexual satisfaction is an essential indicator of sexual health and is strongly associated with empathy, love, emotions, creativity, and the frequency of sexual activity. Sexual satisfaction is obtained from positive sexual experiences.[6] Feelings of failure, frustration, and insecurity due to a lack of sexual

satisfaction will likely endanger the mental health of spouses.[7] A review study by Maxwell et al. (2018) aimed at estimating the effect of intimate partner violence (IPV) on women's use of contraception showed that women who experienced IPV in the year prior to the study were 20% less likely to report the use of male condoms.[8]

Intimate partner violence refers to behavior that causes physical, sexual, or mental pain, including acts of physical animosity, sexual constraint, mental mishandling, and controlling behaviors.[9] The non-participation of men in the use of contraceptive methods is one of the areas of violence in reproductive health. Violence has shown the highest correlation with six domains of reproductive health, including lack of use of contraceptive methods, abortion, reproductive system diseases, poor pregnancy outcomes, and lack of use of reproductive health services.[10]

The empowerment of women with communication skills that allow them to face problems, choose the correct alternative behavior in problem-solving, and use family counseling services can be effective in preventing or reducing IPV.[11]

One of the most comprehensive models for behavior change is the information-motivation-behavioral (IMB) skills model.[12] According to the model, health information, motivation, and behavioral skills are fundamental determinants of preventive behaviors and behavioral skills necessary for taking preventive measures.[13] The study by Mittal et al. (2017) aimed to present a supportive intervention to reduce HIV risk in women with a history of IPV. This supportive intervention included the key elements of the IMB model, the theory of gender and power (TGP) model, and family therapy. The results showed that safe sex and condom use increased at the end of the intervention. There was a significant reduction in violence and a significant improvement in self-esteem, anxiety, and posttraumatic stress disorder (PTSD).[13]

Psychoeducational counseling is another type of counseling in which clients are trained during therapy.[14] Psychoeducational counseling for a particular situation or disease means providing the patient with the necessary information to create a new mental and cognitive understanding of what they have just encountered and helping them change their behavior; this is an essential component of every psychotherapy program.[15] A study by Akbarinejad et al. (2016) investigated the effect of psychoeducational group counseling on the postnatal sexual intimacy of lactating women. Results showed the positive impact of group counseling on the sexual intimacy of women after their first birth in the intervention group and increased sexual intimacy in this group.[14] Psychoeducational counseling is associated with education during therapy, and another feature of this type of counseling is its emphasis on prevention. Given that one of the structures of the IMB model is based on knowledge and cognition, both methods—psychoeducational counseling and IMB—have a psychological and social approach. In face of the mentioned issues, a study was conducted to compare the effect of the information–motivation–behavioral (IMB) model and psychoeducational counseling on sexual satisfaction and contraception method used under the coercion of the spouse in Iranian women.

Methods

This study was a clinical trial (IRCT20151103024866N16), and the statistical population included all married women aged 18 to 45 years who were referred to health centers in Kerman, a city in the south of IRAN; to receive care and family planning counseling. The ethical committee of the university approved the study, and all women signed an informed consent before enrollment. Convenience sampling was used for participants who were women whose husbands did not cooperate in choosing a contraceptive method but complained and made excuses about every method the woman used. These women were under the coercion of spouses in contraception use, according to World Health Organization (WHO) guidelines (refusal of specific contraceptive methods, or insistence on a particular type of method, or resistance to contraceptive counseling, history of repeated pregnancies, or request for a medical termination, and insistence on tubal ligation or insistence on reversal of tubal ligation).[16] Based on the available sampling, each woman who applied for a contraceptive was asked the WHO guideline questions, and if she was under the pressure of her husband to receive a contraceptive and met the inclusion criteria, she was selected. The purpose of the research was explained to these women, and if they were satisfied and willing, they would enter the study (►**Fig. 1**).

The sample size needed to achieve a reliability of 1.96 and study power of 85%, based on the results of the study by Nabavi et al. (2019), was approximately 6 participants for each group; however, 27 people were selected to increase the study capacity and compensate for the loss of samples.[17]

Because the samples were divided into 3 groups, the final sample size was 81 people. The identified women were included in the study if they consented to participate and had the inclusion criteria. Then, all identified persons were randomly divided through a table of random numbers into three groups: control, psychoeducational counseling, and the IMB model.

The inclusion criteria were married women in Kerman aged between 18 and 45, who were the only spouse of their husbands and whose spouses were present in Kerman during the intervention; had at least one of the criteria for violence against women regarding contraceptive methods according to the checklist of the WHO; consented to participate in the study; were literate; had been married for at least 1 year; had no known mental illness; and had access to a smartphone (due to online education) and the ability to use it. The exclusion criteria included pregnancy or participating in other psychological counseling classes simultaneously. Reasons for discontinuation were absence in two or more of the counseling sessions, and unwillingness to continue participation.

The research tool consisted of demographic information, a checklist for evaluating the contraception method requested by the spouse (WHO), and a special researcher-made questionnaire on contraceptive methods and sexual satisfaction. This questionnaire was prepared based on scientific articles.[18–21] The special sexual satisfaction questionnaire

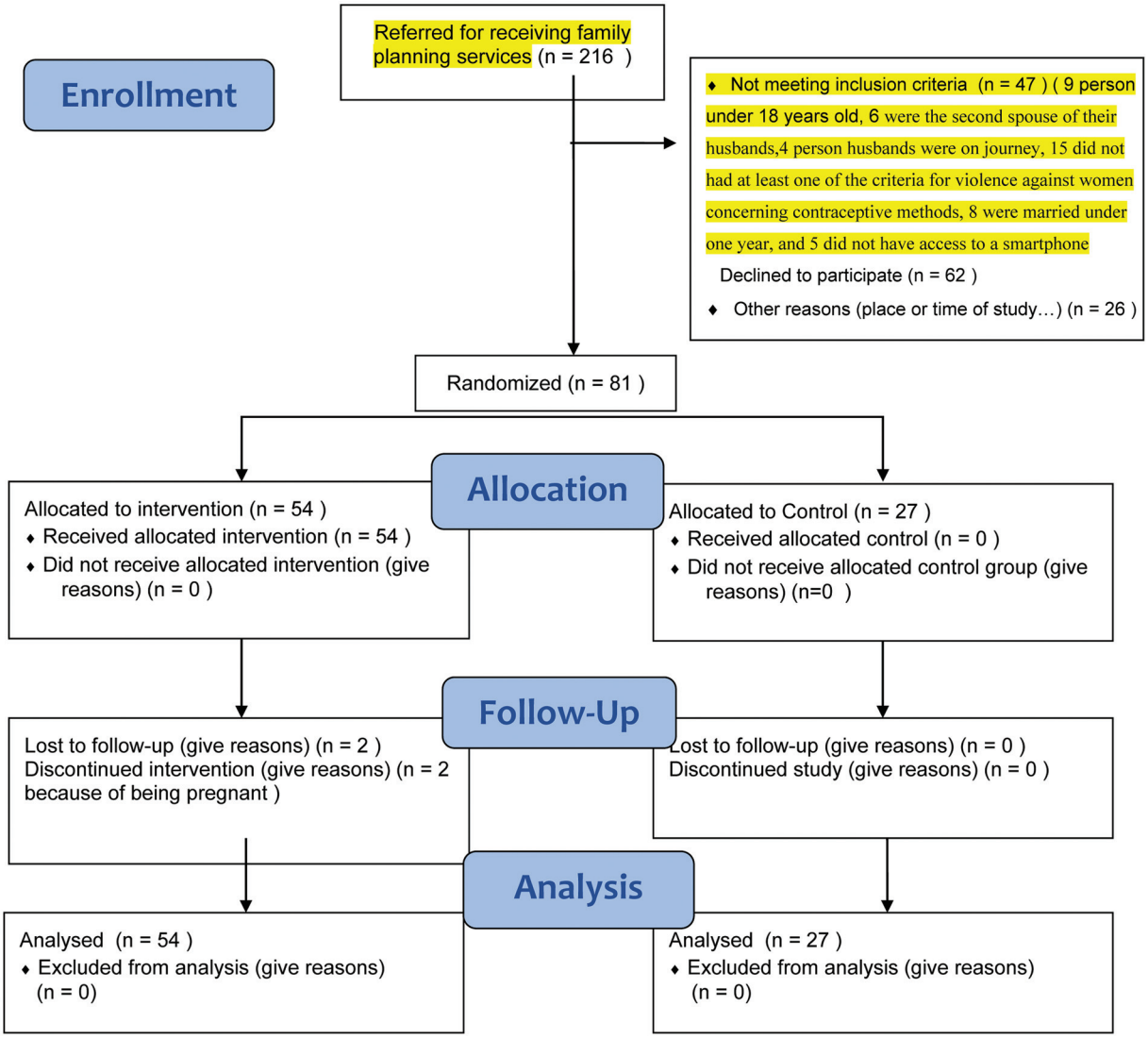

Fig. 1 CONSORT 2010 flow diagram.

examined contraceptive methods and sexual satisfaction with 48 items. The participants expressed their satisfaction with each item on a five-point Likert scale. The questionnaire was sent to expert professors to assess its validity, and the content validity was also determined quantitatively and qualitatively to determine the content validity of the questionnaire. The content validity index (CVI) and content validity ratio (CVR) were 0.93 and 0.98, respectively, and face validity was confirmed using experts' opinions. The questionnaire was then presented to 30 people from the target group to determine its face validity; then, internal consistency was determined using Cronbach α (0.855).

First, the study's objectives were explained to women who met the inclusion criteria, and, if they wished to participate, written informed consent was obtained from them. All three groups completed the questionnaire on sexual satisfaction, specific contraception methods, and contraception type before the intervention, immediately after, and 1 month after the intervention. The study's objectives were first fully explained to participants to prevent information exchange between group members. Introduction sessions were held separately for each group. Given that information exchange is possible in cyberspace, to prevent information exchange between participants, after dividing them into 3 groups (control, psychoeducational, and IMB), a time interval of 2 months was considered for each group. First, a pretest was completed for the control group, and posttests were done 1 month later and 1 month after the initial posttest. Then a pretest was done for the psychoeducational group; the initial posttest was done after the three virtual counseling sessions in Skyroom; the final posttest was completed 1 month after the intervention. The total time spent implementing the intervention and completing the questionnaires was 6 months. In the control group, the clinic midwife provided all routine training. In the intervention group, psychoeducational counseling sessions were held according to a unique package of counseling sessions in 3 90-minute online sessions 1 week apart. In the IMB model intervention group, counseling sessions were held according to a specific package, in 4 online sessions, 120 to 190 minutes each 2 sessions

per week, and all these sessions were held by the same person (the researcher). Finally, immediately after the intervention and 1 month later, the participants in the 3 groups completed the questionnaire. The psychoeducational counseling and IMB program packages were designed, prepared, and implemented using various resources 216 people were surveyed to participate in the study, of which 135 were either not eligible or unwilling to participate in the study. Eighty-one people were included in the study. By lot, they were divided into three groups (one was a control group and two were intervention groups). Since the intervention was performed on and offline, we did not have any sample drop, and, finally, the analysis was performed on 81 people. Data were analyzed using the IBM SPSS Statistics for Windows, version 22 software (IBM Corp. Armonk, NY, USA). Quantitative variables were described by mean and standard deviation, and qualitative variables were defined by frequency and frequency percentage. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normality of dependent variables (sexual satisfaction and changes in contraceptive methods). Due to the abnormality of data distribution, the Friedman test was used to examine the trend of changes. The nonparametric equivalent of one-way analysis of variance, Kruskal-Wallis, was used for comparison (►**Chart 1**).

Chart 1 Psychoeducational counseling content and information–motivation–behavioral model

Session	Objective	Content
Psychoeducational counseling package		
First	Introduction and awareness	Informing people about violent behaviors, teaching contraception methods
Second	Identifying sexual misconceptions	Teaching to improve sexual relations, expressing the importance of sex, talking about sexual misconceptions, extensive training on contraception methods
Third	Effective communication and assertiveness	Assertiveness skill training, communication styles, effective communication skills training
Information–motivation–behavioral package		
First	Identifying distorted dimensions in sex	Defining contraception methods and the benefits and harms of each method, defining spousal violence in contraception, defining sexual satisfaction and sexual satisfaction related to contraception.
Second	Motivational dialogue	Conducting a motivational interview to accept or change the contraception method to make it voluntary and increase sexual satisfaction
Third	Efficient sexual dialogue with the spouse	Improving perceived individual skills and self-efficacy
Fourth	Activate assertive behaviors	Activating avoidance behaviors and improving assertiveness skills by increasing motivation and behavioral skills

Results

The mean age of participants was 32.59 ± 7.04. There was no statistically significant difference between the three groups regarding age, education, occupation, breastfeeding, weight, number of pregnancies, etc. The three groups were similar in demographic characteristics (►**Table 1**).

The results showed that the mean sexual satisfaction score immediately after the intervention was statistically significant between the three groups ($p < 0.01$). According to the Kruskal-Wallis test, the mean sexual satisfaction score 1 month after the intervention was significantly different among the three groups ($p < 0.01$). The sexual satisfaction score increased 1 month after the intervention in the psychoeducational and IMB group, and the increase in sexual satisfaction was more significant in the IMB group (►**Table 2**).

The mean score of sexual satisfaction in the psychoeducational intervention group increased 1 month after the intervention compared to immediately after the intervention, and the difference was significant ($p = 0.03$); in the IMB group, the sexual satisfaction increased significantly 1 month after the intervention compared to immediately after the intervention ($p < 0.01$), but there was no statistically significant difference between the 2 intervention groups in sexual satisfaction ($p = 0.1$). However, the mean score in the IMB group was higher than in the psychoeducational intervention group. Using each contraception method in the three groups (control, psychoeducational, and IMB intervention) was measured before, immediately after, and 1 month after the intervention. The Mann-Kendall statistical test showed that changes in the contraception method in the psychoeducational group were significant ($p = 0.02$) (►**Table 3**).

Discussion

According to the present study results, the sexual satisfaction level in the two intervention groups increased significantly, which shows that both psychoeducational counseling and IMB counseling increased women's sexual satisfaction.

In the study by Alirezaei et al. (2022), the sexual satisfaction of infertile couples increased after psychological intervention, which was consistent with our study.[22] However, due to the long duration of psychological intervention (6 months) compared to IMB counseling (2 weeks) and psychoeducational counseling (3 weeks), it seems that the counseling methods in the present study provide a more appropriate interpretation. Our study is consistent with that of Akbar Nejd et al. (2020), which showed the positive impact of psychoeducational group counseling on the sexual intimacy of lactating women, leading to an increase in sexual intimacy.[14] Considering that sexual intimacy is itself a component in increased sexual satisfaction and improvement in the quality of marital life, it can be concluded that psychoeducational training can raise sexual satisfaction and improve other effective details of sexual satisfaction. The study results by Tahan et al. (2020) showed that women's sexual satisfaction increased after receiving psychoeducational counseling.[23] In the study by Bober et al.

Table 1 Comparison of the distribution of qualitative and quantitative demographic variables between the intervention and control groups

Variables		Group			*P*-value*
		Psychoeducation N (%)	IMB N (%)	Control N (%)	
Women education	High school education	2 (7.4%)	2 (7.4%)	3 (10%)	0.9
	Diploma	13 (48.1%)	13 (48.1%)	11 (36.7%)	
	University education	12 (44.4%)	12 (44.4%)	16 (53.3%)	
Women job	Housekeeper	19 (70.4%)	15 (55.6%)	20 (66.7%)	0.34
	Employee	6 (22.2%)	7 (25.9%)	9 (30%)	
	self-employment	2 (7.4%)	5 (18.5%)	1 (3.3%)	
Spouse education	High school education	3 (11.1%)	7 (25.9%)	5 (18.5%)	0.22
	Diploma	12 (44.4%)	13 (48.1%)	9 (30%)	
	University education	12 (44.4%)	7 (25.9%)	16 (53.3%)	
Spouse job	permanent job	15 (55.6%)	13 (48.1%)	14 (46.7%)	0.83
	Temporary job	10 (37%)	13 (48.1%)	15 (55.6%)	
	workless	2 (7.4%)	1 (3.3%)	1 (3.3%)	
Variable		**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***P*-value****
Age		7.255 ± 34.44	7.704 ± 32.04	31.30 ± 6.199	0.22
Age of onset of sexual activity		4.029 ± 23.19	3.652 ± 21.52	3.151 ± 22.27	0.24
Parity		1.368 ± 2.89	1.812 ± 2.85	1.654 ± 2.77	0.89

Abbreviation: IMB, information-motivation-behavioral.
*Chi-square.
**Kruskal-Wallis test.

Table 2 Mean and standard deviation of sexual satisfaction score before the intervention, after the intervention and one month after the intervention three groups

Sexual satisfaction	Mean ± SD			*P*-value*
	Psychoeducation	IMB	Control	
Before intervention	22.73 ± 166.66	18.43 ± 167.62	18.08 ± 169.33	0.97
After intervention	16.85 ± 184.37	13.01 ± 190.29	15.38 ± 167.30	0.001<
One month after intervention	16.48 ± 189.25	11.05 ± 203.48	15.49 ± 166.13	0.001<
P-value**	0.001<	0.001<	0.71	

Abbreviation: IMB, information-motivation-behavioral.
*Kruskal-Wallis test.
**Friedman test.

(2015), the sexual psychological intervention increased sexual desire, female sexual satisfaction, and female sexual self-efficacy by increasing the sexual information of women with ovarian cancer.[24] In the study by Ali Mohammadi et al. (2018), counseling based on sexual self-efficacy on sexual functioning and sexual satisfaction of newly married women showed that sexual self-efficacy counseling had an effect on sexual functioning but did not affect sexual satisfaction, which was not consistent with our results.[25] It can be concluded that IMB counseling has a higher impact on sexual satisfaction than sexual self-efficacy counseling, despite fewer sessions.

In the present study, the mean score of sexual satisfaction in the two psychoeducational and IMB interventions increased after counseling. Psychoeducational counseling and training on sexual issues and contraception methods can improve marital quality, such as sexual satisfaction, sexual intimacy, and marital satisfaction, and increase the use of safe contraception methods. The IMB approach is also a pattern of behavior change and consists of three components. It helps couples obtain the necessary information about sexual issues and contraception methods. They will be able to acquire appropriate behavioral skills in dealing with the spouse and choosing the proper contraception method. A comprehensive counseling approach can identify women's sexual needs, which leads to improved behavior and change in women's behavior to promote sexual satisfaction.

The results of the study by Cavallaro et al. (2020) show that women who received systematic counseling on family

Table 3 Frequency distribution of contraceptive methods before intervention, after intervention and one month after intervention in three groups

Group	Contraceptive method	Before intervention	After intervention	One month after intervention	*P*-value*
Psychoeducation	Withdrawal	14 (51.85%)	8 (29.62%)	8 (29.62%)	0.02
	Condom	6 (22.22%)	11 (40.74%)	11 (40.74%)	
	Combined oral pills	5 (18.51%)	4 (14.81%)	4 (14.81%)	
	Medroxyprogesterone asetat	1 (3.7%)	2 (7.4%)	2 (7.4%)	
	IUD	1 (3.7%)	2 (7.4%)	2 (7.4%)	
IMB	Withdrawal	13 (48.14%)	10 (37.03%)	5 (18.51%)	0.07
	Condom	5 (18.51%)	8 (29.62%)	9 (33.33%)	
	Combined oral pills	5 (18.51%)	5 (18.51%)	6 (22.22%)	
	Medroxyprogesterone asetat	1 (3.7%)	1 (3.7%)	2 (7.4%)	
	IUD	3 (11.11%)	3 (11.11%)	5 (18.51%)	
Control	Withdrawal	14 (51.85%)	14 (51.85%)	15 (50%)	1
	Condom	9 (33.33%)	9 (33.33%)	8 (29.62%)	
	Combined oral pills	5 (18.51%)	5 (18.51%)	5 (18.51%)	
	Medroxyprogesterone asetat	1 (3.7%)	1 (3.7%)	2 (7.4%)	
	IUD	1 (3.7%)	1 (3.7%)	1 (3.7%)	

Abbreviation: IMB, information-motivation-behavioral; IUD, intrauterine device.
*Kendall test.

planning methods continued to use contraception methods, and interruption of contraceptive use was lower than in the control group, which was consistent with the results of psychoeducational counseling in our study.[26] In a study by Jiang et al. (2019), which examined the predictors of condom use in Chinese gay men based on the modified IMB model, the results showed that using the modified IMB model directly contributes to safe sexual behaviors and leads to increased use of condoms. The results of this study were not consistent with the IMB model in our study.[27] In a survey by Fullerton et al. (2013) on the effect of the IMB model concerning condom use and hormonal methods of contraception as well as the use of both ways simultaneously (dual protection), the results showed that the components of the IMB model support the sexual health of young women and also contribute to dual protective behaviors and the prevention of sexually transmitted infections and pregnancies, which was not consistent with our study.[28] According to the studies, the IMB model leads to the use of safe contraception methods and the prevention of high-risk behaviors. However, in our research, the ineffectiveness of IMB counseling in significantly changing couples' contraception method choice could be due to simultaneous training about sexual satisfaction and contraception methods. The couples were in stable and permanent relationships, and the purpose of this study is to increase sexual satisfaction related to contraception methods.

Choosing and accepting and being satisfied with different contraceptive methods can affect the quality of life and sexual performance of women. Choosing a contraceptive method by husband coercion can cause the non-continuation of using the method or incorrect use, which will result in unwanted pregnancy and illegal abortions and complications.[29]

According to the results, it can be concluded that women whose spouses coerce them to use specific contraception methods not only need to change their contraception methods but increasing their knowledge about contraceptive methods sometimes leads to their complete acceptance. So, it can create positive relationships between partners, they were able to come to an agreement with their spouse in selecting the method of contraception and realized that the new contraceptive method chosen by both was the most appropriate method of contraception for them. After agreeing on the new contraceptive method and improving interpersonal relationships with their spouse, their sexual satisfaction also increased. Because the study was conducted during the coronavirus disease 2019 (COVID-19) outbreak and the sessions were given online, women who were under the coercion of spouses were able to participate in the training course without leaving home and benefit from the counseling courses without facing any resistance from their husbands, which can be considered as the strength of the study. Due to the need for access to smartphones to attend online courses, people from certain social and economic classes could not participate in the counseling courses, which can be considered a limitation of the present study.

Conclusion

Psychological counseling could improve women's sexual satisfaction and lead to change in the contraception method, in cases on which it was not according to the women's wishes. The results also showed that the IMB method

positively impacted women's sexual satisfaction but had no impact on changing the contraceptive method. Using appropriate contraception to prevent unwanted pregnancy is one of the essential parts of reproductive health, and utilization of intervention methods seems crucial. According to the results, using one of these two intervention methods in contraceptive counseling sessions is good.

Contributions

AZ and KA designed the work and drafted the manuscript. AA and ER had prepared a counseling package. FGH had full access to all the data and took responsibility for its integrity. MGH was responsible for the accuracy of the data analysis. KA contributed equally to writing and revising the manuscript and approved its final version. All authors have read and approved the manuscript.

Conflict of Interests

The authors have no conflict of interest to declare.

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Reproductive Planning and the Choice of Long-acting Reversible Contraceptive Primary to Health: A Cross-Sectional Study

Planejamento reprodutivo e a escolha do contraceptivo de longa permanência na atenção primária à saúde: um estudo transversal

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Abstract

Objective Evaluate the different perspectives that involve the choice of long-acting reversible contraceptives (LARCs), the issues related to this process and the consequences of deciding one method in the women's in the primary health care (PHC) center in Sousas, a district in Campinas, SP (Brazil).

Methods This is an analytical cross-sectional study, it was performed at the PHC in Sousas. Data were collected through the analysis of medical records and interviews with women who live in Sousas and had the insertion of the copper intrauterine device (IUD) (D) from April 2021 to April 2022 or the etonogestrel implant (I) from May to December 2022. The study was approved by the Research Ethics Committee of the Medical Science School at the State University of Campinas (UNICAMP).

Results Reason for choosing this LARC: medical (D: 52%; I: 100%), easy adhesion (D: 71%; I: 67%), effectiveness (D: 55%; I: 100%). Indication by health professionals (D: 65%; I: 100%). And improvement of clinical characteristics: mood (D: 77%; I: 67%), body mass index (BMI; D: 52%; I: 33%), and libido (D: 84%; I: 67%).

Conclusion It is suggested that women tend to decide between LARCs when guided by their doctor or PHC health professionals, and they select LARCs because of the ease of use and low failure rates. Therefore, this study highlights how LARCs can positively interfere in the aspects that pervade contraception, such as BMI, libido, and mood.

Keywords
- reproductive planning
- long-acting reversible contraceptive
- primary care
- clinical parameters
- health education

Introduction

Reproductive planning, also known as familiar planning, was advocated in Brazil through Law 9.263/1996 to protect the sexual and reproductive health of adult men and women, young people, and adolescents who practice sex with or without a fixed partner.[1,2] In addition to contributing to more empowerment, reproductive planning enables women

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Resumo

Objetivo Avaliar as diversas perspectivas que envolvem a escolha dos LARCs, as problemáticas relacionadas a esse processo e as consequências da escolha do método na vida das mulheres no centro de Atenção Primária à Saúde (APS) em Sousas, distrito de Campinas, SP.

Métodos Trata-se de um estudo transversal analítico, realizado no Centro de Saúde de Sousas. Os dados foram coletados através da análise de prontuários e de entrevistas das mulheres residentes em Sousas, que inseriram o dispositivo intrauterino (DIU) de cobre (D) entre abril de 2021 a abril de 2022 ou o implante de etonogestrel (I) de maio a dezembro de 2022. O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciência Médicas da Universidade Estadual de Campinas (UNICAMP).

Resultados O motivo da escolha: por indicação médica (D: 52%; I: 100%), pela facilidade (D: 71%; I: 67%) e pela eficácia (D: 55%; I: 100%). Da indicação por profissionais de saúde (D: 65%; I: 100%). E melhora das características clínicas: humor (D: 77%; I: 67%), índice de massa corporal (IMC; D: 52%; I: 33%) e libido (D: 84%; I: 67%).

Conclusão Sugere-se que as mulheres tendem a escolher LARCs quando orientadas pelo seu médico ou por profissionais de saúde da APS e optam pelos LARCs pela facilidade do uso e baixa taxa de falhas. Destaca-se como os LARC's podem interferir positivamente em aspectos que perpassam a contracepção, como o IMC, libido e estado de humor.

Palavras-chave

- planejamento reprodutivo
- contraceptivo de longa permanência
- atenção primária
- parâmetros clínicos
- educação em saúde

to control time between pregnancies, recover after childbirth, have safer pregnancies with lower maternal and child morbidity and mortality, and generate confidence in the decision-making of men and women regarding the type of family they want to build.[3–5] Thus, the need grew to offer methods of efficient and safe contraceptives for all, regardless of orientation, or sexual and gender identity.

The choice of contraceptives, in this context, became the target of several researchers and institutions internationally.[6] So, parameters like efficacy, side effects, ease of use, parity, comorbidities, information, and awareness of duration were placed as great beacons of this choice.[7,8] Finally, other beneficial effects in addition to contraception, such as improvement in weight, mood, and libido, are increasingly discussed when the topic is contraception.[9–11] Thus, offering the ideal method for users in each territory becomes something desired by any location with high rates of unwanted and unplanned pregnancies.

In Brazil, among the various contraceptive methods available in the Brazilian public health system (Sistema Único de Saúde – SUS), the long-acting reversible contraceptives (LARCs) are understood today as first-line methods due to their high efficacy, the similarity of results between the Pearl index in perfect and typical use, as well as for dispensing routine intervention methods, and the high continuity rates.[12–14]

Currently, the SUS network has the availability of a copper intrauterine device (IUD), already widely used in primary health care (PHC), and the etonogestrel implant (Implanon), which was implemented through ordinance 13/2021 in the Ministry of Health. The copper IUD lasts for 10 years after insertion and may present increased bleeding and cramping as side effects.[15] As for Implanon, it has a validity of approximately 3 years, with a lower failure rate. However, it has unwanted side effects like acne and spotting.[16] Because of this, it is worth noting although the rate of use of LARCs in Brazil is low, with around 0.1% for Implanon and 1.4% for copper IUDs, they are associated with an increasing satisfaction rate of 94.7% for copper IUDs and 90% for Implanon.[17–20] This can be directly linked to the continuity of the method and, perhaps, to professionals' indication for known ones, a pattern already observed by scholars.[19,21] In this way, the dissemination of information about the LARCs, the level of satisfaction of the women, and the characteristics reported above must be studied regarding management committed to the reproductive rights of its population.

Primary health care (PHC) is part of the foundation for this adequate reproductive planning. As the main gateway to SUS, these centers contribute to the pregnancy decision based on reliable information about fertility and knowledge about the body. They also ensure that women have access to media and technologies in their territories. Additionally, Health Centers (HC) offer health care based on distance and comprehensiveness, with community and family as a focus, which is associated with clinical skills that can change the paradigms involving women's health and the choice of contraception.[22–24] Because of this, a program called Mais Médicos Campineiro (PMMC) was created in the city of Campinas – SP, in 2020. This strategy seeks to reorient the health model of Campinas for PHC and improve the qualification of medical professionals through specialized medical training promoted by universities such as the State University of Campinas (UNICAMP).[25]

In the meantime, considering the responsibility of the government and the PHC with reproductive planning, the present work aims to evaluate the reason for the choice of

implant and copper IUD by women from the Sousas HC in Campinas – SP. Furthermore, we aim to evaluate the form of acquisition of information about the contraceptive method and other aspects inherent to the process such as discontinuity rates, failures, improvements in the quality of clinical-social parameters, and side effects. Finally, this research is expected to contribute to the improvement of local and municipal reproductive planning.

Methods

This is an analytical cross-sectional study with data collection through interviews with women from the Sousas PHC coverage area and their electronic medical records into the e-SUS. The interviews were structured by two questionnaires. The first questionnaire refers to the moment before using the method, it collected socio-demographic variables, variables on the chosen method, and characteristics of clinics. The second questionnaire refers to 6 months after the beginning of the use of the method, it collected clinical questions related to the chosen method, such as changes in the pattern of bleeding and/or dysmenorrhea, the onset of symptoms such as headache, acne, change in weight and libido. It was also asked about maintenance, failure, or expulsion of the device, if there were complications from its use, and if the woman would recommend the method to others. Both questionnaires were applied at the same time in the study. Cross-sectional refers to different moments of use of the method, previously and after 6 months of the insertion.

The women's data were separated according to the method of choice and subsequently compared with each other. We also compared the pre- and postinsertion data (IUD or Implanon). The selection of subjects consists of women registered at the PHC-Sousas who implanted a copper IUD between April 2021 and April 2022, or who adhered to the subdermal etonogestrel implant (Implanon) from May to December 2022, who agreed to participate in the research and signed the informed consent form. Implant data were collected only from May 2022, because that was when this technology was incorporated into HC respecting the criteria of the Ministry of Health of 2022. Through the database of the program Strategic Management of Materials and Medicines (GEMM), it was verified the withdrawal of 105 copper IUDs from the pharmacy at the Sousas unit, from April 2021 to April 2022.

By searching for intrauterine contraceptive device insertion (CID-10 Z30) in the electronic medical record in e-SUS, it was possible to locate 80 patients. Of these 80 women, 31 were contacted and agreed to participate in this research. It was possible to collect information from the medical records of all 31 women who had the IUD inserted in the selected months. The Implanon were inserted from May 5 to September 2022. It was possible to contact 3 of the 5 women selected, who agreed to participate in the search.

The following data were assessed using the marital question questionnaires (categorical variable): married, divorced, cohabiting, single, and widowed; age (continuous variable); comorbidities (categorical variable); body mass index (BMI, ordinal variable): reported weight (in kilograms) and height (in meters); level of education (discrete variable): in years of study; parity (discrete variable): defined by the number of previous pregnancies. We defined dependent variables as: off-cycle bleeding also known as spotting (present or absent), menstrual flow (increased, decreased, or remained the same), cramps (increased, remained constant, or decreased), discontinuation of treatment by choice, flaws in the method being used (pregnancy using the method correctly), ectopic pregnancy while using the method (presence of pregnancy outside the uterus), the onset of inflammatory pelvic disease (IPD), method satisfaction (satisfied if indicating the method to someone I know), libido (adequate, low and high), mood (happy, sad, apathetic and anxious), acquisition of information about the chosen method: health professionals, relatives or neighbors or friends, television, newspaper, and the internet. The device was considered an independent variable: IUD and Implanon.

The collected coded data were stored anonymously in a database with the Excel (Microsoft Corp., Redmond, WA, USA) software for Windows, created for this purpose. The data were allocated in tables and graphs for descriptive statistical analysis (mean, standard deviation [SD]; absolute, and relative frequency distribution). For analysis, the questionnaires were reviewed to check the readability and quality of the information, after data were organized, archived, typed, and coded. To describe the profile of the sample according to the variables under study, frequency tables were created for the variables categorical with values of absolute frequency (n) and percentage (%), and statistics descriptions of numerical variables with mean values, SD, minimum and maximum values, median, and quartiles. For the BMI, the Student-t test was used to assess statistical significance. Considering $p < 0.05$ and normal distribution or Gaussian for the BMI. For statistical analysis, the following programs were used computational systems: The Statistical Analysis System (SAS; SAS Institute INC., Cary, NC, USA) for Windows, version 9.4, as well as the Prism 5 software.

This study complied with all the principles of the Declaration of Helsinki, and Resolution 466/12 of the National Health Council, according to the guidelines and regulatory norms for research involving human beings. This study was submitted for approval by the Research Ethics Committee (CEP) of the Faculty of Medical Sciences (FCM) at UNICAMP and by the Research Commission of the DTG/CAISM under the number 59440022.5.0000.5404.

Results

Descriptive Variables Referring to the Cross-sectional Study

►**Tables 1** and **2** below show the frequency and descriptive statistics of the categorical variables on the socioclinical, data to characterize the total copper IUD sample ($n = 31$) from 105 patients identified and the Implanon sample ($n = 3$) from 5 patients identified in the GEMM. This discrepancy in numbers may be due to some reasons: It is possible that more

Table 1 Descriptive analysis of categorical variables

Copper IUD					
Humor	**Frequency**	**Percentage**	**Libido**	**Frequency**	**Percentage**
Happy	24	77	Adequate	26	84
Sad/anxious	7	23	Inadequate	5	16
Menstrual flow	**Frequency**	**Percentage**	**Cramps**	**Frequency**	**Percentage**
Increase	19	61	Increase	16	52
Decrease	3	29	Decrease	2	6
Constant	2	10	Constant	13	42
Indicate	**Frequency**	**Percentage**	**Marital status**	**Frequency**	**Percentage**
Yes	30	97	Married/living together	20	65
No	1	3	Single/divorced	11	35
Implanon					
Happy	2	67	Adequate	2	67
Sad/anxious	1	33	Inadequate	1	33
Menstrual flow	**Frequency**	**Percentage**	**Cramps**	**Frequency**	**Percentage**
Increase*	1	33	Increase	0	0
Decrease	0	0	Decrease	1	67
Constant*	2	67	Constant	2	33
Indicate	**Frequency**	**Percentage**	**Marital status**	**Frequency**	**Percentage**
Yes	3	100	Married/living together	2	67
No	0	0	Single/divorced	1	33

Abbreviation: IUD, intrauterine device; Implanon, etonogestrel implant. **Notes:** *Spoting percentage 50%, amenorrhea 0%, and menstrual irregularity 50%; n: numbers of women.

than one IUD was used by each user because there is a percentage of women who remove the device and end up reinserting it afterwards, or it is possible that an IUD was discarded due to contamination during the procedure. Additionally, it is hypothesized that when recording the ICD-10 of the procedure in the medical record, the professional made a mistake in the registration, inserting another CID different from the Z30. Of all interviewed women, only one was without the method at the time of the questionnaire.

Numerical Variables Referring to the Cross-sectional Study

►**Table 3** demonstrates the analysis of numerical variables of parity and evolution of women's BMI to copper IUD and Implanon (►**Table 4**).

The statistics are shown in ►**Fig. 1**.

Discussion

These results show that women choose their method according to their doctors' guidance (D: 47%; I: 77%). Additionally, the choice of these methods also involves the acquisition of information on the effectiveness of the technique through the Pearl index (D 77%; I 88%) and the ease of actual use (D: 71%; I: 67%). Furthermore, these women's rates of recommendation by others are high (D: 97%; I: 100%). Another interesting point is the fact that women's choice of LARCs involves more advice from health professionals (D: 65%; I: 100%) than the internet, newspaper, and television (D: 0%; I: 0%), in addition to the indication coming from friends or neighbors being median (D: 48%; I: 0%), and the indication coming from family members being low (D: 10%; I: 0%). Furthermore, there is an important decrease in BMI of around 2.7 for copper IUD users, with statistical significance, and of 0.22 for Implanon, with no statistical significance; improvement or maintenance of adequate self-reported libido (D: 84%; I: 66.7%) and improvement or maintenance of self-declared happy mood (D: 77%; I: 66.7%). It is also worth noting that most women in both groups were multiparous and were married or had a partner when they started using the methods, as already observed in other previous studies.[17]

Data on the choice of method can be related to worldwide scientific evidence. One of these studies, the contraceptive choice project, reveals how counseling and education about contraception promoted by health professionals themselves can increase the use of LARCs and improve the reproductive planning of a given population.[8] In this sense, to the detriment of other forms of information transmission, campaigns performed by PHC professionals themselves in their territories can increase the use of LARCs by women.[26–29] Additionally, false contraindications and technical unpreparedness of physicians for insertion are also barriers to the use of copper IUD and Implanon.[30–32] In the present study, it is believed that the technical competence of residents in family medicine is associated with better access to inserters, due to the

Table 2 Descriptive analysis of categorical variables relevant to choice and indication

Copper IUD					
Reason for choice					
Effectiveness	**Frequency**	**Percentage**	**Easy access**	**Frequency**	**Percentage**
No	14	45	No	9	29
Yes	17	55	Yes	22	71
No hormones	**Frequency**	**Percentage**	**IFNN**	**Frequency**	**Percentage**
No	14	45	No	26	84
Yes	17	55	Yes	5	16
Doctor	**Frequency**	**Percentage**	**Collateral effects**	**Frequency**	**Percentage**
No	15	48	No	25	81
Yes	16	52	Yes	6	19
Acquisition of information about the method					
HP	**Frequency**	**Percentage**	**FN**	**Frequency**	**Percentage**
No	11	35	No	16	52
Yes	20	65	Yes	15	48
Family	**Frequency**	**Percentage**	**TIJ**	**Frequency**	**Percentage**
No	28	90	No	25	81
Yes	3	10	Yes	6	19
Implanon					
Reason for choice					
Effectiveness	**Frequency**	**Percentage**	**Easy access**	**Frequency**	**Percentage**
No	0	0	No	1	33
Yes	3	100	Yes	2	67
No hormones	**Frequency**	**Percentage**	**IFNN**	**Frequency**	**Percentage**
No	3	100	No	3	67
Yes	0	0	Yes	1	33
Doctor	**Frequency**	**Percentage**	**Collateral effects**	**Frequency**	**Percentage**
No	0	0	No	2	67
Yes	3	100	Yes	1	33
Acquisition of information about the method					
HP	**Frequency**	**Percentage**	**FN**	**Frequency**	**Percentage**
No	0	0	No	2	67
Yes	3	100	Yes	1	33
Family	**Frequency**	**Percentage**	**TIJ**	**Frequency**	**Percentage**
No	3	100	No	3	100
Yes	0	0	Yes	0	0

Abbreviations: FN, friends or neighbors; HP, health professional; IFFN, indication of friends, family, and neighbors; IUD, intrauterine device; Implanon, etonogestrel implant; TIJ, television-internet-newspaper.

bond and comprehensive care obtained in PHC and the use of competent tools by family physicians. This can justify the high correlation between the use of LARCs and medical advice and acquisition of information by health professionals at the Sousas PHC (►**Tables 2**).[22,23,32,34]

The data discussed above are very relevant when we add them to the data also present in the survey on the low rate of contraceptive indication by friends, neighbors, and family members in the choice of LARCs (►**Tables 2** and **4**). As several researchers have already highlighted, consolidated public policies that encourage the use of LARCs by counseling the population about their action, duration, effectiveness, and adverse effects are the future of reproductive planning.[31,32,35,36] Thus, projects such as the National Policy for Population Education in Health in the SUS (PNEPS-SUS), and policies of permanent and continued education in health for professionals, combating disinformation through the HC in the users' territories may favor the onset of LARCs.[37–42]

There are other data discussed in the present work that refer to the IUD and the technical capacity of the PMMC's

Table 3 Data on patients' BMI

Variable	n	Mean	SD	Min	Q1	Median	Q3	Max
Copper IUD								
Pregnancies	31	2	1,14	0	1	2	2	5
BMI before	31	28.7	5.6	18	24.7	29	32.25	46
BMI after	31	27	6.2	18	23	26	30	42
Implanon								
Pregnancies	3	2	2.65	0	1	1	5	5
BMI before	3	28	2.64	25	25	29	30	30
BMI after	3	27.6	3.05	25	25	27	31	31

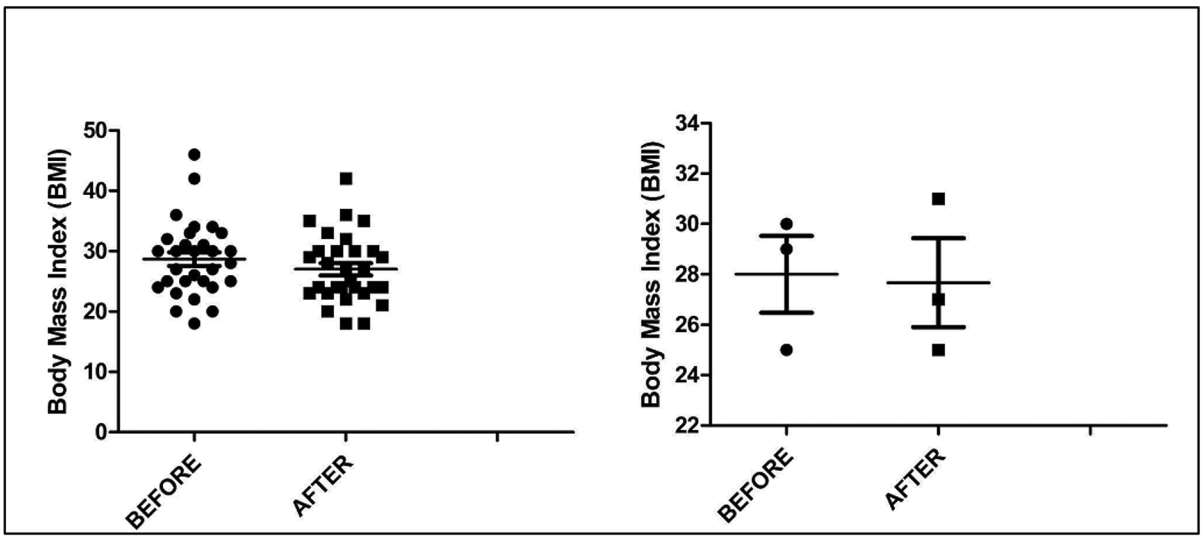
Abbreviation: BMI, body mass index; IUD, intrauterine device; SD, standard deviation. **Notes:** 1: before contraception choice; 2: after contraception choice.

Table 4 Data from medical records

Data from medical records	n	Expulsion	Removal	Pregnancy	IPD	Perforation
Copper IUD	80	4%	5%	0%	0%	0%
Implanon	5	0%	0%	0%	0%	0%

Abbreviations: IUD, intrauterine device; Implanon, etonogestrel implant; IPD, inflammatory pelvic disease; n, number of women.

Family and Community Medicine residents. Expulsion rates of 4%, post-insertion PID of 0%, perforations of 0%, and pregnancy rate of 0% were obtained in the analyzed time interval. Furthermore, among the women in the study, 51% reported an increase in cramps and 61% an increase in bleeding after the insertion of the copper IUD. Such data are in line with the literature denoting the expertise of family doctors.[3,18,43] The literature also demonstrates that approximately 5 to 15% of women do not adapt to the bleeding pattern of copper IUD within 6 months of follow-up.[44] The present study, however, observed that only 5% of the women in the study requested the removal of the copper IUD due to the intense flow of bleeding, and 75% of them would still recommend it to acquaintances. Thus, it is postulated that if



Gain	n	t	IC 95%	p-value
Diu-cu	31	2,92	-2.87 to -0,53	0,006
Implanon	3	0,22	-5.9 to 6.5	0.82

Fig. 1 Data on body mass index (BMI) before and after the onset of copper intrauterine device (IUD) on the left and etonogestrel implant (Implanon) on the right.

the Mirena—a hormonal IUD that can reduce the flow of uterine bleeding—was offered in the PHCs, there would be a good acceptance of the women who did not adapt to the copper device.[45] This study also postulated, with a 0% of expulsion, perforation, IPD, and pregnancy, that PMMC residents would probably also correctly indicate and insert the hormonal IUD, as they did in the case of the copper IUD.

A point of great importance that the present work sought to discuss is the influence of LARCs in changing other aspects of health besides reproduction. As we can see in ►**Table 1**, both copper IUD and Implanon had beneficial effects on the mood state self-referred to as "happy", and libido self-referred to as "adequate," which is similar to other studies.[10,11] It is hypothesized that this happens due to the security that the method offers in avoiding pregnancies, making these women have greater control over planning their lives and avoiding situations of physical, mental, and financial violence.[43]

Another great data acquired in ►**Table 3** was the improvement in the BMI of the women who opted for the copper IUD and not of those who opted for Implanon at 6 months of use, which is consistent with the literature.[46,47] This is probably due to the large number of women who previously used the quarterly injectable as a contraceptive, a method known to cause weight gain, as well as the fact that LARCs are associated with changes in lifestyle and consequent improvement in eating behavior over time.[47,48] However, further research is still needed to better quantify these data.

In this context, other data of notorious interest are the paradigms that involve the level of satisfaction with LARCs, since this is associated with the maintenance of the methods by many authors.[12,14,19,49,50] This relevance is part of the possibility of using the best specific method for each population by understanding the factors that would lead women to discontinue the method, for example. The present research suggests that satisfaction, analyzed by questioning the recommendation of the method to others, is not always linked to the continuity of the treatment despite being often related. Thus, we had withdrawal rate of approximately 5%, a pattern similar to that of the international literature, with a counseling rate of 97% for the copper IUD and 100% for Implanon.[51–53] Given this data, the satisfaction with these methods, in addition to involving several issues such as effectiveness, the expectation regarding the product, and the service quality attributes, may also not always correlate with continuation of treatment.[19,54,55]

Therefore, the present work postulates that adequate global assistance and satisfaction rates provided by the family physician during women's health consultations were higher than in the literature.[30] It is worth highlighting the need for further research to define whether satisfaction with the method is directly related to its continuity.

The Sousas district has a large population that does not depend exclusively on the SUS. As a result, we obtained a small number of women in both samples, and a control group that did not opt for LARCs was not included, which can create confounding biases. We had some limitations in data acquisition: ICD insertion errors, changes of address and phone number, high social vulnerability with low access to healthcare, and the small number of professionals performing Implanon insertion.

In 2020 and 2021, the whole world faced the COVID-19 pandemic, which had a multidimensional impact on health and, therefore, affected some data related to reproductive planning. This partly explains the worsening of the indicators studied from 2020 onwards.

Conclusion

The data presented suggest that women choose methods according to the guidance of their physician or health professionals and opt for LARCs due to their ease of use and low failure rate. Additionally, the possible improvement of important clinical parameters for the general wellbeing of women, such as libido, mood, and BMI related to LARCs, is highlighted. Furthermore, family medicine residents make a correct indication and insertion of LARCs, with adequate advice and assistance provided. Further research and a more longitudinal outlook are needed to detail other aspects relevant to the LARCs in the Sousas territory, as well as to be able to externalize our results to other realities.

Contributions

All authors substantially contributed to the conception and design of the study, data collection, analysis and interpretation, writing of the article, its clinical review and approval of its final version.

Conflict of Interests

The authors have no conflict of interests to declare.

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Combined Aerobic and Strength Training Improves Dynamic Stability and can Prevent against Static Stability Decline in Postmenopausal Women: A Randomized Clinical Trial

O treinamento de força e aeróbio combinado melhora a estabilidade dinâmica e pode prevenir contra o declínio da estabilidade estática em mulheres na pós-menopausa: um ensaio clínico randomizado

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Abstract

Objective To analyze the effect of combined training (CT) in postural control and gait parameters in postmenopausal women.

Methods A parallel-group, randomized, control study was conducted with 16 weeks of combined training ($n = 16$) versus a non-training control group ($n = 12$) in postmenopausal women (aged 59.3 ± 8.0). Pre and postintervention assessments included postural control (using an AMTI force platform – Advanced Mechanical Technology, Inc., Watertown, MA, USA) and gait impairments (using baropodometry). In addition, the upper limb strength and abdominal tests, as well as aerobic capacity, assessed functional indicators.

Keywords
- physical exercise
- menopause
- balance
- concurrent training
- gait

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Results The CT intervention in postmenopausal women resulted in improved gait (stride length ($p = 0.006$); speed ($p = 0.013$); double support time ($p = 0.045$); and improved postural control (displacement area of postural sway in a normal base of support with eyes open ($p = 0.006$). Combined training increased functional indicators (abdominal - $p = 0.031$; aerobic capacity - $p = 0.002$).

Conclusion In conclusion, combined aerobic plus strength training effectively improved gait and balance control in older women. The postmenopausal women from the CT group walked faster and with bigger steps after the intervention than the control group. In addition, they presented decreased postural sway in standing and decreased the percentage of double support time while walking, which means improved static and dynamic balance control and functional indicators.

Resumo

Objetivo Analisar o efeito do treinamento combinado (TC) no controle postural e nos parâmetros da marcha em mulheres na pós-menopausa.

Métodos Foi realizado um estudo controlado randomizado de grupos paralelos com 16 semanas de treinamento combinado ($n = 16$) versus um grupo controle sem treinamento ($n = 12$) em mulheres na pós-menopausa (59,3 ± 8,0 anos). As avaliações pré e pós-intervenção incluíram controle postural (usando a plataforma de força AMTI) e deficiências da marcha (usando baropodometria). Além disso, os testes de força de membros superiores e abdominal, bem como a capacidade aeróbica, avaliaram indicadores funcionais.

Resultados A intervenção do TC em mulheres na pós-menopausa resultou em melhora da marcha (comprimento da passada ($p = 0,006$), velocidade ($p = 0,013$), tempo de apoio duplo ($p = 0,045$) e controle postural aprimorado (área de deslocamento da oscilação postural em base de apoio normal com olhos abertos ($p = 0,006$). O TC aumentou os indicadores funcionais (abdominal - $p = 0,031$; capacidade aeróbia - $p = 0,002$).

Conclusão Em conclusão, o TC de força e aeróbico melhorou efetivamente o controle da marcha e do equilíbrio em mulheres idosas. As mulheres na pós-menopausa do grupo CT caminharam mais rápido e com passos maiores após a intervenção do que o grupo controle. Além disso, elas apresentaram redução da oscilação postural em pé e do percentual de tempo de apoio duplo durante a caminhada, o que significa melhora no controle do equilíbrio estático e dinâmico e dos indicadores funcionais.

Palavras-chave
- exercício físico
- menopausa
- equilíbrio
- treinamento concorrente
- marcha

Introduction

Postmenopausal women present postural control impairments when standing across a variety of conditions (e.g., bipedal and semi-tandem; eyes open and closed).[1–10] Gait impairments are also observed in this population, with slow gait velocity and long double support time.[11,12] Impairments in postural control and gait may result in difficulty in managing daily activities and increase the risk of falls. Sociodemographic (e.g., age) and functional changes (e.g., previous falls) are associated with these impairments in postural control and gait.[13] In addition, postmenopausal women's postural control and gait performance can be influenced by other health and physical indicators such as body mass index, body composition changes, and physical fitness.[14] Many of these physical indicators can be avoided and/or minimized by physical exercise programs, an important non-pharmacological strategy.[15]

Different types of physical exercise programs have been shown to improve the health and physical indicators in postmenopausal women,[16–25] and promote improvements in postural control[22,23] and gait performance.[24,25] Specifically, 8 weeks of aerobic exercise intervention effectively improved several aspects of balance control in older women.[23] In addition to the benefits of aerobic exercise, a meta-analysis indicated that strength exercises promote significant and large effect size (0.84–confidence interval = 0.52–1.56) improvements in gait velocity.[25] In addition, improvements in leg strength after strength exercise were superior to those observed after aerobic exercise. After strengthening exercises, leg extension and flexion strength improvements may contribute to meaningful improvements in static and dynamic balance control.[26]

The impact of different exercise programs in postural control and gait in older women is promising. Moreover, there is a need to further understand and examine the

possible positive effects of other exercises. For Instance, we have shown that combining aerobic and strength exercises (combined training - CT) is important to improve postural control after 12 weeks of training in older women (over 60 years old).[27] Based upon all these results, we wondered about the possible benefits of CT on posture and gait for postmenopausal women.

Due to metabolic changes, postmenopausal women experience an accumulation of total, hip, and trunk fat, which affects posture,[28] leading to an increase in the risk of falls and fractures,[3] and this condition may be associated with frailty.[29] The CT is an efficient training strategy for changing body composition, increasing lean mass, and reducing fat, especially in the trunk.[19] Therefore, CT might constitute an important training protocol to improve postural control and gait parameters. Thus, the purpose of this study was to examine the effects of a 16-week CT protocol on postural control and gait performance in postmenopausal women.

Methods

This study was a prospective, parallel-group, randomized, controlled study with 16 weeks of CT versus a control (C) group. Subjects had pre and postintervention anthropometric, postural control and gait performance assessments, and functional indicators performed during the week before and after the interventions. All the procedures were approved by the Institutional Ethical Committee (protocol 388.070), following the Declaration of Helsinki.[30] Also, the study was registered in the Brazilian databases of clinical trial (RBR-9CBP8S). Furthermore, all participants agreed and signed the consent form prior to enrolment in the study.

Subjects were invited through newspaper and television advertising to participate in the study, and, after phone contact, an appointment was scheduled for a more detailed screening interview. The inclusion criteria were: (a) postmenopausal women, without a menstrual cycle for at least 1 year; (b) to be between the ages of 50 and 79 on the date of the evaluation; (c) medical authorization to participate in the training; (d) no physical limitations or health problems that could prohibit the completion of the assessments and exercise intervention (e.g., uncontrolled diabetes, hypertension, or rheumatoid arthritis); (e) no participation in any systematic physical exercise for at least 6 months before the study; (f) no history of hormone replacement therapy. The exclusion criteria were accumulated 3 consecutive absences or 4 non-consecutive absences in the intervention for 1 month. After this initial screening, participants were allocated randomly to one group (CT or C).[31] Simple randomization techniques were used for allocation (1:1), which ensures that trial participants have an equal chance of being allocated to a treatment group by a researcher who was blinded to the group allocation.

►**Fig. 1** (Consolidated Standards of Reporting Trials [CONSORT] flowchart) shows the recruitment procedures. A total of 361 postmenopausal women registered for the first call, and 131 attended the initial screening meeting. Of these, 61 postmenopausal women were excluded (40 postmenopausal women did not meet the inclusion criteria and 21 refused to participate in the study). After this initial screening, 48 postmenopausal women performed baseline tests and were randomized to one of the groups (CT or C). The participants allocated to the CT group should present medical authorization to participate in the training routine. During the intervention period, 20 participants dropped out of CT ($n = 8$), dropped out of 33.3% and C ($n = 12$), dropped out of 50%. The reasons for dropouts included health problems, personal/family problems; unspecified reasons, which led to failure to participate in the final assessment. Using an effect size for gait velocity (partial eta squared = 0.24), an α value of 5%, a 98% power to our sample size was detected.

The CT group (age = 59.1 ± 8.1 years; height = 155.8 ± 6.4 cm) involved strength and aerobic training in each exercise session. Subjects exercised for 90 minutes, 3 times per week for 16 weeks. Before each exercise session, participants performed 5 minutes of warm-up exercises and 5 minutes of stretching at the end of the training session.

Before starting the program, participants performed 2 weeks of equipment and training routine familiarization (without load). The exercises were performed 3 times a week (Monday, Wednesday, and Friday) for 90 minutes a day. They were comprised of 5 minutes of warm-up, 50 minutes of resistance training, 30 minutes of aerobic training, and 5 minutes of stretching at the end. After that, participants exercised for 16 weeks, keeping the same frequency and time. All sessions were supervised by a professional of physical education or physiotherapist. The protocol training is described below.

Strength training was composed of the following exercises: leg extension; 45° leg press; leg curl; bench press; seated row; triceps extension; arm curl; arm side elevation with dumbbells, and abdominal exercises, according to Rossi et al.[19] The exercise routine was performed always in the same gym. The intensity of strength training was controlled through the zone of maximum repetitions. The series was executed until momentary exhaustion (e.g., the repetitions should be between 12 to 15 repetitions maximum). The load was increased when the participants executed more than 15 repetitions to have the training zone respected.[19] The strength training program consisted of 4 progressive phases: phase 1–1st to 4th weeks, 12 to 15 repetitions, 3 sets per exercise; phase 2: 5th to 8th weeks, 10 to 12 repetitions, 3 sets per exercise; phase 3–9th to 12th weeks, 8 to 10 repetitions, 3 sets per exercise; phase 4–13th to 16th weeks, 8 repetitions, 3 sets per exercise. For all weeks, the participants had a 60-second break between sets. The 20-point scale, as standardized by Borg et al.,[32] was used to determine the rate perceived effort (RPE) after each training session.

Aerobic training involved walking in an external environment. The intensity was performed using the critical velocity protocol,[33,34] already used in our previous studies with postmenopausal women.[16,20,35,36] The critical velocity was determined by having subjects walk as quickly as possible 3 different distances (400, 800, and 1,200 m) on a running track on 3 different and non-consecutive days. The time for

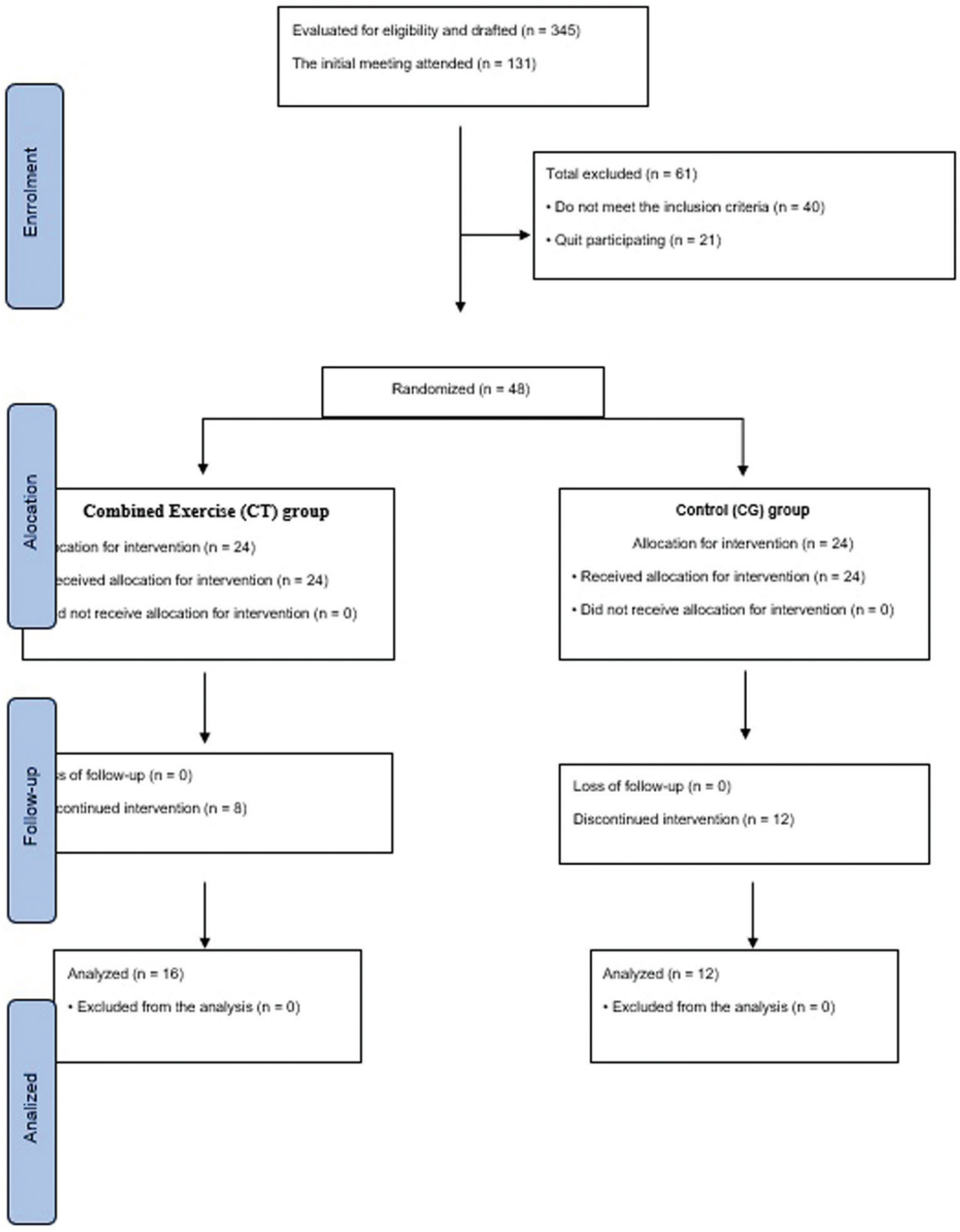

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart of study participants through the 16-week study. CT, combined training; CG, control group.

performing the distance was recorded (digital stopwatch – model S810i or RS800, Polar Electro, Espoo, Finland). The relationship between the distance (m) and the exercise time (s) was linearly adjusted, and we assumed the critical velocity to be the slope of this model,[37] which is the intensity of aerobic training.[38] Women walked at 60 to 70% from their critical velocity during the training sections.

The participants were instructed to refrain from structured train–ng program and to maintain their regular dietary intake during the intervention.

The C group (age = 59.7 ± 8.2 years; height = 155.8 ± 6.7 cm) were instructed to avoid changing their activities or starting any new exercise program for 18 weeks (between the initial and final assessments of the research).

Anthropometric measurements were composed of body weight and height measurements. Bodyweight was obtained using an electronic scale (Filizola PL 50 - Filizola Ltda., Fortaleza, CE, Brazil) (accuracy of 0.1 kg) and height using a stadiometer (Sanny, São Paulo, SP, Brazil) (accuracy of 0.1 cm and length of 2.20 m).

Postural control during standing was tested by measuring postural sway using an AMTI force platform (model-BP600400–Advanced Mechanical Technology, Inc., Watertown, MA, USA) and AMTI-NetForce software (Advanced Mechanical Technology, Inc.. The participants were evaluated under two support bases (normal base with feet parallel at shoulder width and semi-tandem stance) and two visual conditions (eyes open and eyes closed), resulting in four conditions.

The participants were asked to stand upright on the force platform, barefoot, and stand as still as possible, with arms down at the sides of the body for 30 seconds. In the eyes-open condition, they were asked to fixate on a target (white tape – 2×5 cm) placed on the wall, 2-m away, at their eye level. In the eyes-closed condition, participants keep their eyes open in the dark while wearing a pair of goggles covered with black tape, preventing the availability of any visual cues. The order of the conditions was randomly defined.

The center of pressure displacement was recorded at a frequency of 100 Hz. Customized routines written in MATLAB (The MathWorks Inc., Natick, USA) were used to filter (second-order Butterworth digital filter, cut off frequency of 5 Hz) the center of pressure data in both medial-lateral (ML) and anterior-posterior (AP) directions. The center of pressure ellipse area (95% of total area) was used to quantify postural control.

The gait performance was assessed using a 2-m baropodometry gait mat (FootWork Pro - AM cube, Gargas, France). Participants walked along an 8-m walkway, in which the baropodometry mat was arranged in the center with 3m before and after it for acceleration and deceleration, respectively. The participants were instructed to walk at their preferred velocity throughout the walkway, performing three repetitions each way. Data from the baropodometry were obtained at 200 Hz frequency and analyzed by Software Footwork Pro (IST Informatique, Gargas, France). Gait performance was quantified as stride length, stride time, gait velocity, and double support time (percent of gait cycle).[39]

As functional indicators, we adopted the tests of a) upper limb strength, b) Abdominal, and c) Aerobic capacity. This protocol was described in a preview study.[40]

Normality assumption was confirmed (Shapiro-Wilk test), the estimated sphericity was verified (Mauchly's W test), and, when necessary, the Greenhouse-Geisser correction was used. For each outcome measure, a mixed between-group–within-subject multivariate analyses of variance (MANOVA and ANOVA) were employed, having as factors, group (control and CT) and the two evaluation sessions (pre and posttraining), this last factor treated as a repeated measure. When necessary, univariate analyses and posthoc tests, with Bonferroni adjustments, were employed. The partial eta squared (η^{p2}) was reported for time, group and interaction effects, and the threshold values were > 0.001 (small), > 0.06 (moderate), and > 0.14 (large). All statistical analysis was performed using the IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). We adopted a significance level $p \leq 0.05$.

Results

►**Table 1** presents mean ($\pm$ SD) values of body weight and functional indicators for both groups and evaluations and the group. There were no statistically significant differences between groups at baseline for all variables investigated ($p > 0.05$). For functional indicators, there were statistically significant interactions in the abdominal test ($F = 5.53$, $p = 0.029$, $\eta^{p2} = 0.22$) and aerobic capacity ($F = 6.78$, $p = 0.017$, $\eta^{p2} = 0.25$). Posthoc tests showed that the CT group increased repetitions in the abdominal test posttraining compared with baseline ($p = 0.031$) with higher values than the C group ($p = 0.006$), and the CT group showed lower time in seconds in the aerobic capacity compared with the C group ($p = 0.002$). For muscle strength in the upper limb, there was a main effect of time ($F = 17.23$, $p < 0.001$, $\eta^{p2} = 0.46$) and significant difference between groups ($F = 8.20$, $p = 0.010$, $\eta^{p2} = 0.29$) but no interaction was observed. There were no main effects of time or statistically significant differences between groups or interactions for body weight ($p > 0.05$).

►**Fig. 2** depicts postural sway ellipse area mean values for both groups and evaluations for both stance position and visual conditions. In the normal stance position, MANOVA revealed significant pre-post assessment effect (Wilks Lambda $= 0.697$, F (2.25) $= 8.10$, $p = 0.002$) with a significant group and assessment interaction (Wilks Lambda $= 0.736$, (2.25) $= 4.48$, $p = 0.02$). Univariate analyses showed an effect of assessment occurred for both eyes open (panel A) ($F = 5.05$, $p = 0.033$, $\eta^{p2} = 0.16$) and eyes closed (panel B) ($F = 16.39$, $p < 0.001$, $\eta^{p2} = 0.38$) conditions showed that the ellipse area was larger in the post than in the preassessment. Additionally, univariate analyses showed that an interaction effect occurred only in the eyes-open condition ($F = 8.967$, $p = 0.006$, $\eta^{p2} = 0.25$), and Bonferroni posthoc tests showed a significant ellipse area increase in the C group, postevaluation ($p = 0.002$), but no difference in the CT group. In the semi-tandem position with eyes open (panel C), there was no significant difference (Wilks Lambda $= 0.786$, F (2.25) $= 3.39$, $p = 0.543$), but univariate analyses showed an effect of group only in the eyes-closed condition ($F = 5.356$, $p = 0.029$, $\eta^{p2} = 0.17$), with the C group showing larger sway than the CT group (panel D).

Table 1 Mean ($\pm$ SD) values of body weight and functional indicators for both groups and evaluations and the group and evaluation interaction *p*-values

Variables	Control group ($n = 12$)		CT group ($n = 16$)		*P*-value
	Pre	Post	Pre	Post	
Body weight (kg)	65.0 ± 11.4	65.5 ± 11.6	68.1 ± 8.9	68.1 ± 9.1	0.446
Muscle strength (repetitions)	20.2 ± 4.3	22.6 ± 4.0	23.5 ± 3.5	27.1 ± 2.8	0.332
Abdominal (repetitions)	6.0 ± 8.7	4.7 ± 5.7	6.1 ± 9.5	$13.1 \pm 9.3^{*}£$	0.029
Aerobic capacity (seconds)	499.2 ± 44.6	503.8 ± 41.1	500.4 ± 27.5	$469.4 \pm 40.3^{£}$	0.017

Abbreviations: CT, combined training.
*= Bonferroni posthoc test with *p*-value < 0.05 compared with Pre; £ = Bonferroni posthoc test with *p*-value < 0.05 compared with the control group.

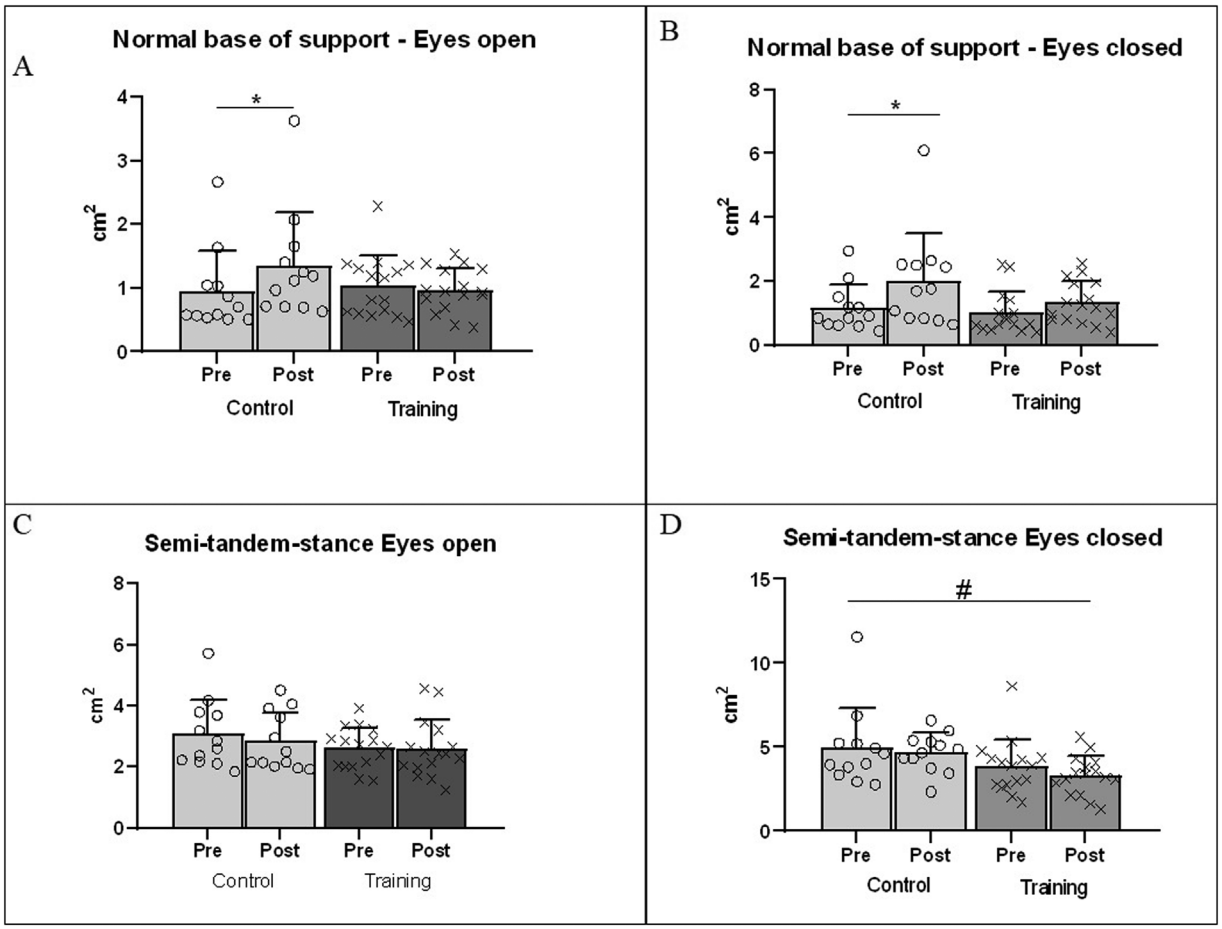

Fig. 2 Comparation of center of pressure ellipse area. CT, combined training – Panel A: Normal base of support eyes open. Panel B: Normal base of support eyes closed. * = Bonferroni posthoc test with p-value < 0.05 compared with pre. # = main difference between groups.

►**Fig. 3** depicts values of gait performance for both groups, pre and postevaluation. For gait velocity (panel A), ANOVA showed a significant pre-post assessment effect ($F = 10.432$, $p = 0.004$, $\eta^{p2} = 0.31$) and a significant group and assessment interaction ($F = 7.169$, $p = 0.013$, $\eta^{p2} = 0.24$). Posthoc tests showed that the CT group increased gait velocity postevaluation ($p < 0.001$). Similar results were observed for the stride length (panel B), with ANOVA revealing evaluation effect ($F = 10.173$, $p = 0.004$, $\eta^{p2} = 0.31$), and group and assessment interaction ($F = 9.037$, $p = 0.006$, $\eta^{p2} = 0.28$). Posthoc tests showed that the CT group increased stride length postassessment ($p < 0.001$). For stride time (panel C), ANOVA revealed only a significant assessment effect ($F = 7.294$, $p = 0.013$, $\eta^{p2} = 0.24$), with both groups reducing stride duration, when comparing post and preevaluation. Finally, for the double support time (panel D), ANOVA revealed only a group by evaluation interaction ($F = 4.508$, $p = 0.045$, $\eta^{p2} = 0.16$). Posthoc tests showed that the CT group reduced double support duration post-evaluation ($p = 0.006$).

Discussion

This study aimed to examine the effects of a 16-week of CT training protocol on postural control and gait performance in postmenopausal women. The 16 weeks of CT intervention improved gait performance in this cohort. In addition, postural sway increased in the C group but not the CT group. To the best of our knowledge, this is the first study to show the effects of CT on gait and postural control in postmenopausal women.

Postmenopausal women walked faster, with longer steps and with shorter double support time after the CT intervention. Conversely, post-menopausal women from the control group did not show any gait change. Dias et al. also observed an increase in gait speed in postmenopausal women after 12 weeks of 2 strength-training protocols (cluster-set and traditional inter-repetitions rest method).[41] Our results, however, add to the existing knowledge showing that such walking velocity increase was due to longer steps and a tendency of shorter stride duration. Thus, the CT intervention promotes several improvements in gait parameters that allow postmenopausal women to walk faster.

Our results also showed that postmenopausal women decreased the double support duration after the CT training protocol compared with pretraining. A shorter double support duration during walking improves gait stability. Aragão-Santos et al. also found gait speed increase in postmenopausal women after element-based functional and task-specific-based functional training protocols but did not find improvements in gait stability.[42] Thus, the CT training

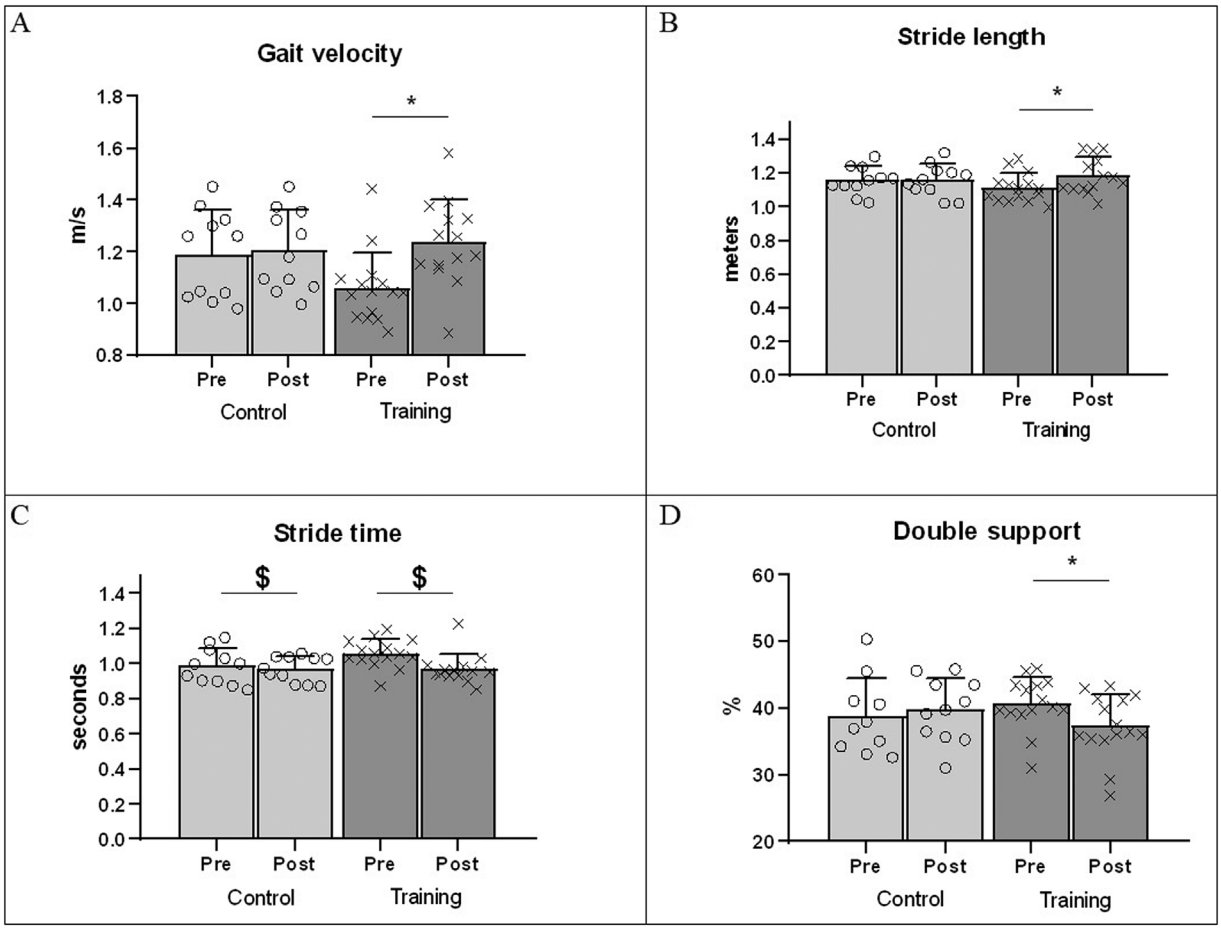

Fig. 3 Comparation of gait parameters. m/s = meters per second. CT = combined training – Panel A: Gait velocity; Panel B: Stride length; Panel C: Stride time; Panel D: Double support. * = Bonferroni posthoc test with p-value < 0.05 compared with pre. $ = Main effect of assessment.

seems to contribute even further than other interventional protocols in terms of improving gait stability, but this issue requires future research. Another important issue related to the CT protocol employed in this study was that postmenopausal women performed the aerobic training walking in an external environment, which improved aerobic capacity by providing a specific stimulus for neural adaptations required for walking in the real world.[26]

The CT protocol did not impact the postural sway, although the C group increased their postural sway after 12 weeks without intervention. The center of pressure displacement ellipse area, under the normal base of support and eyes-open condition, showed that while women enrolled in the 16-week CT maintained the same ellipse area, women in the C group increased the ellipse area. Despite being characterized by large variability, a similar tendency ($p = 0.090$) was observed in the normal base with eyes closed. Thus, the CT employed in this study avoided performance deterioration in postmenopausal women when standing in a normal position. Such observation corroborates previous suggestions that exercise prevents postmenopausal 'women's postural control system deterioration,[43] and, especially in women over 50 years.[44]

We hypothesized that CT could improve muscle strength leading to better postural control performance.[45] However, our results did not improve postural sway between pre and posttraining in the normal stance and semi-tandem stance, although CT improved functional indicators observed by the number of repetitions in the abdominal test and aerobic capacity; thus, the increase in strength in the abdominal region could have influenced postural control performance in the CT group, since, in this region, both the external and internal forces act directly to accelerate or decelerate the body. Perhaps a more challenging postural condition, such as tandem or one-legged stance, would have improved postural control with increased leg and trunk strength. Nevertheless, the CT group showed better postural control performance than the C group, which corroborates results observed after 32 weeks of strength training.[26] Furthermore, besides the improvements in gait and lack of deterioration of postural control showed in the present study, women who practice CT have other benefits demonstrated in other studies, such as improvements in body composition, with a decrease in body fat mass and increase in lean mass,[19] and improvements in strength[46] and cardiovascular condition.[47]

Our study has limitations: the absence of lower limb muscle strength and body composition assessments. In addition, the functional test used in the present study can be enough toidentify an improvement in upper body strength; therefore, maybe a more specific test, such as the

1RM test, would have shown better benefits for upper body strength. Nevertheless, the present study contributes to the literature, since professionals who work with postmenopausal women should include combined aerobic and strength exercises that may improve gait speed and stability. Improvement in dynamic stability when walking can reduce the risk of falls, fractures,[48] consequent hospitalization as well as decrease difficulty in mobility and in the performance of daily activities.[49] Furthermore, we suggest that future randomized control trials are performed, analyzing gait and balance control according to body composition and fitness capacity.

Conclusion

Combined training (aerobic plus strength) improved gait variables and avoided the postural control decline after 16 weeks of intervention in postmenopausal women. In addition, the women from the CT group walked faster and with bigger steps after the intervention than the those in the C group, and they decreased the percentage of double support time and showed improvement of functional indicators.

Contributions

ACFM, FER, LMN: Conceptualization, methodology, formal analysis, investigation, writing original draft, writing review and editing, and visualization. ACFM, FER, LMN, TAD, IAM, JAB, FBH, IFFJ: Methodology, writing of the original draft, and writing of review editing. ACFM, FER, LMN, TAD, IAM, JAB, FBH, IFFJ.: Conceptualization, methodology, formal analysis, writing original draft, writing review: CFM, FER; IFFJ: Supervision. All authors contributed to the article and approved the submitted version.

Conflict of Interests

The authors have no conflict of interests to declare.

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Human Papillomavirus 16 Lineage D is Associated with High Risk of Cervical Cancer in the Brazilian Northeast Region

Papillomavirus humano 16 da linhagem D associado a alto risco de câncer de colo do útero em região do nordeste brasileiro

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Abstract

Objective Similar to Human Papillomavirus (HPV) genotypes, different lineages of a genotype also have different carcinogenic capabilities. Studies have shown that specific genotype lineages of oncogenic HPV are associated with variable risks for the development of cervical intraepithelial neoplasia (CIN2/CIN3) and cervical cancer. The present study aimed to analyze the genetic diversity of the HPV16 genotype in women with CIN2/CIN3 and cervical cancer, from the northeast region of Brazil.

Methods A cross-sectional multicenter study was conducted in the northeast region of Brazil, from 2014 to 2016. This study included 196 cases of HPV16 variants (59 and 137 cases of CIN2/CIN3 and cervical cancer, respectively). The difference of proportion test was used to compare patients with CIN2/CIN3 and cervical cancer, based on the prevalent HPV16 lineage ($p < 0.05$).

Results According to the histopathological diagnosis, the percentage of lineage frequencies revealed a marginal difference in the prevalence of lineage A in CIN2/CIN3, compared with that in cervical cancer ($p = 0.053$). For lineage D, the proportion was higher in cancer cases (32.8%), than in CIN2/CIN3 cases (16.9%), with $p = 0.023$.

Keywords
- HPV16
- lineage A
- lineage D
- CIN2/CIN3
- cervical cancer

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Conclusion HPV16 lineage A was the most frequent lineage in both CIN2/CIN3 and cervical cancer samples, while lineage D was predominant in cervical cancer, suggesting a possible association between HPV16 lineage D and cervical cancer.

Resumo

Objetivo Tanto os tipos quanto as linhagens do Papilomavírus Humano (HPV) parecem ter diferentes capacidades carcinogênicas e estão associados a riscos variados para o desenvolvimento de neoplasia intraepitelial cervical (NIC) e câncer de colo do útero. O presente estudo tem como objetivo analisar a diversidade genética do genótipo HPV 16 nos casos de NIC2/NIC3 e câncer de colo de útero em mulheres da região Nordeste do Brasil.

Métodos Estudo transversal de base hospitalar realizado na região Nordeste do Brasil no período de 2014 a 2016. A amostra foi composta por 196 casos da variante HPV-16 (59 casos de NIC2/NIC3 e 137 de câncer do colo do útero). O teste de diferença de proporção foi usado para comparar os grupos NIC2/NIC3 e câncer de colo do útero por linhagem viral em relação à prevalência da linhagem HPV-16. Foi considerada significância estatística o valor de $p < 0,05$.

Resultados As frequências de linhagem por diagnóstico histopatológico mostraram diferença limítrofe da linhagem A no grupo NIC2/NIC3 em relação ao grupo câncer de colo de útero ($p = 0,053$). Por outro lado, em relação à linhagem D, houve uma proporção maior nos casos de câncer (32,8%) quando comparado ao grupo NIC2/NIC3 (16,9%) e esta diferença se mostrou estatisticamente significante ($p = 0,023$).

Conclusão A linhagem A do HPV-16 foi a mais frequente tanto nas amostras CIN2/CIN3 quanto nas amostras de câncer de colo de útero, enquanto a linhagem D predominou no câncer de colo do útero, sugerindo uma possível associação da linhagem D de HPV-16 com câncer de colo de útero.

Palavras-chave
- HPV16
- linhagem A
- linhagem D
- NIC2/NIC3
- câncer colo útero

Introduction

Cervical cancer is the fourth most common cancer, in terms of incidence and mortality, among women worldwide.[1] In Brazil, it is the third and fourth most common cancer among women, in terms of incidence and mortality, respectively.[2,3] Several studies have shown that the Human Papillomavirus (HPV) is a predominant, but not the only, factor for cervical cancer development. The viral genotype HPV16 is the most prevalent in cervical cancer and is considered a Group 1 carcinogenic agent for humans by the International Agency for Cancer Research.[4] The study of the genetic diversity of HPV16 has enabled the characterization of specific viral lineages associated with a higher risk of cervical intraepithelial neoplasia (CIN2/CIN3) and cervical cancer development.[5–8] For HPV16, the lineages were initially named according to their geographical prevalence and separated into five groups: European (EUR), Asian (As), Asian-American (AA), African 1 (Af1), and African 2 (Af2).[9–12] In 2013, Burk et al., proposed a new α-numeric nomenclature for all HPV lineages based on the differences in the complete viral genome sequence.[13] The lineages for HPV16 were renamed as follows: A (corresponding to EUR and As), B (corresponding to Af1), C (corresponding to Af2), and D (corresponding to AA).

Studies have shown that HPV16 lineages B, C, and D with higher pathogenicity are associated with a higher viral persistence, compared with the lineage A.[4,14,15] Additionally, the HPV16 lineages B, C, and D are also associated with a higher risk of CIN2/CIN3 and cervical cancer.[14,16,17] The D lineage is also associated with adenocarcinoma.[18] A longitudinal study has shown that the HPV16 sub-lineages D2 and D3 are more significantly associated with CIN2/CIN3 and cervical cancer, compared with other lineages/sub-lineages.[16,19] Similar characteristics were reported in lineages of other HPV genotypes, such as HPV 18 and HPV 45.[20]

In this study, we analyzed the genetic diversity of the HPV16 genotype in CIN2/CIN3 and cervical cancer cases in women from the northeast region of Brazil. In this region, cervical cancer was ranked second in terms of cancer incidence, excluding nonmelanoma skin cancer (20.48/100,000),[2] and first in terms of mortality due to cancer (9.52/100.000) among women, in 2020.[3] The present work was part of a multicenter study on the HPV genotypes prior to the introduction of the HPV vaccine in the National Immunization Program, which was performed in two other cities in Brazil (Rio de Janeiro and Belém).[21,22]

Methods

A cross-sectional multicenter study was performed at two hospitals for cancer treatment in Cidade do Recife, Pernambuco, Brazil, between July 2014 and December 2016.

Women ≥18 years old, with pap smear tests indicative of high-grade intraepithelial lesion (HGL; CIN2/CIN3) or cervical cancer, and who were referred for a colposcopy exam, were invited to participate in the present study. Women who underwent a biopsy and were diagnosed for CIN2/CIN3 or cervical cancer, based on histopathological examination, were included in this analysis. The exclusion criteria included women previously treated for cervical cancer (cancer surgery, radiotherapy, or chemotherapy) or those with cognitive or physical disabilities that could prevent them from answering a questionnaire.

After receiving signed consent, the women were interviewed by trained nurses using an epidemiological questionnaire. We collected data about their socioeconomic status, knowledge about cervical cancer prevention, access to healthcare services for diagnosis and treatment, hormonal and reproductive histories, and tobacco usage. Additional clinical information was obtained from their medical records. The biopsy samples were stored in RNALater until nucleic acid isolation, and were then sent to the research laboratory of the hospital.

DNA was isolated from the biopsy samples using the QIAamp DNA Mini Kit (Qiagen; Cat. Number 51306, North Rhine-Westphalia, Germany). HPV was detected through PCR amplification using the primer sets PGMY07 and PGMY09,[23] whereas reactions without PCR products underwent nested PCR, using the primers GP5 +/GP6 +.[24] Samples negative for HPV DNA amplification after nested PCR were subjected to PCR for β-globin, and samples positive for β-globin and negative for HPV through nested PCR were considered negative for HPV. For HPV identification, the PCR products were purified using the Illustra GFX PCR DNA and Gel Band Purification Kit (GE Healthcare; Cat. Number 28403471, Buckinghamshire, UK), and were further subjected to DNA sequencing in both directions, using the Big Dye Terminator Cycle Sequencing Ready Reaction V3.1 Kit (Applied Biosystems; Cat. Number 4336919, Texas, USA), as per manufacturer's instructions, and sequenced in an ABI 3730xL DNA Analyzer (Applied Biosystems, Osaka, Japan). The electropherograms of each sample were checked manually and a consensus sequence of the bidirectional sequencing was subjected to HPV genotype identification using the Blast software (https://blast.ncbi.nlm.nih.gov/Blast.cgi).[25]

Among the 415 samples evaluated for HPV genotyping through DNA sequencing, the 8 most common types were: HPV16 (58.6%), HPV45 (7.2%), HPV18 (7.0%), HPV35 (4.6%), HPV58 (3.6%), HPV31 (3.1%), HPV33 (2.7%), and HPV52 (2.4%). HPV16 was the most common HPV genotype in CIN2/CIN3 (53.9%) and cervical cancer (60.7%). A total of 243 samples contained the HPV16 genotype, and 196 samples (80.7%) were further assessed to identify their lineages.

Samples exhibiting the HPV16 genotypes were subjected to PCR amplification of the viral genomic regions *LCR* and *E6,* in two overlapping fragments, as previously described.[26] The resultant sequence, obtained by sequencing the overlapping fragments, was aligned to HPV16 lineage reference sequences suggested by Burk et al.[13] HPV16 lineage identification was performed by detecting a sequence signature (the presence of specific nucleotides at specific sequence positions), as previously described.[12] HPV16 lineage nomenclature used in this study followed those provided by Burk et al.[13]

The epidemiological data were stored using Epi Info 3.5.1 and then linked to both the clinical and HPV DNA sequence data. The final database was analyzed using Stata v.15.0. the chi-squared test (or the Fisher exact test) was used to compare the distribution of the patients based on selected characteristics, according to their histopathological diagnosis. The ratio difference test was used to compare the prevalence of HPV16 viral strains, considering two groups: CIN2/CIN3 and cervical cancer ($p < 0.05$). The B and C lineages were grouped due to low frequency.

All study procedures were approved by the Institutional Ethics Committees at both hospitals (CAAE 24687713.8.0000.5201 and CAAE 40349014.0.0000.5205).

Results

Selected characteristics of the 196 female patients included in the present study, according to disease status (CIN2/CIN3 versus cervical cancer), are presented in ►**Table 1**. We observed that the women diagnosed with CIN2/CIN3 were younger than those diagnosed with cervical cancer. No statistical differences were found between the women with CIN2/CIN3 and cervical cancer for oral contraceptive use or tobacco exposure. The number of childbirths was greater in women with cervical cancer than in those with CIN2/CIN3.

The LCR and E6 regions of each sample with an HPV16 genotype were aligned with HPV16 reference sequences representing the lineages A, B, C, and D, and the presence of specific SNPs was used to identify HPV16 lineages present in each sample. The distribution of the HPV16 lineages is as follows: lineage A, 130 women; lineage B, 1 woman; lineage C, 10 women; and lineage D, 55 women. We observed distinct frequencies of HPV16 lineages between CIN2/CIN3 and cervical cancer, with lineage A being more frenquent in CIN2/CIN3 ($p = 0.053$). Moreover, based on the histopathological diagnosis, the comparison of HPV16 lineage frequencies showed a higher proportion of the D lineage in cervical cancer than that in CIN2/CIN3 ($p = 0.023$) (►**Table 2**).

Discussion

The lineage A of HPV16 was the most frequent in the samples examined in the present study, for both CIN2/CIN3 and cervical cancer, while lineage D was predominant in cervical cancer samples, suggesting an association between the lineage D of HPV16 and cervical cancer.

The genetic variations in HPV16 can influence the risk of cervical cancer, which vary based on the different lineages or sublineages present in different regions of the world.[8] Previous studies attempted to demonstrate an association between non-European lineages (B/C/D) and a higher risk for developing CIN2/CIN3[14,17] and cervical cancer,[17,27] compared with the European lineage (A). A major limitation of

Table 1 Distribution of female patients based on selected characteristics, according to their histopathological diagnosis

Variable	CIN2/CIN3		Cervical cancer		*p-value*[*]
	n = 59	%	*n* = 137	%	
Age (years old)					
20–39	37	62.7	43	31.4	< 0.001
40–49	16	27.1	40	29.2	
50–59	6	10.2	23	16.8	
≥ 60	0	0.0	31	22.6	
Number of childbirths					
None	3	5.1	3	2.2	
1–2	28	47.5	43	31.4	0.07
3–4	17	28.8	44	32.1	
5–6	5	8.5	14	10.2	
≥ 7	6	10.1	33	24.1	
Oral contraceptive use					
Yes	42	71.2	88	64.2	0.34
No	17	28.8	49	35.8	
Tobacco exposure					
Yes	26	44.1	76	55.5	0.14
No	33	55.9	61	44.5	

Abbraviation: CIN, cervical intraepithelial neoplasia.
(*) Chi-squared test or Fisher exact test.

Table 2 Distribution of female patients, according to HPV16 lineage frequencies and their histopathological diagnosis

HPV16 lineages	Histopatological diagnosis					*p-value*[*]
	Total	CIN2/CIN3		Cervical Cancer		
	n (%)	*n*	%	*n*	%	
A	130 (66.3)	45	76.3	85	62.0	0.053
B/C	11 (5.6)	4	6.8	7	5.1	0.635
D	55 (28.1)	10	16.9	45	32.8	0.023

*Test for proportion difference among patients with CIN2/CIN3 and cervical cancer.

these studies was the grouping of lineages B, C, and D as non-European lineages, which did not allow the differentiation of the carcinogenic potential among these lineages. A recent study on > 3,200 women, comparing women without lesions and with CIN1 and women with CIN2 or CIN3 or invasive cancer, have reported an association between the HPV16 sub-lineages D2 and D3 and CIN3 and/or cervical cancer.[17] Clifford et al. analyzed samples from > 7,100 women, comparing those with normal cells, or atypical squamous cells of undetermined significance, or low-grade squamous intraepithelial lesions or CIN1, with those with invasive cervical cancer, and found an association between the HPV16 lineage D and sublineage A4 and cancer diagnosis.[8]

A recent study on Croatian women confirmed that HPV16, mainly belonging to the European branch, was most frequently associated with histologically confirmed high-grade intraepithelial lesions (CIN2 or CIN3) and cervical cancer.[28]

In the present study, the lineage A of HPV16 was the most frequently detected lineage, and although it was associated with high-grade lesions (CIN2/CIN3), we could not demonstrate a difference between these high-grade lesions and cervical cancer. Another study conducted in a different region in Brazil also found a high prevalence of the lineage A of HPV16 in samples of high- and low-grade lesions, including cervical cancer.[29]

In contrast, the D lineage of HPV16 showed a significant association with cervical cancer, compared with high-grade lesions, suggesting that the lineage D of HPV16 is involved in the progression of HPV16 infection to cervical cancer. Although this is a cross-sectional study, the present study provides novel data on the association between specific lineages of HPV16 and cervical cancer. Our data suggest that the lineage D could be more aggressive with respect to the progression of high-grade lesions into cancer, without

restricting the association from linking normal/low grade lesions and invasive cancer.

Conclusion

The A lineage of HPV16 was the most frequent in both the CIN2/CIN3 and cervical cancer samples, whereas the lineage D of HPV16 was predominant in cervical cancer, suggesting an association between HPV16 lineage D and cervical cancer.

Contributions

Martins L. F. L.: Conceptualization, Methodology, Formal analysis, Writing– Original Draft, Writing– Review and Editing. Moreira M. A. M.: Supervision, Conceptualization, Writing– Original Draft, Writing– Review and Editing. Pinto R. A.: Conceptualization, Writing– Original Draft, Writing– Review. Reis N. B.: Methodology, Writing– Original Draft, Writing– Review and Editing. Felix S. P.: Performed the Experiments, Writing– Review and Editing. Vidal J. P. C. B.: Performed the experiments, Writing– Review and Editing. Torres L. C.: Supervision, Performed the experiments, Writing– Review and Editing. Souza A. I.: Conceptualization, Writing– Original Draft, Writing– Review and Editing. Almeida L. M.: Project administration, Funding acquisition, Conceptualization, Writing– Original Draft, Writing– Review and Editing.

Conflict of Interests

The authors have no conflict of interest to declare.

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Amniotic Sludge and Prematurity: Systematic Review and Meta-analysis

Sludge amniótico e prematuridade: revisão sistemática e metanálise

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Abstract

Objective To perform a systematic review and meta-analysis of studies on maternal, fetal, and neonatal outcomes of women with singleton pregnancies, after spontaneous conception, and with the diagnosis of amniotic sludge before 37 weeks of gestational age.

Data Sources We conducted a search on the PubMed, Cochrane, Bireme, and Theses databases until June 2022.

Selection of Studies Using the keywords *intra-amniotic sludge* or *fluid sludge* or *echogenic particles*, we found 263 articles, 132 of which were duplicates, and 70 were discarded because they did not meet the inclusion criteria.

Data Collection The articles retrieved were analyzed by 2 reviewers; 61 were selected for full-text analysis, 18 were included for a qualitative analysis, and 14, for a quantitative analysis.

Data Synthesis Among the maternal outcomes analyzed, there was an increased risk of preterm labor (95% confidence interval [95%CI]: 1.45–2.03), premature rupture of ovular membranes (95%CI: 1.99–3.79), and clinical (95%CI: 1.41–6.19) and histological chorioamnionitis (95%CI: 1.75–3.12). Regarding the fetal outcomes, there was a significant increase in the risk of morbidity (95%CI: 1.80–3.17), mortality (95%CI: 1.14–18.57), admission to the Neonatal Intensive Care Unit (NICU; 95%CI: 1.17–1.95), and neonatal sepsis (95%CI: 2.29–7.55).

Conclusion The results of the present study indicate that the presence of amniotic sludge is a risk marker for preterm delivery. Despite the heterogeneity of the studies analyzed, even in patients with other risk factors for prematurity, such as short cervix and previous preterm delivery, the presence of amniotic sludge increases the risk of premature labor. Moreover, antibiotic therapy seems to be a treatment for amniotic sludge, and it may prolong pregnancy.

Keywords
- sludge
- prematurity
- amniotic fluid

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Resumo

Objetivo Realizar revisão sistemática e metanálise de estudos que avaliaram os desfechos maternos, fetais e neonatais em gestantes de gravidez única, após concepção espontânea, e com o diagnóstico de *sludge* amniótico antes de 37 semanas de idade gestacional.

Fontes dos dados Realizou-se uma pesquisa nas bases de dados PubMed, Cochrane, Bireme e Teses até junho de 2022.

Seleção dos estudos Usando as palavras-chave *intra-amniotic sludge* ou *fluid sludge* ou *echogenic particles*, foram encontrados 263 artigos, 132 dos quais eram duplicatas, e 70 foram descartados por não corresponderem aos critérios de inclusão.

Coleta de dados Os artigos encontrados foram analisados por 2 revisores; 61 foram selecionados para análise de texto completo, 18 foram incluídos em uma análise qualitativa e 14, em uma análise quantitativa.

Síntese dos dados Entre os desfechos maternos analisados, houve aumento do risco de trabalho de parto prematuro (intervalo de confiança de 95% [IC95%]: 1.45–2.03), rotura prematura de membranas ovulares (IC95%: 1.99–3.79), e corioamnionite clínica (IC95%: 1.41–6.19) e histológica (IC95%: 1.75–3.12). Em relação aos desfechos fetais, houve aumento significativo do risco de morbidade (IC95%: 1.80–3.17), mortalidade (IC95%: 1.14–18.57), admissão em Unidade de Tratamento Intensivo (UTI) neonatal (IC95%: 1.17–1.95) e sepse neonatal (IC95%: 2.29–7.55).

Conclusão Os resultados do presente estudo indicam que a presença de *sludge* amniótico é um marcador de risco para parto prematuro. Apesar da heterogeneidade dos estudos analisados, até mesmo em pacientes com outros fatores de risco para prematuridade, como colo curto e trabalho de parto prematuro anterior, a presença de *sludge* amniótico aumenta o risco de trabalho de parto prematuro na gestação. Além do mais, a antibioticoterapia parece ser um tratamento para o *sludge* amniótico, e pode ser capaz de prolongar a gravidez.

Palavras-chave

- *sludge*
- prematuridade
- líquido amniótico

Introduction

Prematurity is one of the major problems involving obstetrics today. It is considered the main cause of neonatal mortality and morbidity, accounting for ~ 75% of all cases, besides presenting unfavorable long-term outcomes, such as cerebral palsy and delayed neurological development.[1,2]

In 1961, the World Health Organization (WHO) defined preterm birth as those occurring before 37 full weeks, or 259 days, of gestation, regardless of fetal weight. From there, it was observed that those newborns had a higher rate of complications when compared with those born after 37 weeks.[3,4] Since then, prematurity and its causes have been the subject of studies, in an attempt to prevent as much as possible its occurrence and postpone fetal birth.

Among preterm newborns, the prevalence of severe neonatal complications such as respiratory distress syndrome and necrotizing enterocolitis, which are frequent causes of admission to the Neonatal Intensive Care Unit (NICU), is 10 times higher than in those born after 37 weeks of gestation.[5]

Despite the better understanding of the factors involved in premature parturition and the development of resources to inhibit preterm labor, the prevalence of prematurity in recent decades has not decreased, and it is estimated to range from 5% to 18% in the world, and from 6.4% to 15.2% in Brazil, which corresponds on average to the worldwide birth of ~ 15 million preterm concepts.[6,7]

The main cause of preterm labor is idiopathic, corresponding to 50% of the cases. Among the known causes, we highlight the presence of maternal infection, cervical insufficiency, and short cervix.[1,8] In addition, the main risk factor for preterm labor is having a history of preterm labor.[7,8]

In cases of maternal infection, there is endogenous release of proinflammatory cytokines such as interleukins (ILs) 1, 2, 6, and 7, and tumoral necrosis factor alpha (TNF-α), which stimulate the increase in the production of prostaglandins and proteases in the amnion and can thus trigger uterine contractions, cervical alterations, and membrane rupture. The increase in proinflammatory cytokines is also associated with the presence of sludge, another possible marker for an amniotic inflammatory process.[9]

Cervical insufficiency, in turn, is a clinical entity characterized by a cervix unable to remain closed during pregnancy. Its pathophysiology has not yet been fully understood. It is believed to be related to a structural defect in traction force at the cervical-isthmic junction that may be associated with

cervical shortening secondary to tissue inflammation. This weakened cervical sphincter yields to the weight of the fetus and progresses to a late abortion or premature delivery, usually painless and rapidly evolving. This condition is often associated with the occurrence of a cervix shorter than 20 mm to 25 mm.[10,11]

As well as the short cervix, which has already been established as a risk factor for preterm labor, another ultrasound finding suggested the presence of amniotic sludge as a risk factor.[12]

Sludge is mentioned when the presence of hyperechogenic material floating freely within the amniotic fluid near the cervix is observed.[13] Its composition is uncertain, associations with blood clot, meconium, caseous vernix or intraamniotic microbial biofilm have been proposed before.[14] The most accepted theory is that this material, when observed in the first half of pregnancy, is associated with an inflammatory process, whereas, in the second half, it represents a maturational process.[14,15]

Its prevalence tends to increase with gestational age, and it is present in $\sim$ 4% of ultrasounds performed between the first and second trimesters.[15,16] Vaginal diagnosis is more accurate during this period, because, from the third trimester on, the occurrence of meconium and caseous vernix increases, which can lead to a false diagnosis and confuse the examining physician.[15,16]

The present work seeks to understand whether the sludge is a risk marker for preterm labor and whether antibiotic therapy can treat it, as well as prevent prematurity.

Materials and Methods

The present meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) under identification CRD42022343941. The criteria used for the review were those recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. For the selection of articles, the following eligibility criteria were used:

Study design: randomized clinical trials; prospective or retrospective cohort studies; and case control studies.

Population: women with singleton pregnancies out of labor, after spontaneous conception, and with the ultrasound diagnosis of intraamniotic sludge confirmed by a medical sonographer, performed before 37 weeks, in fetuses without malformations or uteruses with anatomical alterations.

Intervention: presence of intraamniotic sludge.

Outcomes: maternal (gestational age during labor, premature rupture of ovular membranes, and clinical and histological chorioamnionitis); and neonatal (need for NICU, morbidity and mortality, and sepsis).

Review articles, case reports, articles that were not fully available, and those that did not meet the necessary criteria were excluded.

The research was conducted using the following keywords: *intra-amniotic sludge* OR *fluid sludge* OR *echogenic particles*.

Searches were performed on the PubMed, Cochrane, Bireme, Teses and Google Scholar databeses, and 263 articles were found. All of these studies were included in the electronic platform Rayyan QCRI, a web application designed to aid in the selection of articles for systematic reviews.

Initially, 132 duplicates were excluded. After reading the titles and abstracts, 70 studies were disregarded because they did not meet the inclusion criteria (41 due to the participants; 6, due to the intervention; 4, due to the outcome; and 19, because of the study design). Finally, 61 articles were selected for full-text reading.

The full-text reading stage resulted in the inclusion of 18 studies for data analysis and the exclusion of 43 studies (10, due to duplicate population; 7, due to the wrong participants; 7, because of wrong intervention; 4, due to wrong outcome; and 11, because of wrong design). The next four were excluded due to failure to meet the inclusion criteria: one was an opinion article, and three were only abstracts from conference presentations without the original published article). Studies in which the patients were in labor at the time of the evaluation were considered to have "wrong participants", and they were excluded.

Finally, of the 18 selected articles, only 14 were eligible to be submitted to a quantitative analysis. From the remaining four, two included only pregnant women with amniotic sludge without a comparative group, and the other two evaluated the use of antibiotic therapy in all participants of the sample, without a control group.

In all stages of the research, which can be evaluated briefly in ►**Fig. 1**, the articles were read blindly and separately by two examiners. Disagreements were resolved after discussion with the head of the Obstetrics Department.

For data analysis, a spreadsheet was created with the following variables: study; author; country of origin; design; retrospective or prospective; duration; inclusion and exclusion criteria; initial and final number of participants; number of losses; number of participants with sludge; number of participants without sludge; gestational age at the diagnosis of sludge; maternal age; parity; history of vaginal delivery; number of abortions; history of short cervix; history of premature delivery; vaginal bleeding; smoking; cervical length in participants with sludge; cervical length in participants without sludge; performance of cerclage or use of pessary; gestational age at delivery comparing participants with sludge and without sludge; neonatal morbidity; neonatal mortality; perinatal mortality; admission to the NICU; clinical chorioamnionitis; histological chorioamnionitis; endometritis; and neonatal sepsis. The risk of bias was also independently and blindly evaluated by the authors according to the PRISMA statement and the suggestions of the Cochrane collaboration. Meta-analyses were performed when two or more studies reported the same result. The fixed-effects model was used when there was no heterogeneity (Higgins I^2 test $< 50\%$), and the random-effects model, when this heterogeneity was present (Higgins I^2 test $> 50\%$). The subgroup meta-analyses were performed as an attempt to reduce the bias and the unclear factors for a better understanding of the results. They were made according to

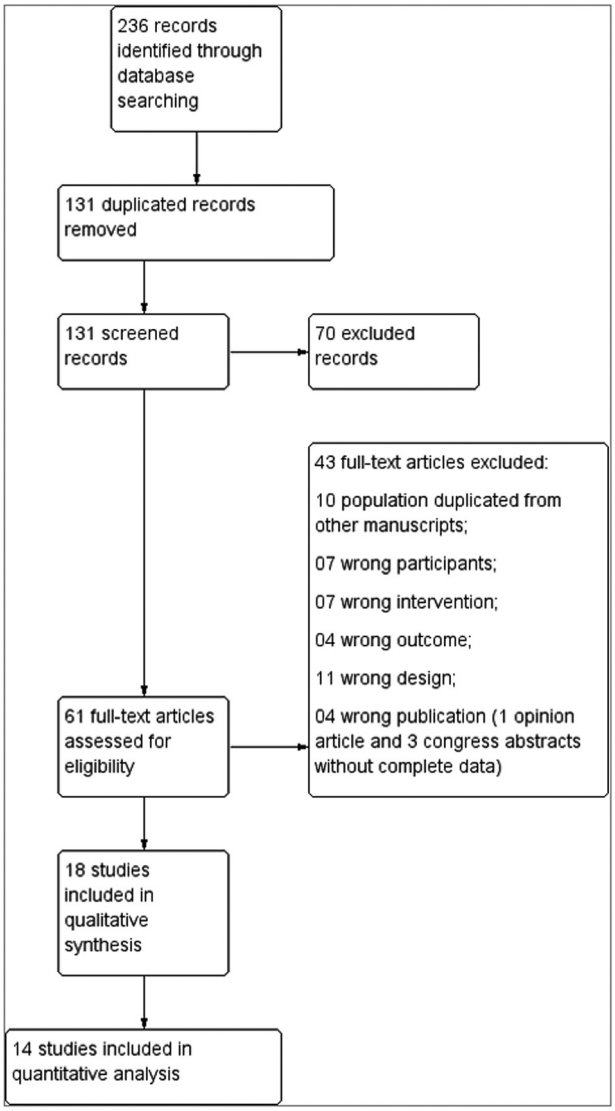

Fig. 1 Flowchart of the selection of studies.

the previous risk for preterm labor. Studies groups were conducted with risk, without risk and with part of the samples with risk.

Results

After the exclusions, 14 studies were quantitatively analyzed, which comprised 546 pregnant women with an ultrasound diagnosis of intraamniotic sludge and their newborns. ►**Chart 1** details the studies regarding the number of participants diagnosed with sludge and the control participants regarding the presence of short cervix and treatment with cerclage or pessary.

The risk factors for the development of intraamniotic sludge, such as the occurrence of first-trimester vaginal bleeding (VB), smoking (S), and history of preterm delivery (HPTD), were also analyzed. From there, the proportion of events in the control group (non-sludge) and the experimental group (sludge) was compared, and the relative risk (RR)

Chart 1 Characteristics on the population of the studies analyzed

Author, year	N sludge	N no sludge	Short cervix	Cerclage or pessary
Adanir et al., 2018[16]	18	74	UR	UR
Bujold et al., 2008[17]	14	75	UR	UR
Espinoza et al., 2005[18]	19	65	UR	4/16 and 4/65
Gorski et al., 2010[19]	60	117	Part	YES
Hatanaka et al., 2014[20]	49	146	Part	UR
Himaya et al., 2011[21]	16	200	Part	UR
Huang et al., 2022[22]	45	251	Part	YES
Kovavisarach and Jongfuangprinya, 2019[23]	72	258	Part	NO
Kusanovic et al., 2007[24]	66	215	Part	28/215 and 21/66
Saade et al., 2018[25]	78	579	YES	UR
Ting et al., 2012[26]	5	15	YES	YES
Tsunoda et al., 2020[27]	29	81	YES	6/29 and 10/81
Vaisbuch et al., 2010[28]	64	45	YES	UR
Yasuda et al., 2020[29]	11	43	UR	UR

Abbreviations: N, number of participants; UR, unreported.

and its 95% confidence interval (95%CI) were as follows: VB – 1.7292 (1.2227–2.4455); S – 0.8652 (0.5087–1.4716); and HPTD – 1.2248 (0.9637–1.5566) (►**Chart 2**).

Despite their exclusion from the quantitative analysis, the four studies on were submitted to a qualitative analysis, and are summarized in ►**chart 3**.

All studies were analyzed to establish a relationship between the risk of developing sludge and preterm delivery (before 37 weeks of gestation). Then, we observed that the Higgins I^2 test was of 97%. To decrease such heterogeneity and improve the statistical analysis, we divided the patients into three subgroups according to the presence or not of risk factors for premature labor, such as short cervix, HPTD or cervical insufficiency. Thus, we analyzed studies in which all patients had risk factors for preterm labor (►**Fig. 2**); studies in which some patients had these risk factors and others did not (►**Fig. 3**); studies in which the patients were not at risk for detected preterm labor (►**Fig. 4**). In the group of high-risk patients, we also analyzed a subgroup in which all participants had a short cervix (►**Fig. 5**).

For the analysis of the secondary outcomes, since there was no interference regarding the presence of risk factors, there was no need for subdivision. Thus, the risk caused by the sludge was analyzed for the following variables: premature rupture of ovular membranes in preterm delivery (►**Fig. 6**); clinical chorioamnionitis (►**Fig. 7**); histological chorioamnionitis (►**Fig. 8**); neonatal morbidity (►**Fig. 9**); neonatal mortality (►**Fig. 10**); perinatal mortality (►**Fig. 11**); admission to the NICU (►**Fig. 12**); and neonatal sepsis (►**Fig. 13**).

Chart 2 Clinical characteristics of the participants of the studies analyzed

Author, year	VB sludge	VB no sludge	S sludge	S no sludge	HPTD sludge	HPTD no sludge
Adanir et al., 2018[16]	9\18	16/74	UR	UR	YES	YES
Bujold et al., 2008[17]	UR	UR	UR	UR	4/14	20/75
Espinoza et al., 2005[18]	6\19	3\65	UR	UR	3\19	21/65
Gorski et al., 2010[19]	10\60	19\117	5\60	8\117	18/60	34/117
Hatanaka et al., 2014[20]	UR	UR	UR	UR	UR	UR
Himaya et al., 2011[21]	UR	UR	UR	UR	3\16	13/200
Huang et al., 2022[22]	UR	UR	UR	UR	7\45	40/251
Kovavisarach and Jongfuangprinya, 2019[23]	UR	UR	UR	UR	UR	UR
Kusanovic et al., 2007[24]	16/66	25/215	10/57	43/192	21/66	74/215
Saade et al., 2018[25]	UR	UR	UR	UR	UR	UR
Ting et al., 2012[26]	UR	UR	UR	UR	UR	UR
Tsunoda et al., 2020[27]	3\29	2\81	0/29	0/81	7\29	10\81
Vaisbuch et al., 2010[28]	UR	UR	UR	UR	UR	UR
Yasuda et al., 2020[29]	UR	UR	1\11	0\43	3/11	5/43

Abbreviations: HPTD, history of preterm delivery; S, smoking; UR, unreported; VB, first-trimester vaginal bleeding.

Discussion

Sludge is a controversial subject due to the scarcity of studies and the heterogeneity of the diagnostic criteria. To investigate its nature, several studies have assessed the presence of risk factors, such as vaginal bleeding during the first trimester, S and HPTD. Of those, statistical significance was observed only for vaginal bleeding during the first trimester, whose RR was of 1.7292 (95%CI: 1.2227–2.4455). Rust et al.[34] proposed that intraamniotic sludge is composed of blood clot secondary to vaginal bleeding, which, in the first trimester of pregnancy, is a risk factor for sludge, and, consequently, for premature labor, as described in the present study. In addition, the blood clot can be a means for bacterial growth and feeding, favoring the formation of local biofilms.[35]

Regarding S and HPTD, no conclusion was deemed possible due to the heterogeneity of the published studies. According to Iams et al.,[36] S can alter the physiological vaginal flora. This vaginal dysbiosis is a well-established risk factor for premature labor and premature rupture of ovular membranes, since the main route of intraamniotic infection is the microbial ascension of the lower genital tract.[35,36]

To reduce the heterogeneity of studies in the risk analysis of preterm delivery, the presence of sludge in different groups was evaluated. Then, we noticed that the presence of sludge was an important risk marker for premature labor in studies involving only high-risk patients (RR: 1.72; 95%CI: 1.45–2.03), when the population was heterogeneous (RR: 2.57 (95%CI: 1.68–3.93), and in patients with short cervix (RR: 1.56; 95%CI: 1.29–1.88).

However, caution should be exercised in the analysis of these results among low-risk patients. Yasuda et al[29] showed that low-risk patients also present a higher risk of preterm labor when they have intraamniotic sludge, unlike the study by Kovavisarach and Jongfuangprinya.[23] This

Chart 3 Characteristics of the studies involving antibiotic therapy

Author, year	N sludge + ATB	N no sludge	Antibiotic scheme	Outcome
Cuff et al., 2020[30]	46	51	Azithromycin OA + moxifloxacin OA	There was no reduction in the incidence of PTD
Hatanaka et al., 2019[31]	64	0	Clindamycin OA + cephalexin OA, clindamycin IV + cefazolin IV	Reduction in the incidence of PTD
Hu Jin et al., 2021[32]	58	0	Ceftriaxone IV + clarithromycin OA + metronidazole IV	Reduction in the incidence of PTD and neonatal complications
Pustotina, 2020[33]	14	47	Clindamycin VA, butoconazole VA, cefoperazone + sulbactam IV, amoxicillin + clavulonate OA	Reduction in the incidence of PTD, intrauterine and amniotic infection

Abbreviations: IV, intravenous; N, number of participants; OA, oral administration; PTD, preterm delivery VA, vaginal administration.

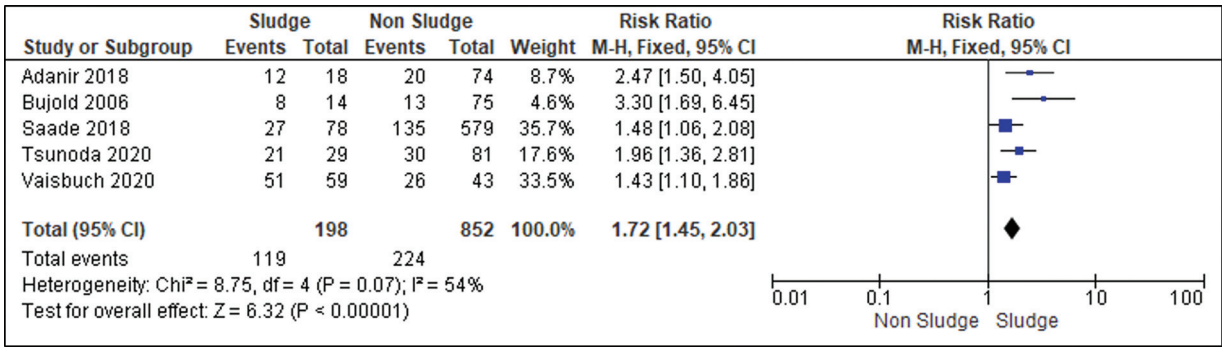

Fig. 2 Studies in which all patients had risk factors for preterm labor.

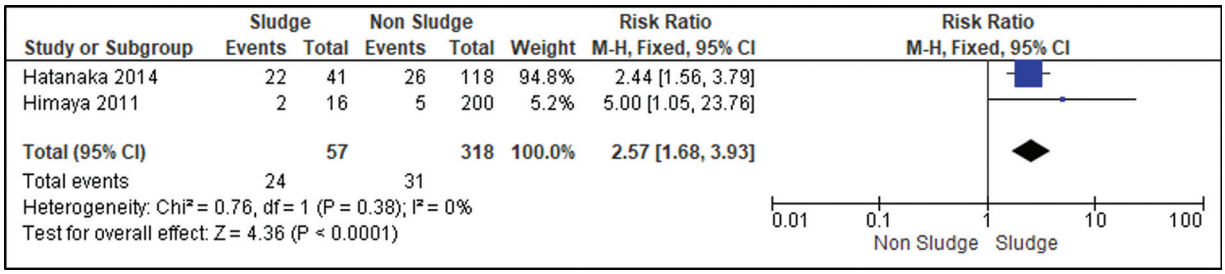

Fig. 3 Studies in which some patients had risk factors for preterm labor and others did not.

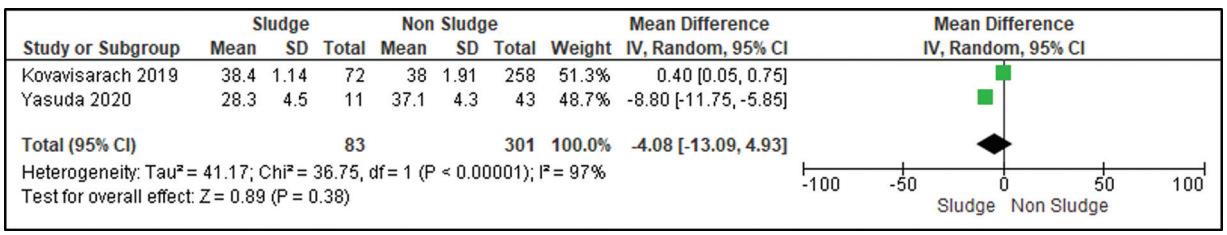

Fig. 4 Studies in which the patients were not at risk for detected preterm labor.

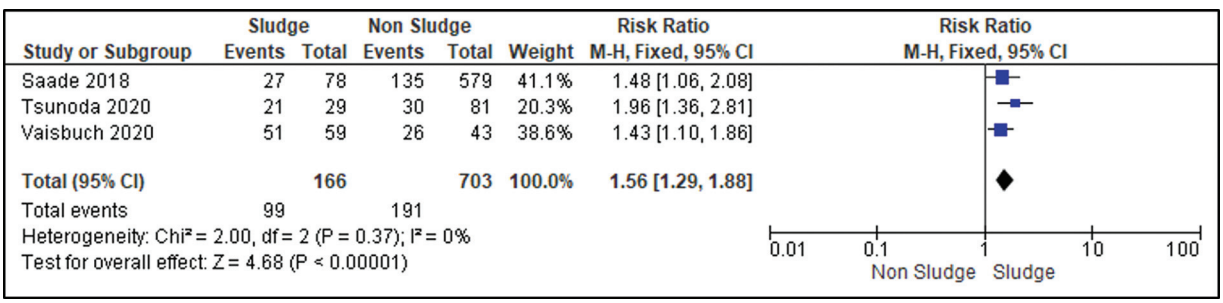

Fig. 5 Subgroup analysis of patients with short cervix.

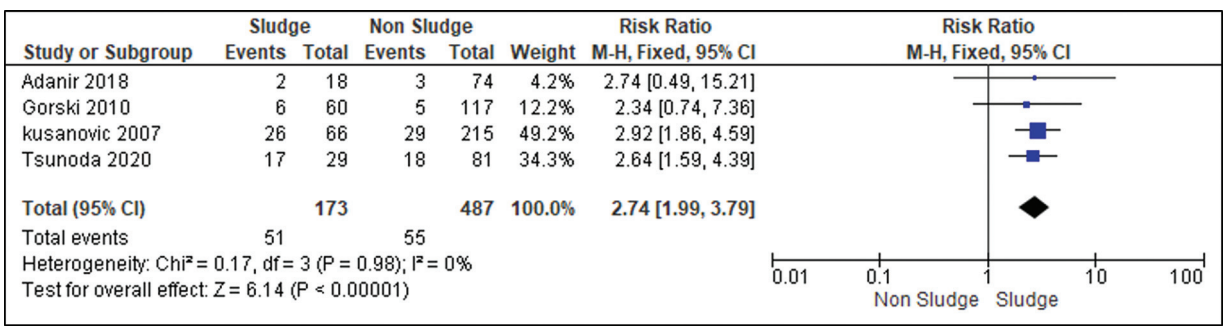

Fig. 6 Risk of premature rupture of ovular membranes according to the presence of sludge.

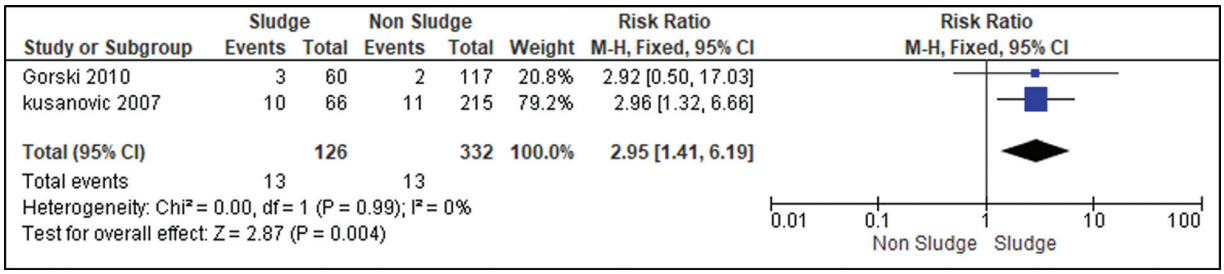

Fig. 7 Risk of clinical chorioamnionitis according to the presence of sludge.

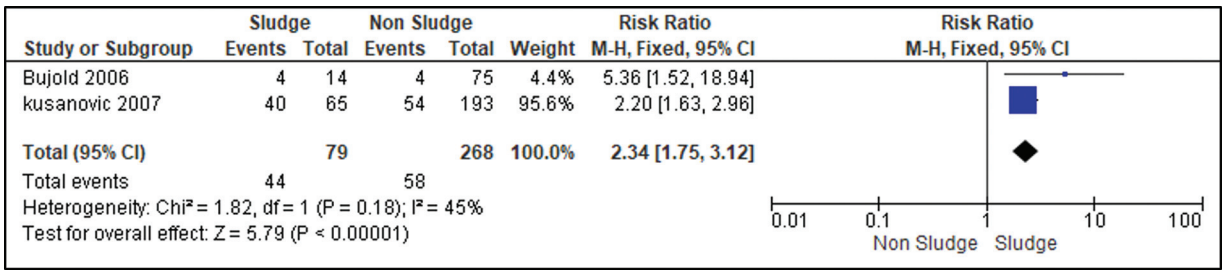

Fig. 8 Risk of histological chorioamnionitis according to the presence of sludge.

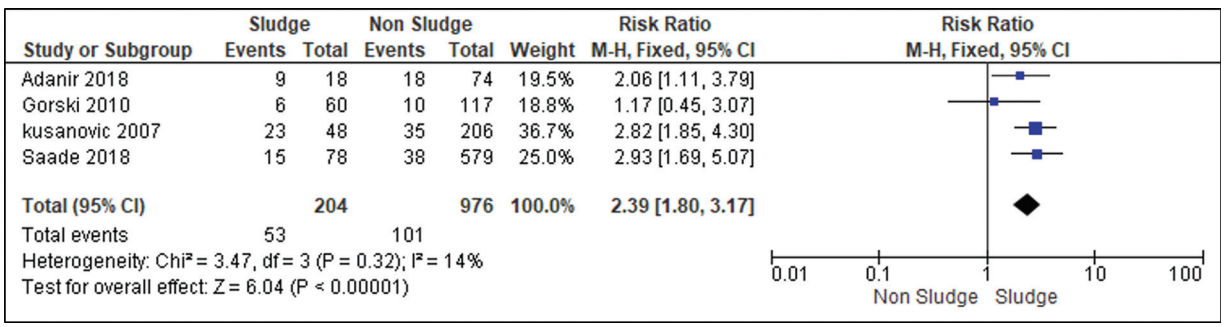

Fig. 9 Risk of neonatal morbidity according to the presence of sludge.

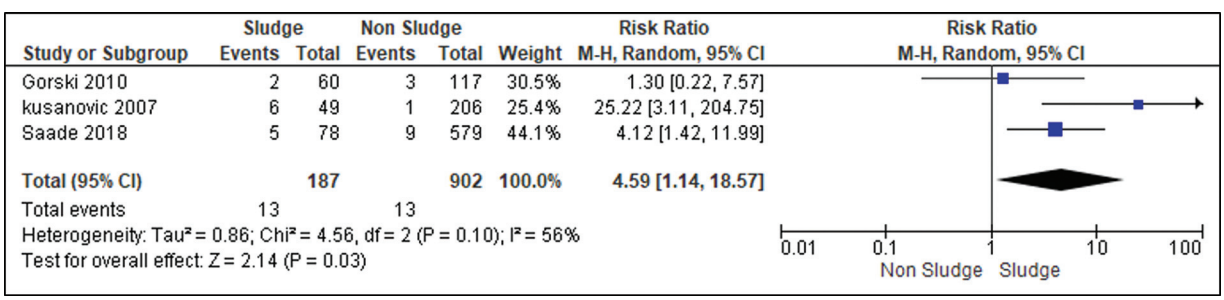

Fig. 10 Risk of neonatal mortality according to the presence of sludge.

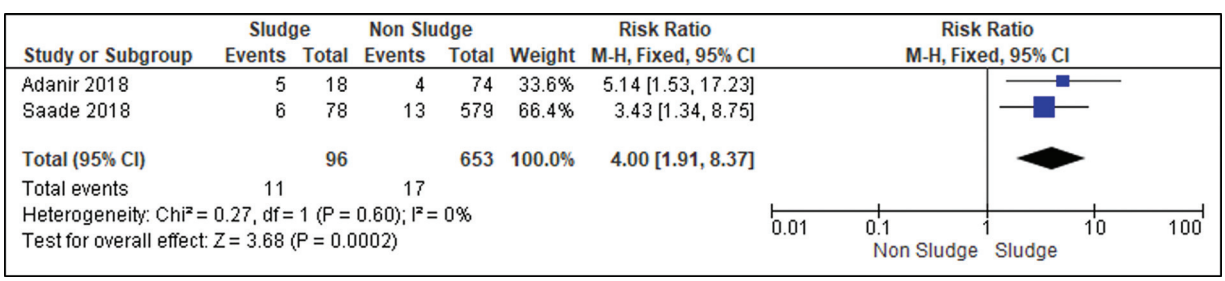

Fig. 11 Risk of perinatal mortality according to presence of sludge.

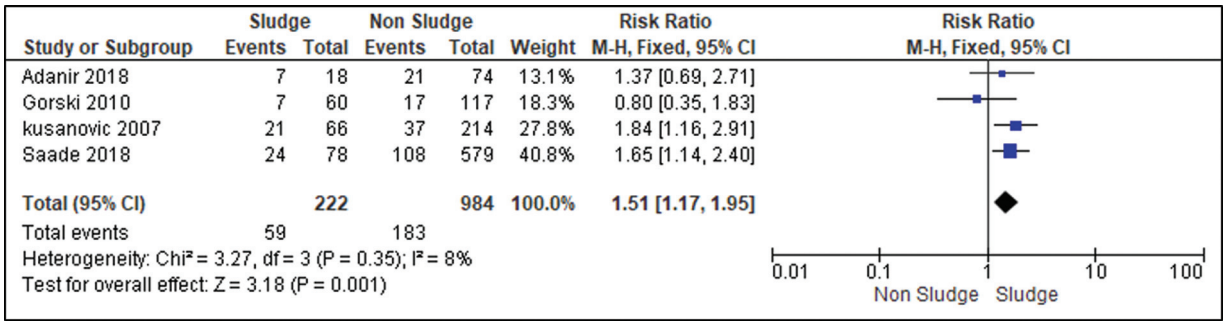

Fig. 12 Risk of admission to the NICU according to presence of sludge.

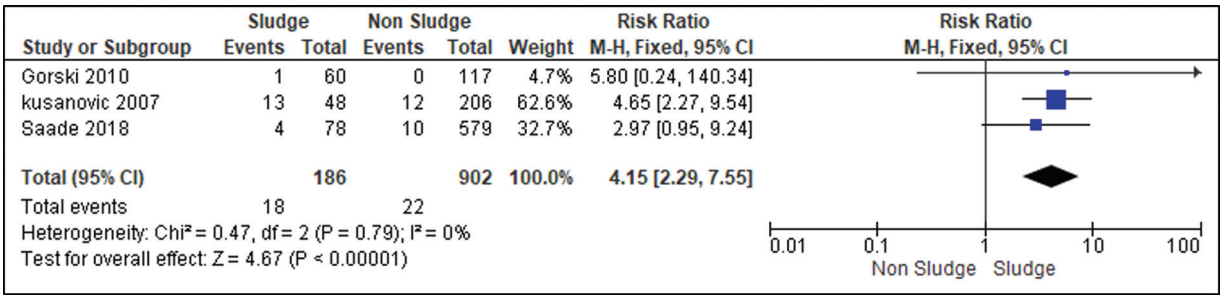

Fig. 13 Risk of neonatal sepsis according to presence of sludge.

research, conducted in 2019 in Thailand, is the only one in which the presence of intraamniotic sludge was only analyzed by one operator, and it was a study designed to determine the prevalence of sludge in patients at low risk for premature labor. In addition to the possibility that this study design may have hindered statistical analysis, the choice of low-risk patients for preterm labor may have excluded patients with risk factors for sludge, skewing their analysis.

Although amniotic fluid is not considered a sterile environment, the presence of intraamniotic sludge was associated with the risk of developing both clinical (RR: 2.95; 95%CI: 1.41–6.19) and histological chorioamnionitis (RR: 2.34; 95% CI: 1.7–3.12), which strengthens the hypothesis that sludge is a marker of microbial infection, which is the main known cause of premature labor.[37]

These facts reiterate the hypothesis that sludge is an indicator of microbial invasion within the amniotic cavity, which would explain its relationship to clinical and histological chorioamnionitis, premature labor, and neonatal sepsis.

In the present study we have also attempted to evaluate the relationship between sludge and the use of antibiotic therapy. However, the literature on this subject is scarce, making the meta-analysis impracticable. Pustotina[33] conducted a prospective study with 29 patients with sludge who were submitted to several antimicrobial regimens, such as clindamycin 100 mg vaginally for 3 days, a single intravaginal dose of 5g of butoconazole 2% cream, cefoperazone in combination with sulbactam 2 g intravenous twice a day for 5 days, and amoxicillin in combination with clavulanate 1 g orally twice a day for 5 days. In addition, all patients received oral treatment with probiotics as proposed by De La Cochetière et al.[38] not to alter the vaginal microbiota. Even if not following a pattern, the study by Pustotina[33] showed that antibiotic therapy reduced the incidence of premature labor and intrauterine and intraamniotic infection. However, there was no group that did not receive antibiotic therapy. So, to avoid confusion, this study[33] was excluded from the present meta-analysis, since there is no suggestion in the literature that this therapy may influence the outcomes related to sludge, whether positive or not.

In 2021, Jin et al.[32] conducted a retrospective cohort study in which 58 patients with uterine contraction with sludge received intravenous ceftriaxone once a day, clarithromycin 500 mg orally every 12 hours, and metronidazole 500 mg intravenously every 8 hours for up to 4 weeks. These patients were followed up until delivery, and the authors[32] observed that, in patients in which the sludge did not disappear after antibiotic therapy, there was a higher rate of premature labor and neonatal complications. They concluded that antibiotics in some patients with uterine contractions were able to eradicate intraamniotic sludge, and, in comparison with patients in whom the sludge remained, they presented a higher rate of premature labor and unfavorable neonatal outcomes.

In 2019, Hatanaka et al.[31] published a retrospective cohort of 86 patients with sludge, in which low-risk patients received clindamycin 300 mg orally every 6 hours and cephalexin 500 mg orally every 6 hours for 7 days, and high-risk patients received intravenous clindamycin 600 mg every 8 hours and cefazoline 1 g every 8 hours for 5 days, followed

by another 5 days of oral treatment. This study[31] presented results similar to those of Pustotina[33] and Jin et al,[32] with the authors concluding that antibiotic therapy reduced the incidence of premature labor.

On the other hand, Cuff et al.[30] conducted a retrospective cohort study on patients diagnosed with sludge who received azithromycin 500 mg orally on day 1 followed by 250 mg orally on days 2 to 5, or moxifloxacin 400 mg orally for 5 days, and compared them with patients who did not receive antibiotic therapy. The authors[30] did not observe a reduction in the rates of preterm labor, and clinical or histological chorioamnionitis, which may suggest that either the dosage was inadequate, or such antibiotics are not effective in the treatment of sludge. This would explain why the results of this study[30] are different from those of the others previously described, which used antibiotics such as clindamycin and β-lactams and showed a reduction in the incidence of premature labor.

In view of what was exposed, one of the greatest limitations of the present study was the heterogeneity of the studies analyzed, which did not enable a meta-analysis of the articles on antibiotic therapy in the treatment of sludge, since Pustotina[33] administered antibiotic therapy to all patients, without a control group, Hatanaka et al.[31] and Cuff et al.[30] only analyzed patients with sludge, with no control group, and Jin et al[32] assessed patients with uterine contractions, unlike all other studies analyzed.

Another relevant aspect is that retrospective studies using ultrasound criteria, like all those herein evaluated, should be analyzed with caution, since they study a static image that may indicate a false diagnosis and skew the entire result.[22] Moreover, there is still no consensus on the diagnosis of sludge, which is often confused with vernix and meconium, especially when ultrasound is performed later during pregnancy.[22]

Furthermore, the studies tend to publish only positive results, which may explain why each study evaluated a different outcome. This may also explain the difficulty in finding outcomes that were evaluated by more than two or three authors, as well as elucidate why the current study has so many statistically significant results.

Nevertheless, we could analyze and conclude that intraamniotic sludge is related to unfavorable neonatal outcomes. From the moment that sludge is related to preterm labor, it becomes an indirect risk factor for peri- and neonatal morbidity and mortality, since the lower the gestational age in childbirth, the higher the risk of severe complications, admission to the NICU, and neonatal sepsis, as demonstrated in the present study.[16,19,24,26]

Even with the limitations of the present study, it is worth considering intraamniotic sludge as an important risk marker for premature labor, including in high-risk women, such as those with short cervix. This finding at the beginning of pregnancy should justify the referral of pregnant women to high-risk prenatal care, a more careful analysis to screen for prematurity and consideration regarding the administration of prophylactic corticotherapy in the third trimester.

Conclusion

Despite the heterogeneity of the studies reviewed, we concluded that sludge is a risk marker for preterm labor, as well as an independent risk factor for high-risk patients, such as those with short cervix. It also appears to be a marker of intraamniotic infection, and it is related to first-trimester vaginal bleeding. Nevertheless, further studies are necessary to investigate the efficacy of antibiotic therapy in the treatment and prevention of prematurity.

Conflict of Interests

The authors have no conflict of interests to declare.

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What Factors Affect Pain Tolerance during Hysteroscopy?

Quais fatores afetam a tolerância à dor durante a histeroscopia?

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Hysteroscopy is considered the gold standard for the evaluation and management of intrauterine pathologies because it is capable of simultaneously offering diagnosis and treatment for many of them. Genital tract infections, pregnancy, pelvic inflammatory disease, active herpetic infections, or human papilloma virus infections are contraindications for its performance. The indications are diverse, including suspected intracavitary mass, abnormal endometrial thickening, infertility, congenital anomalies, intrauterine adherence, in addition to post-treatment follow-up, and biopsy may be performed when necessary.[1]

Initially, outpatient hysteroscopy was restricted to diagnostic procedures. With advances in technology, there has been an increase in their practice in the office, rather than in the operating room with anesthesia. Despite this, the outpatient method is associated with higher levels of pre- and intraprocedure anxiety, which impairs patient satisfaction with the intervention and is associated with a greater perception of pain.[2] Furthermore, higher levels of pain during the intervention were associated with high rates of refusal to perform the procedure in the future, as well as higher rates of unsuccessful procedures.[3] Thus, the impact of pain on the continuity of health care by patients is notorious, as well as its interference in the adequate control of their pathologies.

The article by Coimbra et al.,[4] entitled Predictive Factors of Tolerance in Office Hysteroscopy – a 3-Year Analysis from a Tertiary Center, addresses a topic of great relevance in the management of women's health. However, we would like to point out suggestions for improvement in the production of results that are of practical use.

We understand that in longitudinal and cross-sectional research designs, where the investigated outcome has a high prevalence or incidence ($>$ 10%), the effect measure used to estimate the relationship/prediction between the independent variable and the outcome cannot be the odds ratio estimated by logistic regression.[5] Applying this analytical approach produces overestimated point and interval estimates. The best strategy is the application of Poisson or Cox regression, depending on the type of outcome, generating measures such as relative risk or hazard ratio, respectively.[5]

In the study by Coimbra et al.,[4] it is possible that the oversizing interfered with the significance of the age variable and the risk values of the other variables presented in Table 2, since the considered outcome is low tolerance (terrible and poor), which has an incidence of 14.9%. In addition, the reason for not including the variable intracavitary pathology, which revealed a difference in the outcome, and others such as parity number, was not identified in the model.

It is extremely important to create a raw model with the estimates of effects for the independent variables as a whole and the selection criteria for them to appear in the final

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model. Commonly, factors may have a marginal relationship with the outcome in the crude analysis and in the adjusted model if it reveals a significant predictor, such as age, for example. Furthermore, overestimated estimates may limit findings in systematic reviews with meta-analysis.

Conflict of Interests

The authors have no conflict of interests to declare.

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Recommendations for the Screening of Breast Cancer of the Brazilian College of Radiology and Diagnostic Imaging, Brazilian Society of Mastology and Brazilian Federation of Gynecology and Obstetrics Association

Recomendações para o rastreio do câncer de mama do colégio brasileiro de radiologia e diagnóstico por imagem, sociedade brasileira de mastologia e associação da federação brasileira de ginecologia e obstetrícia

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Abstract

Objective To present the update of the recommendations of the Brazilian College of Radiology and Diagnostic Imaging, the Brazilian Society of Mastology and the Brazilian Federation of Associations of Gynecology and Obstetrics for breast cancer screening in Brazil.

Methods Scientific evidence published in Medline, EMBASE, Cochrane Library, EBSCO, CINAHL and Lilacs databases between January 2012 and July 2022 was searched. Recommendations were based on this evidence by consensus of the expert committee of the three entities.

Recommendations Annual mammography screening is recommended for women at usual risk aged 40–74 years. Above 75 years, it should be reserved for those with a life

Keywords
- breast cancer screening
- mammography
- ultrasound
- magnetic resonance imaging

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expectancy greater than seven years. Women at higher than usual risk, including those with dense breasts, with a personal history of atypical lobular hyperplasia, classic lobular carcinoma in situ, atypical ductal hyperplasia, treatment for breast cancer or chest irradiation before age 30, or even, carriers of a genetic mutation or with a strong family history, benefit from complementary screening, and should be considered individually. Tomosynthesis is a form of mammography and should be considered in screening whenever accessible and available.

Resumo

Objetivo Apresentar a atualização das recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama no Brasil.

Métodos Foram pesquisadas evidências científicas publicadas nas bases de dados Medline EMBASE Biblioteca Cochrane EBSCO CINAHL e Lilacs entre janeiro de 2012 e julho de 2022. As recomendações foram baseadas nessas evidências por consenso do comitê de especialistas das três entidades.

Recomendações A mamografia anual é recomendada para mulheres com risco habitual entre 40 e 74 anos. Acima de 75 anos deve ser reservado para aqueles com expectativa de vida superior a sete anos. Mulheres com risco maior do que o normal incluindo aquelas com mamas densas com história pessoal de hiperplasia lobular atípica carcinoma lobular in situ clássico hiperplasia ductal atípica tratamento para câncer de mama ou irradiação de tórax antes dos 30 anos ou ainda portadoras de doença genética mutação ou com forte histórico familiar beneficiam-se de triagem complementar e devem ser considerados individualmente. A tomossíntese é uma forma de mamografia e deve ser considerada na triagem sempre que acessível e disponível.

Palavras-chave
- rastreamento de câncer de mama
- mamografia
- ultrassom
- imagem de ressonância magnética

Introduction

In 2021, breast cancer became the most frequently diagnosed cancer in the world, and the main cause of premature death in women.[1] In Brazil, 73,610 new cases of breast cancer were estimated for the year 2023, which represents an adjusted incidence rate of 41.89 cases per 100,000 women.[1] Screening is an effective measure to detect the disease at an early stage and reduce its mortality. In addition, the early diagnosis of breast cancer allows for a greater range of therapeutic options and a reduction in treatment morbidity.[2–4]

In 2012 and 2017, the Brazilian College of Radiology and Diagnostic Imaging (CBR), the Brazilian Society of Mastology (SBM) and the Brazilian Federation of Associations of Gynecology and Obstetrics (Febrasgo), through the National Mammography Commission (CNM), published recommendations for breast cancer screening.[5,6] The purpose of this update is to publish the available evidence on screening and provide information for decision-making in women at different risks for developing the disease.

Methods

Searches were performed in the Medline (via PubMed), EMBASE, Cochrane Library, EBSCO, CINAHL and Lilacs (via Bireme) databases using as many keywords, descriptors and MeSH terms as possible to find scientific evidence of breast cancer screening with mammography, ultrasound (US), magnetic resonance imaging (MRI) and tomosynthesis (TS) in women at usual, intermediate and high risk for breast cancer, published between January 2012 and July 2022 in Portuguese, English, French and Spanish. Complementary searches were performed on Web sites, online tools and in the references of the analyzed studies. The most recent, higher quality evidence processed (systematic reviews and meta-analyses) that better answered the structured questions were selected for analysis. In the absence of these, primary studies (clinical trials or cohorts) were included. The risk of bias in the studies was assessed using the following tools: ROBIS (Risk of Bias in Systematic Reviews), RoB 2.0 (Cochrane Risk of Bias Tools for Randomized Controlled Trials version 2.0), QUADAS-C (Quality Assessment of Diagnostic Accuracy Studies – Comparative) and ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions). The overall quality of the evidence set for each outcome was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

The recommendations were based on this evidence through consensus of the committee of experts from the three entities (CBR, SBM and Febrasgo), defined when the members reached at least 75% agreement with the recommendation. In the absence of an initial agreement, in a second round of discussion and voting, a simple majority

was needed to define consensus. The recommendations were classified into five categories:

- **Category A** – **Strong** recommendation **in favor** based on **high-quality** evidence.
- **Category B** – **Strong** recommendation **in favor** based on **moderate-quality** evidence.
- **Category C** – **Weak** recommendation **in favor** based on **low-quality** evidence.
- **Category D** – Recommendation **in favor**, based only on **expert** consensus.
- **Category E** – Recommendation **against** as there is insufficient evidence to support its use.

Screening Recommendations

Screening of Women at Usual Population Risk

- ***Mammography:***
  - Annual mammography screening is recommended for women aged 40–74 years, preferably with digital technology (Category A).
  - From the age of 75, it is recommended to continue screening if there are no comorbidities that reduce life expectancy and if any, life expectancy should be of at least seven years (Category D).
- ***Ultrasound:***
  - US is not recommended as supplementary screening or as an isolated method for women at usual risk (Category E).
  - *Note: the use of US is considered in specific higher risk situations (see section on dense breasts, intermediate risk and high risk).*
- ***Magnetic resonance imaging:***
  - MRI is not recommended as supplemental screening or as an isolated method for women at usual risk (Category E).
  - *Note: the use of MRI is considered in specific higher risk situations (see section on dense breasts, intermediate risk and high risk).*
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized mammography (SM) or standard mammography (combination mode) in screening when affordable and available (Category B).
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Screening of Women with Dense Breasts

- ***Mammography:***
  - Annual screening with mammography is recommended for women aged 40–74 years, preferably with digital technology (Category A).
  - From the age of 75, it is recommended to continue screening if there are no comorbidities that reduce life expectancy and, if any, life expectancy should be of at least seven years (Category D).
- ***Ultrasound:***
  - It is recommended to consider annual US as an adjunct to mammography in women with dense breasts, except when MRI is performed (Category B).
- ***Magnetic resonance imaging:***
  - It is recommended to consider biennial MRI as an adjunct to mammography in extremely dense breasts (Category C).
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Screening of Women with a Personal Biopsy History of Atypical Lobular Hyperplasia (ALH), Classic Lobular Carcinoma in Situ (LCIS), and Atypical Ductal Hyperplasia (ADH)

- ***Initial remark:***
  - It is recommended to evaluate women with ALH, LCIS or ADH by risk calculation models that include these variables in conjunction with other clinical data, including family history and breast density, to estimate breast cancer risk.
- ***Mammography:***
  - For women with estimated lifetime risk $< 20\%$, annual mammography is recommended from age 40 (Category A).
  - For women with estimated lifetime risk $\geq 20\%$, annual mammography is recommended from diagnosis (not before age 30) (Category B).
- ***Ultrasound:***
  - For women with an estimated 15–20% lifetime risk, US can be considered as an adjunct to mammography (Category D).
  - For women with an estimated lifetime risk $\geq 20\%$, US is recommended as an alternative method for those who, for whatever reason, cannot undergo MRI (Category B).
- ***Magnetic resonance imaging:***
  - For women with estimated lifetime risk $\geq 20\%$, annual MRI should be considered as an adjunct to mammography from diagnosis (not before age 25) (Category B).
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Screening of Women with a Personal History of Treatment for Invasive Breast Cancer or Ductal Carcinoma in Situ (DCIS)

- ***Mammography:***
  - Women treated with **conservative surgery** should undergo mammography annually (Category A), starting at least six months after the end of radiotherapy.

- Women treated with **mastectomy** should undergo annual mammography of the contralateral breast only, starting one year after the end of treatment (Category A).
- Women undergoing **adenomastectomy** may consider performing mammography within one year to assess residual fibroglandular tissue to determine the need for continued mammographic screening (Category D).

- ***Ultrasound:***
  - US can be used in complementary screening to mammography when MRI is indicated but for whatever reason cannot be performed (Category C).
- ***Magnetic resonance imaging:***
  - Women treated with **conservative surgery** or **mastectomy** (to evaluate the contralateral breast) who were diagnosed with breast cancer before age 50 or with dense breasts should undergo annual MRI (Category C), starting one year after the end of treatment.
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Screening of Women with a Personal History of Chest Radiotherapy

- ***Mammography:***
  - Women with a history of chest irradiation before the age of 30 should undergo mammography **annually from the eighth year after radiotherapy treatment (not before age 30)** (Category A).
- ***Ultrasound:***
  - US should be used for screening only when MRI, for whatever reason, cannot be performed (Category B).
- ***Magnetic resonance imaging:***
  - Women with a history of chest irradiation before the age of 30 should undergo **MRI annually from the eighth year after radiotherapy treatment (not before age 25)** (Category A).
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Screening of Women with a Genetic Mutation or a Strong Family History of Breast Cancer (Lifetime Risk $\geq$ 20%)

- ***Mammography:***
  - Women with a pathogenic mutation of the BRCA1 gene or not tested, but with first-degree relatives who are carriers should undergo mammography **annually from the diagnosis of the mutation (not before age 35)** (Category A).
  - Women with a pathogenic mutation of the TP53 gene or not tested, but with first-degree relatives who are carriers should undergo mammography **annually from the diagnosis of the mutation (not before age 30)** (Category A).
  - Women with a pathogenic mutation of the BRCA2 gene or other genes at moderate or high risk for breast cancer, in addition to those not tested but with first-degree relatives who are carriers should undergo mammography **annually after the diagnosis of the mutation (not before age of 30)** (Category A).
  - Women with a lifetime risk $\geq$ 20%, as calculated by one of the mathematical models based on family history should undergo mammography **annually, starting 10 years before the youngest relative's age of diagnosis (not before age 30)** (Category A).
- ***Ultrasound:***
  - US should be used for screening only when MRI, for whatever reason, cannot be performed (Category B).
- ***Magnetic resonance imaging:***
  - Women with a pathogenic mutation of the BRCA1 gene or not tested, but with first-degree relatives who are carriers should undergo MRI annually from the diagnosis of the mutation (not before age 25) (Category A).
  - Women with a pathogenic mutation of the TP53 gene or not tested, but with first-degree relatives who are carriers should undergo MRI annually from the diagnosis of the mutation (not before age 20) (Category A).
  - Women with a pathogenic mutation of the BRCA2 gene or other genes at moderate or high risk for breast cancer, in addition to those not tested, but with first-degree relatives who are carriers should undergo MRI annually from the diagnosis of the mutation (not before age 30) (Category A).
  - Women with a lifetime risk $\geq$ 20% calculated by one of the mathematical models based on family history should undergo MRI annually, starting 10 years before the youngest relative's age of diagnosis (not before age 30).
- ***Tomosynthesis:***
  - It is recommended to consider TS in combination with synthesized 2D mammography (SM) or standard 2D mammography (combination mode) in screening when affordable and available (Category B).

Rationale

The benefits of mammographic screening have been evaluated using cohort studies, systematic reviews and randomized clinical trials, demonstrating a reduction of 22–30% in specific mortality from breast cancer in women aged 40 to 74 years.[2–4,7] When other important outcomes were analyzed, a better quality of life measured using the QALY (quality-adjusted life-years) was also observed, given the less aggressive treatments,[2] in addition to a higher rate of initial tumors with better prognostic characteristics and negative axilla,[3] and 28% fewer advanced tumors.[4]

Starting Age and Frequency of Screening

Starting screening at age 40 reduces 10-year mortality from breast cancer by 25%, but increases false-positive rates from 4.8% to 7%.[7] In Brazil, 41.1% of women diagnosed with breast cancer are younger than 50 years.[8] Regarding the screening interval, the two-year interval is related to a higher risk of advanced tumors (RR: 1.28), larger than 15 mm and with worse prognostic factors.[7] Thus, the CNM recommends annual mammography screening starting at age 40.

Considerations for Women under 40

Screening in this age group is not recommended given the lower incidence of breast cancer (~7% of cases). However, the AMAZONA III study showed this number is 17% in Brazil, with larger tumors and worse prognosis at diagnosis compared with women over 40 years of age.[9] Therefore, in agreement with other international societies,[10,11] the CNM recommends that the attending physician performs an assessment of the estimated risk of breast cancer for all women over 30 years of age using mathematical models to better stratify those at high risk, who could benefit from differentiated screening.

When to Stop Screening

As prospective, controlled and randomized studies did not include women over 74 years of age, direct data on screening in this age group are not available. However, the life expectancy of women has increased, with an increasing incidence of breast cancer in the age group above 75 years. Currently, 26% of deaths from breast cancer occur in women diagnosed after the age of 74.[12,13] Considering these factors, many medical organizations recommend individualizing the decision that should be discussed with the woman.

Adverse Effects of Screening

Although some adverse effects are reported, the quality of evidence for analyzing them is low. Overdiagnosis is a debated effect, but its estimation is variable given the difficulty in determining which tumor would or would not cause the patient's death.[14] The risk of carcinoma induced by the radiation used in mammographic screening is low, although higher in women with large breasts, in whom the radiation dose is higher, as well as in those undergoing supplemental incidences.[15] It was also associated with a 2.9% increase in the risk of biopsies with benign lesions, which can cause anxiety.[14] However, the reduction in mortality of cancer detected early by screening outweighs the risks of damage caused by exposure to radiation.

Considerations about Breast Tomosynthesis

TS is an evolution of the digital mammography. Numerous studies confirm the effectiveness of this technology in breast cancer screening, which increases the detection rate by up to 50%,[16–20] and reduces the recall rate for additional images by 9% to 29%.[19,20] The detected tumors have histological and immunohistochemical characteristics similar to those detected by mammography,[21–23] and results are maintained in subsequent rounds.[24] Therefore, TS is recommended by the CNM as a screening method when accessible and available, as well as by various medical societies, including the *American College of Radiology* (ACR),[10] the *American Cancer Society* (ACS),[25] the *European Society of Breast Imaging* (EUSOBI),[26] the *Société d'Imagerie de la Femme* (SIFEM),[27] the *National Comprehensive Cancer Network* (NCCN)[11] and the *European guidelines on breast cancer screening and diagnosis*.[28]

Tomosynthesis should be used in combination with standard 2D mammography (combination mode) or with synthesized 2D mammography (SM); the latter has the advantage of reducing the radiation dose.[15,17,18] As the National Health Surveillance Agency (Anvisa) has not established the reference and tolerance levels of the glandular dose for TS in Brazil yet, the recommendation is that each service should carry out a survey of the mean glandular doses using a sample of patients with breasts of different thickness, thereby establishing local reference and tolerance levels.[29,30]

Screening Considerations for Women with Dense Breasts

Dense breast is a risk factor for breast cancer and associated with reduced mammographic sensitivity. For these reasons, supplementary methods have been proposed. All supplemental modalities have improved sensitivity over mammography alone, allowing the detection of early-stage cancers hidden in mammograms.[31–38]

Magnetic resonance imaging is the supplementary technique with the highest rate of additional cancer detection.[31] This increases the likelihood of less invasive and curative treatments. Data on critical outcomes such as mortality are not available. However, randomized trials have shown that the supplemental use of US in dense breasts and MRI in extremely dense breasts reduced the rate of interval cancer, an important patient-centered surrogate outcome.[24,34,39] Regarding harm, the use of supplemental modalities is associated with increased false positives and biopsies.[31,33,35–38] Thus, for women with dense breasts without other risk factors, the CNM recommends annual mammography screening starting at age 40, with the option of using supplementary methods such as US or MRI. For extremely dense breasts, there is scientific evidence suggesting the superiority of MRI.

Screening Considerations for Women with a Personal History of ALH, LCIS, and ADH Diagnosis

Atypical ductal hyperplasia, ALH and LCIS are considered non-obligate precursor lesions for DCIS and invasive carcinomas,[40] and confer an increased relative risk for their subsequent development throughout life, ranging from 2.6–5.0 times for ADH, 3.2–4.8 times for ALH and 6–10 times for LICS.[41–49]

Studies evaluating screening in this group are scarce and based on retrospective series that estimated the risk for in situ and subsequent invasive carcinomas. The current strategy for defining screening in this subgroup is based on calculating the lifetime risk for breast cancer.[11] Factors such as age at diagnosis and breast density directly impact the risk of cancer, which can be estimated using risk calculation tools based on mathematical models.[47] Currently, few models include this group in the risk calculation, namely the Breast Cancer Risk Assessment Tool and the IBIS Breast Cancer Risk Evaluation Tool, and these should be preferably used.[11,47]

Screening Considerations for Women with a Personal History of Treatment for Invasive Breast Cancer and DCIS

Women with a personal history of breast cancer are seven times likelier to develop a second malignant neoplasm in the ipsilateral or contralateral breast.[48] In patients treated with conservative surgery, mammography is less sensitive because of the surgical alterations and higher incidence of interval carcinoma,[49] which explains the need for additional screening.

Complementary screening with MRI can detect 8.2–18.1 additional cancers to mammography per 1,000 women.[50–55] The performance of MRI in this scenario has shown to be similar to that of patients at high genetic risk, considering the sensitivity, detection rate, false positive and positive predictive value (PPV) of biopsies.[56–58] However, the scientific evidence for MRI in this population is weak, based on predominantly retrospective studies.[49,50,55–59] Among this heterogeneous group, the benefit of MRI is better established in young patients (diagnostic age < 50 years) and with dense breasts.[49–52]

Few studies have evaluated the accuracy of US, with a detection rate of additional cancers to mammography of 2.4 to 4.3/1,000 women, but with an increase in false positives and lower PPV for biopsies. When performed in addition to MRI, US does not improve sensitivity,[53,54] but it can be used as supplemental screening when MRI is not available.

In patients with a personal history of breast cancer treated with mastectomy, imaging screening of the treated breast with or without reconstruction is not indicated given the low detection rate of asymptomatic cancers by mammography, US or MRI.[59]

Screening Considerations for Women with a History of Thoracic Radiotherapy

Women treated with thoracic radiotherapy before the age 30 have a 13.4 times higher average risk of developing breast cancer than the general population, similar to those carrying the BRCA1 gene mutation.[60] The increased incidence occurs ~10 years after treatment, persisting 30 years later. The highest incidence occurs when treatment is performed at 10–14 years of age (RR = 22.0) and 15–19 years of age (RR = 14.3).[61] For this group, there is evidence of the importance of screening with mammography and MRI starting at 25 years of age or eight years after radiotherapy, in accordance with the recommendations of other medical entities, such as the Children's Oncology Group and the International Guideline Group.[60]

Screening of Women with a Genetic Mutation or a Strong Family History of Breast Cancer (Lifetime Risk $\geq$ 20%)

Mutations in genes that predispose to breast cancer are classified as high risk, when they cause an increase of five times or more in relation to non-carrier women (BRCA1, BRCA2, TP53, PTEN, among others), or intermediate risk, when they increase 1.5–5 times (ATM, CHECK2, BARD1, among others).[62–64] In Brazil, a study demonstrated that the most common mutation genes were BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%) and PALB2 (5.1%).[64] The Brazilian variant TP53 R337H was strongly associated with the risk of breast cancer (OR = 17.4).[64] In the case of women with a strong family history of breast cancer but without known mutation, those with an estimated $\geq$ **20% lifetime risk** calculated by mathematical models were defined as high risk.[62] These women have the cancer at an early age, with peak incidence at 20–35 years for the PT53 mutation, 30–39 years for the BRCA1 mutation, 30–49 years for BRCA2 mutations, and 40–59 years for the high familial risk.[62–65]

For this risk group, there is strong scientific evidence of the importance of MRI screening because of the reduction of interval cancers and the higher detection rate of tumors in early stages, which may reduce the need for chemotherapy and mortality, despite the higher number of false positives.[54,55,65–67] As for mammography, its role in patients with BRCA1 mutation has recently been questioned. A meta-analysis[68] demonstrated that the addition of mammography to MRI in patients with BRCA1 mutation modestly increased sensitivity (3.99%) and reduced specificity (4%). As for the BRCA2 mutation, the increase in sensitivity was greater (12.6%), with a small reduction in specificity (5%). Thus, the CNM recommends screening with MRI, associated with mammography, but not starting mammography before age 35 for BRCA1 and 30 for the other groups. Additional US examinations do not yield additional detection of cancer if MRI is performed and should be reserved for further evaluation or to guide biopsy of findings identified on MRI.

As for the impact on mortality, an important study was published by Bae et al.[54] Even though this was a retrospective study, it was demonstrated that high-risk women screened with mammography and MRI had better overall survival and tumors diagnosed at stages of better prognosis than patients in the mammography-only group.

Conclusion

This guideline brought the consensus of recommendations based on current data for breast cancer screening in Brazil, subdivided into sections according to the risk for developing

breast cancer, from women at usual risk, who represent ~80% of patients diagnosed with breast cancer, to women at higher risk.

Note

Work performed at the National Mammography Commission (CNM) of the Brazilian College of Radiology and Diagnostic Imaging (CBR), São Paulo, SP, together with the Brazilian Society of Mastology (SBM), São Paulo, SP, and the Brazilian Federation of Associations of Gynecology and Obstetrics (Febrasgo), Rio de Janeiro, RJ. As it is the result of a joint directive, it will be published in the respective journals of the three societies involved.

Conflicts of Interest

None to declare.

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- Inform the registration number referring to the research approval report at the National Council for the Control of Animal Experimentation (Concea). Studies involving animal experiments must comply with Law No. 11.794, of October 8, 2008, which establishes procedural rules for the scientific use of animals in Brazil. International manuscripts must submit local ethical documentation to proceed with the submission process. Any manuscript involving animal or human experiments submitted without proof of approval by institutional or local research committees will not be reviewed and will be returned to authors.
- Inform potential conflicts of interest in a written statement signed by all authors.
- Inform the journal editor when a major error is found in the study and provide all necessary information for publication correction, errata and retraction.
- Provide data records associated with the study when requested by the editor.
- Provide the definitive list of authors and their order at the time of original submission, containing the author registration with the respective Open Researcher and Contributor Identifier (ORCID) at https://orcid.org/signin. Any addition, removal or rearrangement of authors' names in the authorship list should be done only before the manuscript is accepted and only if approved by the journal editor. If that is the case, the corresponding author must obtain agreement of the other authors in writing, justifying the reason for alteration (addition, removal or rearrangement), and send the request by letter or e-mail. The editor will consider adding, deleting or rearranging authors after acceptance of the manuscript only in exceptional circumstances. If the manuscript has already been published in an online edition, any requests approved by the editor will result in rectification.
- Meet the deadlines for corrections and clarifying answers to questions made by reviewers.
- Use language that promotes social inclusion. The manuscript content must respect readers and not contain anything that could imply that an individual is superior to another because of age, sex, race, ethnicity, culture, sexual orientation, disability or health condition. Writing must be free from prejudice, stereotypes, slang, references to the dominant culture and/or cultural assumptions. The recognition of diversity is sensitive to differences, promotes equal opportunities and expresses respect for all people.

Scientific misconduct

Presenting results of animal or clinical research conducted without proper approval and written informed consent, as set out above, is considered unethical scientific behavior. Duplicate publication or when results are falsified, fabricated or plagiarized is also considered unethical. The RBGO allows the partial presentation of data from a manuscript in another means of dissemination, although in these cases, the author must acknowledge the previous presentation and identify the source. The citation of the original publication is essential in the disclosure. Splitting data, analysis and presentation of the same study into smaller units (practice called "salami slicing") should be avoided. Thus, the author must acknowledge in his or her cover letter any similar publications or manuscripts that have been submitted for publication based on the same material.

Investigation of scientific misconduct

Submission of an article implies that the work described has not been previously published, except in the form of an abstract, published lecture or academic thesis. Scientific misconduct may be suspected during the manuscript review process by reviewers. Thus, the RBGO may use additional resources to investigate the author's unethical conduct in order to certify the originality or plagiarism of the article (examples: Crossref Similarity Check, iThenticate and others). All suspected cases will be investigated initially by the Editor-in-Chief and by the Ethics and Professional Defense Committee of the Brazilian Federation of Gynecology and Obstetrics Associations. The author will be notified in writing of the allegations and asked to provide useful information to the investigation, including access to all original data, notes and copies of previous publications. The author's affiliation may also be contacted.

Retraction policy

The retraction policy of the RBGO is based on COPE's Retraction guidelines for advice and guidance for editors (DOI: https://doi.org/10.24318/cope.2019.1.4).

Editors will consider a publication retractable in case:

- It is plagiarism;
- It reports unethical research;
- It contains material or data without authorization for use;

- The copyright has been infringed or there is any other serious legal issue (e.g. defamation, privacy);
- There is clear evidence that results are unreliable, either as a result of a major error (e.g. miscalculation or experimental error) or as a result of fabrication or falsification of data and/or images, for example;
- Findings have been previously published elsewhere without proper attribution to prior sources or disclosure to the Editor, permission for republication or justification (i.e. cases of redundant publication);
- It has been published solely based on a compromised or manipulated peer review process;
- The author(s) have not disclosed a major conflict of interest which, in the Editor's opinion, may have unduly affected the interpretations of the work or the editors' and reviewers' recommendations.

Retraction notices must:

- Be linked to the retracted article in all versions printed or online;
- Clearly identify the retracted article (e.g. including the title and authors in the retraction header or citing the retracted article);
- Be clearly identified as a retraction (i.e. distinct from other types of correction or comment);
- Be published promptly to minimize harmful effects;
- Be freely available to all readers (i.e. open access or available only to subscribers);
- Inform who is removing the article;
- Indicate the reason(s) for the retraction;
- Be objective and factual and avoid aggressive language.

Retractions are generally inappropriate if:

- Authorship is disputed, even though there is no reason to doubt the validity of findings;
- The main conclusions of the work are still reliable and the correction can sufficiently address the errors or concerns;
- An editor has inconclusive evidence to support the retraction or is awaiting additional information, such as from an institutional investigation;
- Authors' conflicts of interest were reported to the journal after publication, but in the editor's opinion, they likely did not exert influence in interpretations, recommendations or conclusions of the article;

The RBGO will follow the flowchart suggested by COPE (DOI:**https://doi.org/10.24318/cope.2019.2.7**) to track an undisclosed conflict of interest in a published article.

Receipt of articles deposited in preprint repositories

Manuscripts submitted and coming from preprint repositories will necessarily be peer-reviewed and receive the definitive DOI issued by the RBGO if approved. Manuscripts submitted for analysis by the RBGO editorial board cannot contain references to articles that have not been published in scientific journals and that have fully complied with the peer review process.

Instructions to authors for manuscript submission

The material sent for analysis must not have been submitted simultaneously for publication in other journals or previously published. The selection of manuscripts for publication involves evaluation of originality, relevance of the topic, quality of the methodology used, its updating and whether it is appropriate and interesting to readers, in addition to adequacy to the editorial standards adopted by the journal.

Evaluation of manuscripts

Manuscripts in English submitted to the journal are received by the editorial office that checks the mandatory documentation and analyzes if the editorial rules contained in instructions to authors have been complied with. If the process is in accordance, the manuscript is sent to the editor-in-chief, who will make an initial merit assessment of the submitted manuscript. If the editor-in-chief concludes the work is in favorable scientific and technical conditions, the manuscript will be forwarded to associate editors, who, in turn, will appoint reviewers (double mind process) to evaluate the work. The reviewers' opinions and the editor's instructions will be sent to authors so they are aware of the editor's decision, criticism and eventual changes to be introduced. Authors must resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections must be highlighted in the text (marked in yellow). In cases of disagreement with the suggestions, the authors must include the justifications and observations in comment balloons. Authors must be assertive and punctual with the inquiry, supporting the hypothesis with references. **IMPORTANT!** Authors must comply with the deadlines. Failure to do so will result in a delay in their publication or even in the shelving of the process. Authors can request the suspension of the process and withdrawal of the work at any point in the process of analyzing and editing the text, except when the manuscript is accepted for publication. The concepts and statements contained in the articles are the responsibility of the authors.

Preparing a manuscript for submission

Mandatory documents for submission

When submitting a manuscript to the RBGO, documents listed below must be attached to the ScholarOne submission platform. Note that failure to submit or incomplete documentation will result in cancellation of the submission process. Mandatory documentation for online submission:

- Authorization for copyright transfer signed by all authors (scanned and attached) – **Template**;
- In accordance with chapter XII.2 of CNS Resolution No. 466/2012, in Brazil, research involving human beings needs to inform the registration number referring to the Certificate of Presentation for Ethical Assessment (CAAE) or the number of the research approval report (CEP/Conep) in the Research Ethics Committee. In the case of manuscripts involving animal experimentation, it must be indicated if it complies with Law No. 11.794 of 8 October, 2008, which establishes procedures for the scientific use of animals in Brazil, informing the registration number referring to approval of the research at the National Council for the Control of Animal Experimentation (Concea). International manuscripts must submit local ethical documentation to proceed with the submission process;
- The cover letter must be written with the purpose of justifying the publication. Authors must be identified with the respective Open Researcher and Contributor Identifier (ORCID), the authors' affiliation institution and the intention of publication. The qualification/title of the corresponding author must be included.

Title page:

- Title of the manuscript in English with a maximum of 18 words;
- Full name of authors without abbreviations (include a maximum of 8 authors per article, except in the case of multicenter studies, consensus, guidelines and position statements of societies or research groups);
- Corresponding author (full name, qualification/title and contact e-mail);
- Institutional affiliation of each author. Example: Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil (Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil);
- Conflicts of interest: authors must inform any potential conflict of interest, whether of resources, political, economic for developing the study or of intellectual property;
- Acknowledgments: acknowledgments are restricted to people and institutions that contributed in a relevant way to the development of the study. Any financial support, whether from funding agencies or private companies, must be mentioned in the **Acknowledgments** section. For Brazilian authors, RBGO requests that funding

from the agencies Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes), or any other state research support agency (eg. Fapesp), should be mentioned with the number of the research process or grants awarded;

- Contributions: according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on three conditions that must be fully met: (1) substantial contributions to conception and design, data collection or analysis and interpretation of data; (2) article writing or relevant critical review of intellectual content; and (3) final approval of the version to be published.

Manuscript

The Revista Brasileira de Ginecologia e Obstetrícia(RBGO) publishes the following categories of manuscripts:

- **Original articles:** full prospective, experimental or retrospective works.
- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
- **Letters to the Editor:** Must address editorial matters or not, but present relevant information to readers. The letters may be summarized by the editorial board, always keeping the main points. In the case of criticism or comments on published works, the letter is sent to the authors of the cited article so their response can be published simultaneously. All data presented in the letter must be fully citable and cited in the supporting reference list (unpublished data should not be described in the letter).
- **Editorial:** By invitation of the editor only.

OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

When writing a scientific article, the researcher must pay attention to the title of the manuscript. The title is the business card of any publication. It should be prepared with great care and preferably be written only after the article is finished. A good title adequately describes the content of the manuscript. It is usually not a sentence, as it does not contain the subject or arranged verbs and objects. **Abbreviations, chemical formulas, excess of adjectives, names of cities and institutions, among others, should be avoided in titles.** The titles of manuscripts submitted to the RBGO must contain a maximum of 18 words.

Abstract

The abstract must provide the context or basis for the study, establish the objectives, basic procedures of the methodology used, main results and main conclusions. It should emphasize new and important aspects of the study or observations. As abstracts are the only substantive part of the article that is indexed in many electronic databases, authors must ensure they accurately reflect the content of the article and highlight the research contribution/innovation to the topic. Abbreviations, symbols and references should not be used in the abstract. In case of original articles from clinical trials, the authors must inform the registration number at the end of the abstract.

1. Abstract: for original articles

Abstracts of original articles submitted to the RBGO must be structured in four sections and contain a maximum of 250 words:

Objective: Retrospective on the topic and the question posed by researchers.

Methods: How it was done; the method employed, including the material used to achieve the objective.

Results: What was found; the main finding and, if necessary, the secondary findings.

Conclusion: What was the conclusion; the answer to the question asked.

2. Abstract: for systematic review articles

Abstracts of systematic review articles submitted to the RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: State the main objective of the article.

Data sources: Describe the data sources examined, including dates, indexing terms and limitations.

Study selection: Specify the number of studies reviewed and criteria used in their selection.

Data collection: Summarize the conduct used in data extraction and how it was used.

Data synthesis: Present the main results of the review and the methods employed to obtain them.

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

It must contain the essence of the article, covering the purpose, method, results and conclusions or recommendations. Expose enough detail so readers can decide on the convenience of reading the entire text (word limit: 150).

NOTE: An abstract in Portuguese may be optionally added by the authors.

Keywords

The keywords of a scientific work indicate the thematic content of the text they represent. The identification of thematic content, the indexing of the work in databases and the quick location and retrieval of the content are considered the main objectives of the mentioned terms. The keyword systems used by the RBGO are DeCS (Health Sciences Descriptors – Lilacs Indexer) and MeSH (Medical Subject Headings – MEDLINE-PubMed Indexer). Five descriptors that represent the work must be chosen on these platforms.

Manuscript body

Manuscripts submitted to the RBGO should have a maximum of 4,000 words. Tables, charts and figures in the **Results** section, as well as references, are not counted.

Introduction

This part of the article prepares the reader to understand the investigation and the justification for its development. It should include the current state of knowledge on the subject, offering only strictly relevant and up-to-date references. The content to be reported in this section should provide context or background for the study, that is, the nature of the problem and its importance, and state the specific purpose, research objective, or hypothesis tested in the study or observation. The research objective is the final part of the introduction and both the main and secondary objectives must be clear and any analyzes in a pre-specified subgroup must be described. The introduction should not include data or conclusions from the work being reported.

Methods

The **Methods** section of a scientific work aims to present the study in a clear and concise way so that it is understandable and can be replicated. It should state how, when and where the study was developed. The

method comprises the material and procedures adopted in the study in order to be able to answer the main question of investigation. The **Methods** section should be structured starting with the type of study design, to show if it is appropriate to achieve the research objective; the research setting (the place and time in which it was developed); the data collection; the intervention to be performed and evaluated (if any) and also the alternative intervention; the statistical methods used and the ethical aspects of research.

NOTE: the RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, aimed at improving the presentation of research results. Check related interactive guides:

Randomized clinical trial:

http://www.equator-network.org/reporting-guidelines/consort/

Systematic reviews and meta-analyses:

http://www.equator-network.org/reporting-guidelines/prisma/

Observational studies in epidemiology:

http://www.equator-network.org/reporting-guidelines/strobe/

Qualitative studies:

http://www.equator-network.org/reporting-guidelines/srqr/

Results

The purpose of the **Results** section is to show the findings of the research. These are original data obtained and synthesized by the author in order to provide an answer to the question that motivated the investigation. Results should be presented in a logical sequence in the text, tables and illustrations, mentioning the most important findings first. Whenever appropriate, the statistical significance of results should be indicated. All information in tables or illustrations should not be repeated in the text, and only important observations should be emphasized or summarized. Additional or supplementary materials and technical details may be placed in an appendix, accessible via a link, that will not interrupt the flow of the text. When data are summarized in the **Results** section, numerical results must be presented not only in derived values (e.g. percentages) but also in absolute values from which the derived values were calculated, and specify the statistical methods used to analyze them. Only the tables and figures necessary to explain the argument of the work and to assess its basis should be used. When scientifically appropriate, analyzes of data with variables such as age and sex should be included. The limit of a maximum of five tables, five charts or five figures must not be exceeded. Tables, charts and/or figures must be included in the body of the manuscript and do not account for the requested limit of 4,000 words. For clarification on the resolution of figures, please check https://www.ncbi.nlm.nih.gov/pmc/pub/filespec-images/.

Discussion

In the **Discussion** section, new and important aspects of the study and the conclusions derived from them should be emphasized. Data or other information presented in the **Introduction** or **Results** sections should not be repeated in detail. In experimental studies, it is useful to start the discussion with a brief summary of the main findings, compare and contrast the results with those of other relevant studies, state the limitations of the study and explore the implications of the findings for future research and clinical practice. Claiming precedence and alluding to incomplete works should be avoided, as well as discussing data not directly related to the results of the research presented. New hypotheses may be proposed when justified, but they must be clearly qualified as such. The last paragraph of the **Discussion** section should include the information of the study that relatively contributes to new knowledge.

Conclusion

The **Conclusion** section is intended to relate the conclusions to the objectives of the study. Authors should avoid unsubstantiated statements and conclusions not appropriately supported by their data. In particular, authors should avoid making claims about economic benefits and costs unless their manuscript includes economic analysis and appropriate data.

References

In manuscripts submitted to the RBGO, authors must number references in order of entry in the work and use these numbers for citations in the text. An excessive number of references should be avoided, selecting the most relevant for each statement and giving preference to more recent works. Do not use citations of difficult to access, such as abstracts of works presented at conferences, theses or publications with restricted circulation (not indexed). Cite primary and conventional references (articles in scientific journals and textbooks). References such as "unpublished observations" and "personal communication" should not be used. Authors' publications (self-citation) should only be used if there is a clear need and they are related to the topic. In this case, include only original works published in regular journals (do not cite chapters or reviews) among the bibliographic references. The number of references should be limited to 35, except for review articles. Citations of references must be placed after the period in superscript, without space after the last word (sequential and numerical citations). Authors are responsible for the accuracy of data contained in the references. To format your references, check **Vancouver:** https://www.ncbi.nlm.nih.gov/books/NBK7256/.

Submission of manuscripts

Articles must be submitted electronically, according to instructions available on the website: http://mc04.manuscriptcentral.com/rbgo-scielo.

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