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Editorial

635 Importance of an Interdisciplinary Approach in the Treatment of Women with Endometriosis and Chronic Pelvic Pain
Júlia Kefalás Troncon, Gabrielle Barbosa Anelli, Omero Benedicto Poli-Neto, and Julio Cesar Rosa e Silva

Original Articles

Obstetrics

638 Factors Related to Low COVID-19 Vaccination Rate in Pregnant and Postpartum Women with and without COVID-19
Dilek Menekse Beser, Derya Uyan Hendem, Deniz Oluklu, Ezgi Turgut, Necati Hancerliogullari, Sule Goncu Ayhan, Ozlem Moraloglu Tekin, and Dilek Sahin

646 Evaluation of the Effect of Low-dose Aspirin on the Prevention of Preterm Delivery in Women with a History of Spontaneous Preterm Delivery
Masoumeh Mirzamoradi, Zahra Dehghani, Pegah Azadi, Maryam Mohammadi, Armin Khavandegar, and Mahmood Bakhtiyari

Contraception

654 Five-year Contraceptive Use of 52-mg Levonorgestrel Releasing Intrauterine System in Young Women, Menstrual Patterns, and New Contraceptive Choice
Elaine Cristina Fontes de Oliveira, and Ana Luiza Lunardi Rocha

Sexual Violence/ Pediatric and Adolescent Gynecology

661 Adolescent Female Victims of Sexual Violence: Analysis of Loss of Follow-up after Emergency Care and Outpatient Follow-up
Alejandra Suyapa Becerra Torres, Otávio Prado Alabarse, Ândria Cléia Alves, Ana Luiza Teixeira, Renata Cruz Soares de Azevedo, and Arlete Fernandes

Infertility

676 Endometrial Progesterone and Estrogen Receptors in Relation to Hormonal Levels in Women with Unexplained Recurrent Miscarriage
Ihab Adel Gomaa, Ahmed Sabry, Ihab Serag El-Din Allam, Sherif Ashoush, and Ahmed Reda

683 The Role of Thyroid Hormones, Vitamins, and Microelements in Female Infertility
Sveta Aghayeva, Murat Sonmezer, Yavuz Emre Şükür, and Aytaj Jafarzade

Oncology

689 Risk Profile of High-grade Cervical Lesions and Cervical Cancer Considering the Combination of Cytology, HPV Genotype, and Age among Women Undergoing Colposcopy
Júlio César Possati-Resende, Thais Zilles Fritsch, and Karen Cristina Borba Souza

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Teaching and Training

699 Effectiveness of an Educational Intervention with Guidelines from the Total Acceleration of Postoperative Recovery Project (ACERTO) in Gynecology
Juliana Marques Marra, Isabela Corrêa Samper, Laura Aparecida Xavier de Abreu, Rafaela Pereira Anelvoi, Maria Gabriela Baumgarten Kuster Uyeda, Marair Gracio Ferreira Sartori, and Gisele Vissoci Marquini

Review Articles

706 Fetal Macrosomia and Postpartum Hemorrhage in Latin American and Caribbean Region: Systematic Review and Meta-analysis
Araceli Quezada-Robles, Fiorella Quispe-Sarmiento, Guido Bendezu-Quispe, and Rodrigo Vargas-Fernández

724 Effect of Lubricant Use on Cervicovaginal Cytology – What's the Evidence?
Diana Magalhães dos Santos, Maria Beatriz Freire Oliveira Coelho de Matos, Ana Raquel Borges Sousa, Francisco Correia de Almeida Fertusinhos, and Rosa Maria Couceiro Pendás

729 Sexual Function of Patients with Deep Endometriosis after Surgical Treatment: A Systematic Review
Graziele Vidoto Cervantes, Paulo Augusto Ayroza Galvão Ribeiro, Mariana Carpenedo Tomasi, Daniela Farah, and Helizabet Salomão Abdalla Ayroza Ribeiro

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Editorial

Importance of an Interdisciplinary Approach in the Treatment of Women with Endometriosis and Chronic Pelvic Pain

Importância de uma abordagem interdisciplinar no tratamento de mulheres com endometriose e dor pélvica crônica

Júlia Kefalás Troncon[1] Gabrielle Barbosa Anelli[1] Omero Benedicto Poli-Neto[1] Julio Cesar Rosa e Silva[1]

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Endometriosis, from a pathophysiological standpoint, can be defined as active endometrium-like tissue outside the uterus. However, to better understand and approach this complex disease, it should be addressed as a chronic inflammatory disease that can cause pelvic pain during a long period of a women's reproductive lifetime.[1] Due to nociplasty, women affected by endometriosis can also maintain pain despite adequate organic treatment, especially considering that this disease has no objective cure.[1,2] On the other hand, chronic pelvic pain(CPP) can be defined as pain perceived in the lower abdomen, lasting for at least six months, that has a negative impact on quality of life and that demands treatment.[2] CPP may have a gynecologic etiology such as endometriosis, but most frequently has a multifactorial nature, involving gastrointestinal, urinary, psychological, and musculoskeletal systems.

Furthermore, women suffering from endometriosis frequently manifest other overlapping pain conditions such as irritable bowel syndrome, painful bladder syndrome, fibromyalgia, migraine headaches, among others.[3] This may be due to a lower pain threshold, cross-organ sensitization,[3] enhanced visceral pain or a common pathophysiological origin yet to be elucidated. Therefore, when managing pain in women suffering from endometriosis and/or CPP, an isolated gynecological approach will usually be insufficient.

For optimum care, the treatment must be patient centered, rather than disease centered.[4] So nowadays, more attention has been given in studies on the beneficial impact of an interdisciplinary approach toward CPP and endometriosis. Preferably, a true interdisciplinary team discusses together the best treatment for each individual patient, instead of a mere multidisciplinary setting where different health care professionals focus only in their own specific intervention. Quality of life assessment and improvement should be one of the main goals since a cure is most often unattainable.

An interdisciplinary team ideally would be composed by medical staff with specific training in this area of expertise, and by a nurse, psychologist, physical therapist, occupational therapist, nutritionist, and physical educator. The medical team should be composed of not only gynecologists, but also urologists, gastroenterologists, psychiatrists, and pain management specialist.

Patients with endometriosis and CPP commonly have associated mood disorders, with high levels of anxiety and depression. Up to 73% of anxiety and 40% of depression was the prevalence found in a cross sectional controlled study.[5] Notably, these women manifest a pain catastrophizing profile[3,6] that worsens the experiencing of the pain. So, a psychological approach is of upmost importance, as well as a program in pain education,[3] which will help the patient feel more responsible for her own improvement. Coping strategies and constructive attitudes can positively modulate the well-being of these women. A qualitative study showed that daily life attitudes can influence the experience of pain; the categories identified were: shaping life by pain, isolating from social contact, avoiding sexual relationship, seeking pain relief, and seeking positive strategies.[7]

Endometriosis can also lead to dyspareunia, which is pain during sexual intercourse. This symptom can aggravate the negative impact of the disease in personal and loving relationships; up to 30% of women reported they frequently had to interrupt sexual intercourse because of pain, and 66% are

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afraid of pain before intercourse which can lead to avoidance of contact.[8] The prevalence of sexual distress was of 78% in one study,[8] and its origin multifactorial, associated with increased tone of the pelvic floor muscles,[9] due to a possible history of sexual, physical or moral abuse[10] or due to endometriosis itself.

In addition to a medical and psychological approach toward the sexual dysfunction and distress, the evaluation by a physical therapist is mandatory. Besides form dyspareunia, a physical therapist will also improve symptoms of myofascial syndrome which are common in women suffering from endometriosis and other causes of CPP, what might improve dyspareunia. Approximately 85% of women with CPP have musculoskeletal associated disorders; myofascial pain syndrome can be managed, among other strategies, by trigger point anesthetic injections, therapeutic ultrasound[11] and also by acupuncture.[12] Despite the lack of robust evidence, some studies show beneficial effects of acupuncture in the treatment of these conditions.[12] Physical exercise is another domain that should be addressed and encouraged. Even though without high-quality level of evidence, the practice of physical activity has almost no adverse effect, if there is no medical contraindication. Supposedly, the mechanism involved should be reduction of oxidative stress; regular practice of aerobic and other forms of physical activity apparently have a positive impact in diseases with an inflammatory background such as endometriosis.[13] In CPP in general, both aerobic and anaerobic activities seem to have an analgesic effect, conditioning hypoalgesia by pain modulation and effects on baroreceptors.[14] However, women with endometriosis apparently have altered mechanisms of central nociceptors, and also greater tendency to avoid the practice of physical activity.[14]

Regarding the dietetic effects on endometriosis, a wide variety of data are available, even though with low grade of evidence. Nutritional aspects influence hormonal and inflammatory balance and as so have been implicated in the physiopathology of endometriosis.[15] There appears to be a protective impact on the consumption of dairy products and calcium and tryptofan,[16] probably through the induction of anti-oxidative mechanisms and improving general well-being.[15,16] Red meat and saturated fatty acids, on the other hand, appear to have a negative effect on the disease.[17]

Consequently, dietary interventions seem to have a positive implication on the management of CPP and endometriosis. Especially when considering other associated diseases such as irritable bowel syndrome and painful bladder, for example, that could also benefit from dietary modifications. Nirgianakis et al.[18] suggest a symptom based approach in which patients with gastrointestinal related symptoms could mostly benefit from low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and/or gluten-free diet, and a Mediterranean diet could be encouraged in general to improve global health.[18] Most importantly, nutritional changes could help patients to perceive how lifestyle habits can influence on their perceived pain, and how engaging in their own treatment is of great relevance toward improvement.[19]

Finally, occupational therapists could help patients develop adaptative strategies when managing the burden that CPP has on almost all domains of social and professional aspects of their life.[20] Not only occupational activities, but also self-care, self-esteem and leisure are affected. Patients should benefit from the help of an occupational therapist in rehabilitation, and developing tools toward coping.[20]

Endometriosis is a chronic disease that affects women in productive age and has significant economic impact.[21] CPP often accompanies endometriosis but also has other frequent etiologies, for this, questionnaires that assess quality of life and the involvement of other organs should be incorporated into the initial and ongoing evaluation of these patients as current practice.

Therefore, we recommend that an interdisciplinary approach would be of benefit in providing an optimum patient centered care.

Conflicts to Interest
None to declare.

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Factors Related to Low COVID-19 Vaccination Rate in Pregnant and Postpartum Women with and without COVID-19

Fatores relacionados à baixa taxa de vacinação contra COVID-19 em gestantes e puérperas com e sem COVID-19

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Abstract

Objective This study focused on pregnant and postpartum women during the COVID-19 pandemic, aiming to determine the attitudes and behaviors of vaccinated and unvaccinated groups, and the vaccination behaviors in the groups with and without the disease. The reasons for refusing the vaccine were also questioned.

Methods This cross-sectional study was performed from September 2021 to October 2021. The study data were collected using a face-to-face questionnaire. The participants were pregnant women who applied to the hospital for routine antenatal care and were hospitalized, and women in the postpartum period. Additionally, pregnant and postpartum patients who were diagnosed with COVID-19 at the time of admission and were hospitalized and admitted to the intensive care unit due to this disease were also included in the study.

Results A total of 1,146 pregnant and postpartum women who completed the questionnaire were included in our study. Only 43 (3.8%) of the participants were vaccinated; 154 (13.4%) of the participants had comorbidities. The number of COVID-19-positive patients was 153. The lack of sufficient information about the safety of the COVID-19 vaccine is the most common reason for the refusal.

Conclusion Vaccine refusal can significantly delay or hinder herd immunity, resulting in higher morbidity and mortality. Considering the adverse effects of COVID-19 on pregnancy, it is essential to understand pregnant and postpartum women's perceptions toward vaccination to end the pandemic.

Keywords
- COVID-19 vaccine
- postpartum women
- pregnancy
- vaccine acceptance
- vaccine hesitancy

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Introduction

The coronavirus disease 2019 (COVID-19) is considered one of the most widespread, global public health crises due to being one of the leading causes of death internationally.[1] While this disease may have a mild process in pregnant women, severe illness with hospitalization, admission to the intensive care unit (ICU), mechanical ventilation, or death were seen. Pregnant and postpartum women are more vulnerable to developing severe symptoms of infection because of the physiological changes in the immune system that occur during pregnancy.[2] Furthermore, the COVID-19 virus can potentially alter immunological responses at the maternal–fetal interface, affecting both mother and baby.[3] Thus, pregnant women with COVID-19 are at increased risk of adverse pregnancy outcomes.[4,5]

The pandemic has weakened healthcare systems, disrupted supply chains, and sparked a mental health crisis; thus, it caused significant public health problems. Although two years have passed since the identification of the disease, an effective and safe treatment has not been found during pregnancy. Vaccination is the best way to protect women and babies against the risks of COVID-19. By the end of 2020, vaccines that became available in many parts of the world were considered the most promising attempt to prevent SARS-CoV-2 infection and defeat the pandemic).[6] Several vaccines have been developed rapidly and authorized for use in many countries. None of the COVID-19 vaccines contained live viruses, thus indicating their suitability for pregnant and postpartum women. Many studies have shown that the vaccines do not raise any concerns about the safety of female reproduction, intrauterine or postnatal development, and their safety and efficacy in pregnancy.[7,8] Therefore, many authorities recommend vaccination.[9,10]

Vaccination is considered a keystone, along with other interventions, to overcome the pandemic. However, vaccine hesitancy – defined as the rejection or delayed vaccine acceptance – has the potential to hinder this attempt and is considered to be a significant global health threat.[11,12] It was thought that without a general approach to acceptance by the public, COVID-19 vaccines would not defeat the pandemic. Therefore, vaccination willingness and hesitancy among different populations have been studied since the early process of availability.[13–15] According to the results of these studies, it has been observed that pregnant women are more worried about vaccination than the general population. There is a lot of misinformation and concerns about vaccines, especially since pregnancy was excluded from studies in the past years. Moreover, this hesitancy is affected by various factors in vulnerable populations. Therefore, it is important to understand the factors affecting vaccine acceptance and hesitation in pregnant and postpartum women, who are more vulnerable than the general population.

This study aimed to determine the vaccination status of pregnant and postpartum women, the attitudes and behaviors of vaccinated and unvaccinated groups, and the vaccination behaviors in the groups with and without COVID-19. The reasons for refusal to be vaccinated were also questioned.

Methods

This cross-sectional study was performed in Ankara City Hospital from September 2021 to October 2021. This tertiary hospital is a significant pandemic center with approximately 20,000 births per year. The participants of this study were pregnant women who were were hospitalized during routine antenatal appointments, and women in the postpartum period. Additionally, pregnant and postpartum patients who were diagnosed with COVID-19 at the time of admission and were hospitalized due to COVID-19 and admitted to the ICU were also included in the study. Written informed consent was obtained from all subjects. The applied protocol was approved by the Medical Research Ethics Department of the hospital (E2–21–820).

The study's data were collected using a face-to-face questionnaire by three maternal-fetal specialists. There was no accompanying person with the participants, so no one was affected by their decision at the time of the questionnaire. The patients have similar characteristics regarding religion, language, and race. All the patients had information about how to get the vaccine, whether it was cost-free, and in which centers it could be administered. All pregnant and postpartum women were again informed about the vaccination program of the societies and the Turkish Ministry of Health. All participants had the autonomy to get vaccinated without permission from their husbands or any family member.

Vaccination guidelines were created according to the careful investigation of studies, statements, and assessments performed throughout the world and within Turkey by the Coronavirus Scientific Committee of the Turkish Ministry of Health. It is applied by offering inactive virus and mRNA COVID-19 vaccine options, including for pregnant and postpartum women. If a person wants to be vaccinated, they can book an appointment after checking eligibility online. The COVID-19 vaccines are administered free of charge, mainly at the Family Health Centers and public and private hospitals where the Provincial Health Directorates provide vaccination services. Immunization teams from the Community Health Centers and District Health Directorates provide on-site vaccination services at stations in other public areas. The healthcare staff of the Home Healthcare System administers the vaccines to individuals with their home addresses recorded.

The first section of this study's questionnaire determined maternal characteristics, including age, parity, comorbidities, and sociodemographic characteristics. The second part focused on data about COVID-19 vaccination, the type of vaccine, and gestational age at vaccination. Regarding COVID-19 vaccination, the participants were divided into two groups, vaccinated and unvaccinated. The participants were also asked about their previous vaccination status and their attitudes toward pregnancy tetanus and influenza vaccination. Additionally, questions about COVID-19 contact were asked. The status of relatives regarding the disease and vaccination and whether the participant was encouraged to vaccinate were evaluated. The participants who were not

vaccinated were asked about their reasons in the third part of the questionnaire.

Furthermore, COVID-19 infection in patients was confirmed by reverse-transcription polymerase chain reaction (RT-PCR) testing. Patients who were intubated due to severe infection could not be included in the study because they could not complete the questionnaire. Refugees were not included in the study because of language problems.

Statistical analyses were performed using the Statistical Package Social Sciences (SPSS, Inc., Chicago, IL, USA) software version 17. Categorical data were expressed as numbers (percentages) and compared with the Chi-square test in two independent groups. Numerical data were shown in mean ± standard deviation (SD) and median (minimum-maximum) A type-1 error below 0.05 was considered statistically significant. Descriptive statistics, proportions, frequency distribution, and mean values were calculated, and the findings were presented in text, tables, and figures.

Results

In total, 1,146 pregnant and postpartum women who completed the questionnaire were included in this study. The vaccination rate among the participants was 3.8%. Sociodemographic features are shown in ►**Table 1**. The participants were mostly pregnant women in the third trimester. There were 154 (13.4%) participants with comorbidities diagnosed before pregnancy: chronic hypertension ($n = 45$), hypothyroidism ($n = 27$), asthma ($n = 17$), Hashimoto disease ($n = 15$), epilepsy ($n = 11$), and type 1 diabetes ($n = 10$). Patients followed up due to high risk during antenatal care included women with threatened preterm labor ($n = 98$), gestational hypertension ($n = 78$), and gestational diabetes mellitus ($n = 57$). Both comorbidity and risk during antenatal care were considered as high-risk pregnancies. The distribution of these patients among all participants is shown in ►**Fig. 1**.

The responses of all participants and the statistical significance of the answers in vaccinated and unvaccinated women are shown in ►**Table 2**. If the influenza vaccine was recommended during this pregnancy, the rate was significantly higher in the vaccinated group (58.1%, $p = 0.018$). Also in the same group, getting the influenza vaccine during this pregnancy was higher than in the unvaccinated group (7%, $p = 0.020$). The fear of the vaccine harming the baby was higher in the unvaccinated group (69.6%). Hospitalization due to COVID-19 was 2.3% in the vaccinated group and 10.5% in the unvaccinated group. There were 12 patients admitted to the intensive care unit due to COVID-19, and all were unvaccinated. The number of COVID-19-positive patients at the time of inclusion in the study was 153 (13.4%). Among them, those who were vaccinated were only 4. The attitude of these patients toward vaccination was registered in ►**Table 3**.

Although there is no statistical significance, the vaccination rate of the participants' partners was also higher in the COVID-19 negative group than in the positive one (71.2% vs. 68.6%). The overall vaccination rate in the study was 3.8%.

Table 1 Sociodemographic Data

Variables	All participants ($n = 1146$)
Age	28.1 ± 5.3
Gravidity	2 (1–8)
Parity	1 (0–5)
Gestational week	33 (5–42)
First trimester	44 (3.8%)
Second trimester	217(18.9%)
Third trimester	637 (55.6%)
Postpartum period	248 (21.7%)
Day after birth ($n = 248$)	3 (0–18)
Number of householders	3 (2–12)
Number of school-age children	1 (0–5)
Number of the person with comorbidity	0 (0–2)
Number of >65-yeard-old householders	0 (0–2)
Income (month, Turkish Lira)	4,216 ± 1,615
Length of hospital stay (days) ($n = 117$)	6 (1–22)
Comorbidity	154 (13.4%)
High-risk pregnancy	483 (42.2%)
Education status	
None	45 (3.9%)
Primary school	168 (14.7%)
Secondary school	572 (49.9%)
University	361 (31.5%)
Career	
Housewife	873 (76.2%)
Government official	127 (11.1%)
Private sector	26 (2.3%)
Worker	120 (10.5%)
Husband career	
Worker	402 (35.1%)
Government official	270 (23.6%)
Merchant	166 (14.5%)
Private sector	93 (8.1%)
Unemployed	215 (18.8%)

Notes: †Values are given as mean ± standard deviation and median (min–max) or as number (percentage).

Participants were vaccinated mainly in the second trimester (37.2%). The pregnancy periods during which they received the vaccine was 16.3% before pregnancy, 9.3% in the first trimester, 37.2% in the second trimester, and 25.6% in the third trimester. The most common vaccine was the single-dose BNT162b2 mRNA (Pfizer-BioNTech, 19.9%). The reasons for vaccine refusal are shown in ►**Table 4**. The lack of sufficient information about the safety of the COVID-19 vaccine is the most common reason for refusal. Other frequent reasons were worry that it would be harmful to the

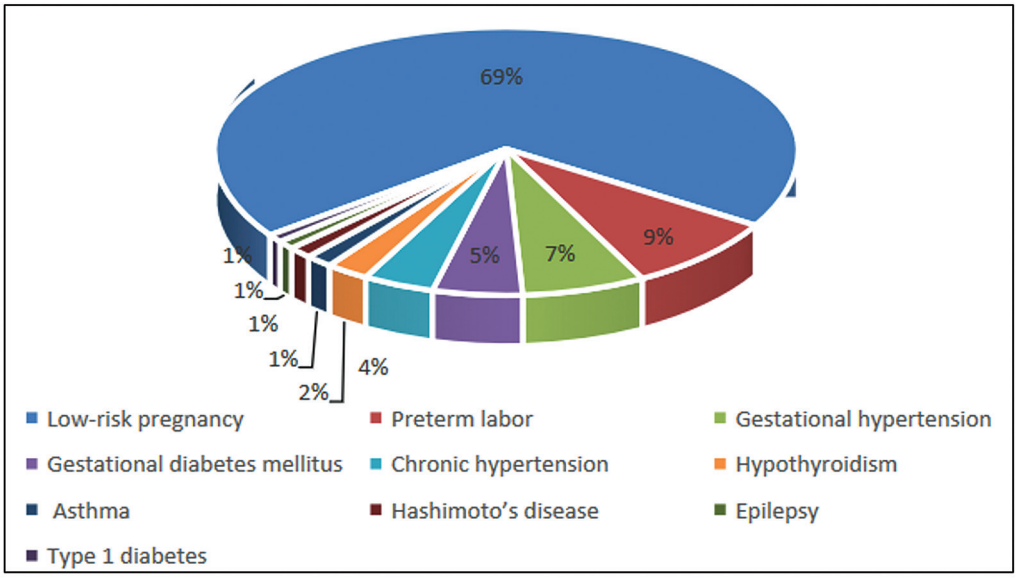

Fig. 1 Distribution of high-risk pregnancies among all participants.

baby, belief that the vaccine would not work, and family members' refusal to vaccinate.

Discussion

The present study showed a very low vaccination rate of 3.8% in pregnant and postpartum women. This low vaccination rate was unexpected for us. In a previous study from our clinic, before the vaccination began, 37% of pregnant women had the intention to get the vaccine if it was offered during pregnancy.[16] In another study that showed vaccine acceptance in postpartum women, 33.3% of participants were accepting.[17] Despite the acceptance rates in our previous studies, vaccination during pregnancy and postpartum was relatively low in the present study. In our previous study with pregnant women, the group that accepted the vaccine thought they were sufficiently informed about the COVID-19 vaccine compared with the group that refused it. In the group with vaccine refusal, the most common reasons for rejection were lack of knowledge and worry that it might be harmful to the baby. The most common reasons for vaccine refusal in postpartum women were insufficient knowledge about the application to women in this period and doubts over its effectiveness. Similar to these studies, we found that the lack of knowledge about vaccines and the belief that they would harm the baby were the majority of the reasons for low vaccination acceptance in pregnant and postpartum women. These results show the need to fight not only the pandemic but also incomplete or wrong information, and knowledge must be disseminated.

Pregnant women are notably vulnerable to infectious diseases due to changes in immunity and respiratory and cardiovascular physiology that happen during pregnancy. The Centers for Disease Control (CDC) data and other publications showed that pregnant women were three times more likely to be admitted to the ICU or need intubation and 1.5 times more likely to die from COVID-19 than nonpregnant women.[18] A comprehensive study from our clinic, a tertiary pandemic center sharing experiences of pregnant women with COVID-19 and comparing clinical outcomes of pregnancy trimesters, showed that pregnant women are at higher risk of developing severe illnesses and complications.[5]

In the present study, 13.4% of the participants had comorbidities. Although it is well known that individuals with chronic illness have a higher risk of severe disease and death, those participants still avoided getting vaccinated. We believe this is a very dramatic finding.

The COVID-19 vaccination process in Turkey started in January 2021. Vaccinations are given free of charge to determined age groups through appointments at family health centers and hospitals. According to this procedure, COVID-19 vaccination can be applied before, during, and after pregnancy. A previous study showed that the rates of COVID-19 vaccine acceptance among pregnant women vary significantly, such as 28.8 to 84.4% according to Turkey's official data.[19] Despite the guidelines and recommendations, pregnant and postpartum women's vaccination rate was relatively low in the present study.

Vaccination is the only way to defeat the pandemic. Although medical organizations and committees recommend vaccination for pregnant and lactating women, the rates are still low. In clinical studies, the vaccine has shown a >85% reduction in symptomatic COVID-19 and risk of transmission.[20,21] In our research, the number of patients with the disease was 153 (13.4%).

In studies conducted before the COVID-19 outbreak, gender-related vaccination challenges affected populations.[22,23] Women were less likely than men to receive relevant or reliable information due to a lack of education and access to information, as well as work and home care obligations. Additionally, women were less reliant on vaccines and were less able to make health-related decisions due

Table 2 Answers of all participants with statistical significance comparison of the answers

Questions	Answers	Participants ($n = 1,146$)	Vaccinated n = 43 (3.8%)	Not vaccinated n = 1,103 (96.2%)	*p*-value
Did you ever get vaccinated?	Yes	990 (86.4%)	36 (83.7%)	954 (86.5%)	0.603
	No	156 (13.6%)	7 (16.3%)	149 (13.5%)	
Did you get vaccinated in the last five years?	Yes	923 (80.5%)	39 (90.7%)	884 (80.1%)	0.086
	No	223 (19.5%)	4 (9.3%)	219 (19.9%)	
Is the influenza vaccine recommended in this pregnancy?	Yes	46 (4%)	4 (9.3%)	42 (3.8%)	0.090
	No	1,100 (96%)	39 (90.7%)	1060 (96.2%)	
If the influenza vaccine was recommended, would you get vaccinated in this pregnancy?	Yes	466 (40.7%)	25 (58.1%)	441 (40%)	**0.018**
	No	679 (59.3%)	18 (41.9%)	661 (60%)	
Did you get the influenza vaccine during this pregnancy?	Yes	16 (1.4%)	3 (%7)	13 (%1.2)	**0.020**
	No	1,130 (98.6%)	40 (93%)	1,090 (98.8%)	
Is the tetanus vaccine recommended in this pregnancy?	Yes	918 (80.1%)	33 (76.7%)	885 (80.2%)	0.574
	No	228 (19.9%)	10 (23.3%)	218 (19.8%)	
Did you get the tetanus vaccine during this pregnancy?	Yes	879 (76.7%)	33 (76.7%)	849 (77%)	0.273
	No	267 (23.3%)	10 (23.3%)	254 (23%)	
Do you prefer your baby to be vaccinated?	Yes	1,122 (97.9%)	41 (95.3%)	1,081 (98%)	0.228
	No	24 (2.1%)	2 (4.7%)	22 (2%)	
Do you have a high risk of COVID-19 transmission at work?	Yes	92 (8%)	3 (7%)	89 (8.1%)	0.796
	No	1,054 (92%)	40 (93%)	1,014 (91.9%)	
Did you have close contact with COVID-19 positive person?	Yes	330 (28.8%)	11 (25.6%)	319 (28.9%)	0.635
	No	816 (71.2%)	32 (74.4%)	784 (71.1%)	
Has your husband gotten vaccinated for COVID-19?	Yes	812 (70.9%)	36 (83.7%)	776 (70.4%)	0.05
	No	334 (29.1%)	7(16.3%)	327 (29.6)	
Did you support your relatives in getting the COVID-19 vaccine?	Yes	595 (51.9%)	40 (93%)	555 (50.3%)	**<0.001**
	No	551 (48.1%)	3 (7%)	548 (49.7%)	
Have you ever had a relative admitted to ICU due to COVID-19?	Yes	95 (8.3%)	13 (30.2%)	82 (7.4%)	**<0.001**
	No	1,051 (91.7%)	30 (69.8%)	1,021 (92.6%)	
Have you had a relative who died due to COVID-19?	Yes	32 (2.8%)	0	32 (2.9%)	0.629
	No	1,114 (97.2%)	43 (100%)	1,071 (97.1%)	
Positive COVID-19 status now?	Yes	153 (13.4%)	4 (%14,8)	149 (13.5%)	0.426
	No	993 (86.6%)	39 (%85,2)	954 (86.5%)	
Have you been hospitalized due to COVID-19?	Yes	117 (10.2%)	1 (2.3%)	116 (10.5%)	0.082
	No	1,029 (89.8%)	42 (97.7%)	987 (89.5%)	
Have you been admitted to ICU due to COVID-19?	Yes	12 (1%)	0	12 (1.1%)	0.999
	No	1,134 (99%)	43 (100%)	1,091 (98.9%)	
Do you think that the vaccine is harmful to you?	Yes	37 (3.2%)	2 (4.7%)	35 (3.2%)	0.646
	No	1,109 (96.8%)	41 (%95.3)	1,068 (96.8%)	
Do you think the COVID-19 vaccine will harm your baby?	Yes	774 (67.5%)	6 (14%)	768 (69.6%)	**<0.001**
	No	372 (32.5%)	37 (86%)	335 (30.4%)	

Abbreviation: COVID-19, coronavirus disease 2019; ICU, intensive care unit. **Notes:** † Chi-square test. ‡ The bold characters were used to define the significant *p*-values < 0.05. ¶ Values are given as numbers (percentage).

Table 3 Attitudes to vaccines between COVID-19 positive and negative groups

Questions	Answers	Positive n = 153 (13.4%)	Negative n = 993 (86.6%)	*p*-value
Has your husband gotten vaccinated for COVID-19?	Yes	105 (68.6%)	707 (71.2%)	0.515
	No	48 (31.4%)	286 (28.8%)	
Did you support your relatives in getting the COVID-19 vaccine?	Yes	94 (61.4%)	501 (50.5%)	**0.011**
	No	59 (38.6%)	548 (%49.5%)	
Have you ever had a relative admitted to ICU due to COVID-19?	Yes	29 (19%)	66 (6.6%)	<**0.001**
	No	124 (81%)	927 (93.4%)	
Have you had a relative who died due to COVID-19?	Yes	12 (7.8%)	20 (2%)	<**0.001**
	No	141 (92.2%)	973 (98%)	
Have you been hospitalized due to COVID-19?	Yes	51 (33.3%)	66 (5.6%)	<**0.001**
	No	102 (66.7%)	927 (93.4%)	
Have you been admitted to ICU due to COVID-19?	Yes	9 (5.9%)	3 (0.3%)	<**0.001**
	No	144 (94.1%)	990 (99.7%)	

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit. **Notes:** † Chi-square test. ‡ The bold characters were used to define the significant *p*-values < 0.05. ¶ Values are given as a number (percentage).

Table 4 Reasons for the COVID-19 vaccine refusal?

Questions	Not vaccinated n = 1,103
Lack of sufficient information about the safety of the COVID-19 vaccine	535 (48.5%)
The vaccine is harmful to my baby	329 (29.8%)
I don't think that vaccine will work	209 (18.9%)
I think the virus will mutate	119 (10.8%)
Family members disagree with the COVID-19 vaccine	114 (10.3%)
The vaccine is harmful to my body	94 (%8.5)
The vaccine will cause COVID-19 infection	93 (8.4%)
COVID-19 is not a severe disease	68 (6.2%)
I have a low risk of getting a COVID-19 infection	67 (6.1%)
I believe that even if I am sick, my baby and I will not encounter any adverse events	55 (5%)
Afraid of injection	33 (3%)

Abbreviations: COVID-19, coronavirus disease 2019. **Notes:** † Values are given as a number (percentage).

to limited household decision-making power. Furthermore, they had more difficulty reaching vaccination locations due to limited mobility. All of the patients in our study group were informed about how to access the vaccine, and that it is cost-free and can be immediately included in a vaccination program by their health provider if they so desired. Understanding how genders norms and power dynamics affect admission and requests for vaccination in different conditions is crucial for extending vaccine access. Gender-related barriers should be considered when planning and expanding vaccine distribution to reach all populations.

Vaccine hesitancy is a global problem, posing a significant threat to controlling the COVID-19 pandemic.[24] Previous studies have determined several factors associated with this disease's vaccine hesitancy.[25,26] Socioeconomic and demographic characteristics (age, gender, income, occupation, and marital status), incomplete or incorrect information about vaccines, religious beliefs, confidence in the content of vaccines, and possible side effects are some of these factors. Despite vaccine hesitancy, requests have increased over time, and the inequality of access to vaccines within and between countries is remarkable. It is due to vaccination that diseases such as smallpox, poliomyelitis, and yellow fever, which used to cause millions of deaths and disabilities in many parts of the world, are now almost completely extinct. In light of this information, we believe that if COVID-19 vaccines are optimally and equitably received worldwide, they could have a similar impact on the pandemic.

The COVID-19 pandemic has led to the administration of "social distancing" strategies, which are critical to limiting the spread of the virus, but this situation had some psychological consequences. A recent study examined the effects of loneliness and social distance on human health.[27] Furthermore, a previous study found increased anxiety levels in high-risk pregnant women compared with normal pregnancies during the COVID-19 pandemic.[28] Mortazavi et al. suggest that health professionals can reduce anxiety levels by supporting pregnant women and improving their well-being.[29] In addition to this support, COVID-19 vaccination can also reduce anxiety. Family members' decisions about vaccination influence the patients' decisions; therefore, it is essential to support pregnant women's decisions in this situation.[19] According to our study, in the vaccinated group, the COVID-19 vaccination rate of their husbands was higher than in the unvaccinated one (83.7 vs. 70.4%). We found that the rate of supporting relatives for vaccination was significantly higher in the COVID-19-positive group. In this group, the rate of mortality and ICU admittance among relatives because of COVID-19 was also higher. Accordingly, these results may indicate the influence of experiencing unfavorable situations in understanding the severity of the disease.

Counseling on vaccination should include the disease's risks and the benefits of vaccination before, during, or after pregnancy, while breastfeeding. Insufficient data on vaccine safety was the main reason participants were against it. This result was similar to a previous study on COVID-19 vaccine acceptance before the beginning of the vaccination program.[16]

A lack of sufficient research on the effects of these vaccines in pregnancy could influence the vaccination rate in pregnant and postpartum women. No side effects of the vaccine have been reported among women who participated in clinical trials in the early stages of vaccine testing and became pregnant at the end.[30,31] Nevertheless, the worry that it could harm the baby was higher in the unvaccinated group.

It is essential to build public confidence in vaccination with consistent communication programs by the government. At the same time, detailed information about the dangers of the disease should be given through effective vaccination campaigns. It has been shown that COVID-19 causes many adverse pregnancy outcomes, such as preterm birth and miscarriage.[5] While the maternal and fetal effects of COVID-19 have proven so much, the reasons for vaccine refusal in pregnant and postpartum women should be investigated further. Future studies should focus on the reason for this low vaccination rate, whether reporting the adverse outcomes of COVID-19 is enough, or whether further explanations are needed about the positive effects of the COVID-19 vaccine. A previous study about the tetanus vaccine showed a high vaccination rate in pregnant women who were well informed about vaccination.[32] To ensure herd immunity, the effects of vaccines and the necessary doses for protection should be explained to the public in detail. Reliable health communication and encouraging the public about vaccination can influence positive health behaviors. Lessons learned from previous epidemics of infectious diseases, such as HIV, H1N1, and SARS, have shown us the importance of reliable sources of information in the fight against infections.

The main strengths of the present study were the large number of participants, which included patients who were COVID-19 positive, as well as the vaccination rates in high-risk pregnancies. The study's main limitation was the short study period.

Conclusion

Vaccine refusal can significantly delay or hinder herd immunity, resulting in more significant rates of morbidity and mortality. Considering the adverse effects of COVID-19 on pregnancy, it is essential to understand pregnant and postpartum women's perceptions toward vaccination to end the pandemic.

Contributors

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, and read and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Evaluation of the Effect of Low-dose Aspirin on the Prevention of Preterm Delivery in Women with a History of Spontaneous Preterm Delivery

Avaliação do efeito da aspirina em baixa dose na prevenção do parto prematuro em mulheres com história de parto prematuro espontâneo

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Abstract

Objective Currently, uteroplacental vascular disorders are considered one of the main mechanisms of spontaneous preterm delivery (PTD). Low-dose aspirin is used to prevent pre-eclampsia, which has a similar mechanism; hence, the present study aimed to investigate the effect of low-dose aspirin on the prevention of PTD in women with a history of spontaneous PTD.

Methods The present pilot randomized clinical trial was conducted on 54 pregnant women in the aspirin group (taking 80 mg daily until the 36th week and classic treatment) and 53 patients in the control group (only receiving classic treatment).

Results Forty-three patients (40%) presented before 37 weeks due to symptoms of PTL. Preterm delivery ($<$ 37 weeks) occurred in 28 patients (26%), and there was no significant difference between the aspirin and control groups (10 patients [19%] and 18 patients [34%], respectively; $p = 0.069$). The time of preterm delivery was early ($<$ 34 weeks) in 6 patients (21%), and its cause was spontaneous labor in 23 patients (82%) which was not significantly different between the two groups ($p > 0.05$). Out of 40 patients with spontaneous labor, 25 patients (63%) had a PTD, which was significantly lower in the aspirin group than in the control group (9 patients [45%] versus 16 patients [80%], respectively; $p = 0.022$).

Conclusion The findings of the present study demonstrated that despite the reduction in the incidence of PTD using low-dose aspirin, the reduction rate was not statistically significant. On the other hand, in patients with spontaneous labor prone to PTD, aspirin was effective in reducing the incidence of PTD.

Keywords
- spontaneous PTL
- PTD
- preterm premature rupture of the membrane
- low-dose aspirin

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Resumo

Objetivo Atualmente, os distúrbios vasculares uteroplacentários são considerados um dos principais mecanismos de parto prematuro espontâneo (PTD). A aspirina em baixa dose é usada para prevenir a pré-eclâmpsia, que tem um mecanismo semelhante; portanto, o presente estudo teve como objetivo investigar o efeito da aspirina em baixa dosagem na prevenção de PTD em mulheres com história de PTD espontâneo.

Métodos O presente ensaio clínico piloto randomizado foi realizado em 54 gestantes do grupo aspirina (tomando 80 mg diários até a 36ª semana e tratamento clássico) e 53 pacientes do grupo controle (somente tratamento clássico).

Resultados Quarenta e três pacientes (40%) apresentaram-se antes de 37 semanas devido a sintomas de PTL. O parto prematuro (< 37 semanas) ocorreu em 28 pacientes (26%) e não houve diferença significativa entre os grupos aspirina e controle (10 pacientes [19%] e 18 pacientes [34%], respectivamente; $p = 0{,}069$). O tempo de parto prematuro foi precoce (< 34 semanas) em 6 pacientes (21%) e sua causa foi trabalho de parto espontâneo em 23 pacientes (82%) que não foi significativamente diferente entre os dois grupos ($p > 0{,}05$). Das 40 pacientes com trabalho de parto espontâneo, 25 pacientes (63%) tiveram PTD, que foi significativamente menor no grupo aspirina do que no grupo controle (9 pacientes [45%] versus 16 pacientes [80%], respectivamente; $p = 0{,}022$).

Conclusão Os achados do presente estudo demonstraram que, apesar da redução na incidência de DPT com o uso de aspirina em baixa dosagem, a taxa de redução não foi estatisticamente significativa. Por outro lado, em pacientes com trabalho de parto espontâneo propensas a PTD, a aspirina foi eficaz na redução da incidência de PTD.

Palavras-chave

- PTL espontâneo
- PTD
- ruptura prematura da membrana
- aspirina em baixa dosagem

Introduction

Preterm labor (PTL) before the 37th week of gestation is the most common cause of worldwide morbidity and mortality in newborns.[1] The prevalence of PTL in developed and developing countries is 5 and 25%, respectively.[2] Preterm labor is responsible for 75% of all cases of neonatal mortality and for 40% of all cases of neurologic neonatal morbidities.[3] Since currently there is no effective medical treatment for termination of the PTL process, the best and most reasonable solution is to identify women at risk and utilize preventive medical interventions.[4]

Despite an intensive bulk of studies on PTL pathophysiology, there is still much controversy on its mechanism. One of the most acceptable theories is bypassing or early stimulation of "parturition complex cascade", known to be responsible for on-time labor triggering.[5–7] Besides, labor is believed to be a proinflammatory event. Preterm labor as an overwhelming inflammatory event occurring earlier in the midtrimester has been reported to be followed by an intraamniotic infection in almost 50% of PTL cases.[8,9]

The most important risk factors for preterm delivery (PTD) are a previous history of PTD, smoking, vaginal bleeding, and preterm premature rupture of the membrane (PPROM).[4] The most important risk factor is a history of previous PTL.[10] There is a bulk of studies that report that placental uterine ischemia plays a crucial role in spontaneous PTL[11–14] and women with a PTL history are at a higher risk of cardiovascular disease in the future.[15,16] These findings indicate that the mechanism of PTL is similar to that of other ischemic placental diseases such as pre-eclampsia. Low-dose aspirin is used to inhibit platelet aggregation and prevent pre-eclampsia.[17]

Due to the similarity between the mechanisms of spontaneous PTL and pre-eclampsia, it has been suggested that low-dose aspirin may also be used to prevent spontaneous PTL. Some studies have performed secondary analyses of data on the effect of low-dose aspirin on the prevention of pre-eclampsia to evaluate the effect of low-dose aspirin on the prevention of PTL. Although some studies have reported the effectiveness of low-dose aspirin in preventing PTL, other studies did not prove it.[18–21] Moreover, a randomized clinical trial was conducted to compare the effect of low-dose aspirin on the incidence of PTL,[2] but its clinical results have not been reported yet. Therefore, it seems that no independent study has been conducted in this field so far, and the results of studies on the effect of low-dose aspirin on the prevention of PTL are secondary analyses in patients with risk factors for pre-eclampsia. Therefore, the present study aimed at evaluating the effect of aspirin on the prevention of PTD in women with a history of preterm delivery.

Methods

The present randomized clinical trial was conducted as a pilot study on pregnant women with a history of PTD who were referred to the Mahdieh and Shohada Tajrish hospitals in Tehran, Iran, in 2019 and 2020. The inclusion criteria consisted of age > 18 years old, singleton pregnancy,

gestational age of 8 to 16 weeks, and a history of spontaneous PTD. The exclusion criteria were the following: twin or multiple pregnancies, history of non-spontaneous PTD due to maternal problems such as pre-eclampsia, HELLP syndrome, or fetal problems such as intrauterine growth restriction (IUGR), taking aspirin for treating other diseases, including vasculitis, lupus, type 1 and 2 diabetes, hypertension kidney problems, and antiphospholipid syndrome. Thrombocytopenia, fetal malformations in the current pregnancy or previous PTD, and simultaneous participation in another trial were other exclusion criteria.

Using the following formula and considering the likely incidence of PTD of 15%, $\alpha = 0.05$, and $d = 0.1$ (10% accuracy), the calculated sample size was 50 people in each group

$$n = \frac{Z_{1-\frac{\alpha}{2}}{}^2 * P(1-P)}{d^2}$$

Considering a patient dropout of 30%, the required sample size for each group increased to 66 patients in each group. Eligible patients were selected via convenience sampling in the order of referral, and after explaining the study method and obtaining written consent, the subjects were enrolled in the study. Utilizing a random number table, the patients were divided into two groups: the intervention group, taking aspirin with a dosage of 80 mg daily, and the control group, without intervention. During the study, 12 patients in the aspirin group and 13 patients in the control group withdrew, and eventually, 54 patients in the aspirin group and 53 patients in the control group completed the study, and their data were analyzed (►**Figure 1**).

Using a form, we collected the data on patients, including age, history of pregnancy (gravidity, parity, history of abortion and stillbirth, number of alive and dead children), etiology for previous spontaneous PTD (spontaneous labor, PPROM), and PTD category based on the fetal age (early: < 34 weeks, late: from 34 to 37 weeks). Then, the patients were randomly divided into two groups. Patients in the aspirin group took an 80 mg tablet, manufactured by Hakim Pharmaceutical Company, Iran, daily and preferably in the evening until the 36th week of pregnancy, in addition to the classic treatment. The control group received only classic treatment for PTL. All patients received the classic treatment, including receiving preventative weekly injections of Proluton (from the 16th to the 36th week). 17-alpha-hydroxyprogesterone caproate 250 mg, also known as Proluton 250 mg, is administered intramuscularly on a weekly basis to inhibit PTL contractions. Routine pregnancy visits were performed for both groups. Moreover, in cases with a cervix length < 25 mm, cervical cerclage or pessary was used. In the presence of PTL symptoms. such as spontaneous labor or PPROM, tocolytic (at 33 weeks or less)[22] and betamethasone (at 37 weeks or less)[23,24] were used if indicated according to available studies. However, at 34 to 37 weeks of gestation, betamethasone was not used if there was an impending delivery or for diabetic mothers. Gestational age at delivery and characteristics of the infant (sex and Apgar scores at minutes 1 and 5), presence of symptoms of PTL, administration of betamethasone, administration of tocolytic agents and its type, PTD cause, infant need for neonatal intensive care unit (NICU) and duration of stay in NICU were also recorded. Finally, the incidence of PTD (in < 37 weeks) and its time and causes were compared between the two groups. IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY, USA) was used for data entry and analysis. Qualitative variables were described using frequency and percentage, and quantitative variables were described using the mean and standard deviation (SD) or median and interquartile range (IQR). The chi-squared test, the Fisher Exact test, the independent t-test, and the Mann-Whitney U test were used to analyze the data. The significance level was set as $p < 0.05$.

All methods used in the present study are based on the principles of Helsinki Human Studies. Patient information will be kept entirely confidential during and after the study. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (Registration code: IR.SBMU.MSP.REC.1398.528) and was registered in the site of the Iranian registry of clinical trials (www.irct.ir) (Registration code: IRCT20191031045289N1).

Results

►**Table 1** compares the two groups, aspirin and control, in terms of the characteristics of the patients. Pessary and cervical cerclage, respectively, were used in 4 patients (4%) and 16 patients (15%), and there was no significant difference between the two groups ($p > 0.05$). Only two stillbirths occurred in the present study, one in the case group and one in the control group. Forty-three patients (40%) presented symptoms of PTL before 37 weeks, which was not significantly different between the aspirin and control groups (21 patients [39%] and 22 patients [42%], respectively; $p = 0.782$). Among them, the cause of referral was spontaneous labor in 40 patients (93%) (20 patients in each group) and PPROM in 3 patients (7%) (1 patient in the aspirin group and 2 patients in the control group). Among all patients, a betamethasone injection was applied in 40 patients (37%), and there was no significant difference between the aspirin group and control group (18 patients [33%] versus 22 patients [42%]; $p = 0.382$). In three patients, betamethasone was not used due to impending delivery or maternal diabetes. In general, tocolytic agents were used in 16 (40%) patients, that is: magnesium sulfate in 8 patients, indomethacin in 7 patients, and nifedipine in 1 patient. There was no significant difference between the aspirin and control groups in terms of the frequency of tocolytic administration (6 patients [11%] versus 10 patients [19%], respectively; $p = 0.261$). Preterm delivery occurred in 28 patients (26%), and there was no significant difference between the aspirin group and the control group (10 patients [19%] versus 18 patients [34%]; $p = 0.069$). The time of PTD was early in 6 patients (21%), and its cause was spontaneous labor in 23 patients (82%), which was not significantly different between the aspirin group and control group (►**Table 2**) ($p > 0.05$). Out of 40 patients with spontaneous labor, despite using methods for preventing PTL, 25 patients (63%) had PTD,

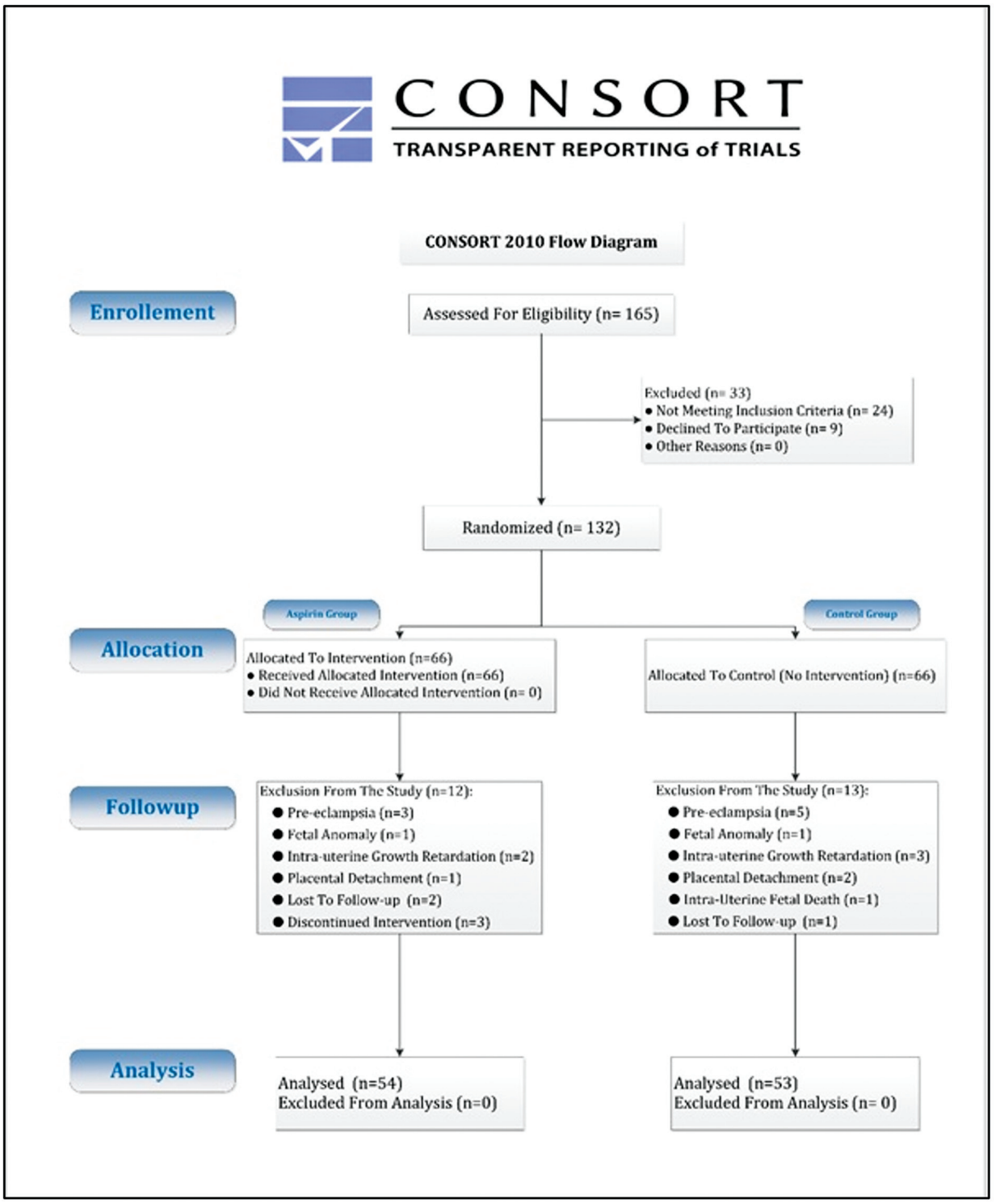

Fig. 1 Consort algorithm of our study.

which was significantly lower in the aspirin group than in the control group ($p = 0.022$) (►**Table 3**).

In 16 patients receiving tocolytic agents, the IQR and median duration of prolongation of pregnancy were 1 to 7 weeks and 3.5 weeks, respectively. The effect of tocolytic factors on the prolongation of pregnancy in the aspirin group was significantly higher than that in the control group (7 weeks versus 2 weeks, respectively; $p = 0.007$). ►**Table 4** also presents the characteristics of infants.

Discussion

In the present study, we aimed to assess the preventive effect of low-dose aspirin on PTL in pregnant women with a history of PTD. Although not being statistically significant, the findings of the present pilot study revealed that low-dose aspirin prescription in women with a history of PTD reduced the incidence of PTD. Moreover, we realized that in patients with a history of spontaneous PTD, receiving low-dose aspirin

Table 1 Comparison of patient characteristics between the two groups

Variables		Aspirin group ($n = 54$)	Control group ($n = 53$)	*p-value*
Age (years old)	Mean ± SD	31 ± 5	30 ± 5	0.134†
Gravity	2	21 (39%)	23 (44%)	0.891‡
	3-4	25 (46%)	23 (44%)	
	≥5	8 (15%)	7 (12%)	
Abortion history	None	34 (63%)	34 (64%)	0.701‡
	1	9 (17%)	12 (23%)	
	2	7 (13%)	5 (9%)	
	≥3	4 (7%)	2 (4%)	
Children count	None	9 (17%)	11 (21%)	0.667‡
	1	31 (57%)	30 (56%)	
	≥2	14 (26%)	12 (23%)	
Dead child history	No	37 (68%)	37 (70%)	0.609‡
	Yes	17 (32%)	16 (30%)	
Previous PTD cause	Spontaneous labor	48 (89%)	42 (79%)	0.172‡
	PPROM	6 (11%)	11 (21%)	
Time of previous PTD	Early (< 34 weeks)	31 (57%)	28 (53%)	0.634‡
	Late (34–37 weeks)	23 (43%)	25 (47%)	

Abbreviations: PTD: preterm delivery; PPROM: preterm premature rupture of membrane; SD: standard deviation.
†Independent t test
‡Chi-squared test;

Table 2 Comparison of preterm delivery characteristics between the two groups

	Aspirin group ($n = 10$)	Control group ($n = 18$)		*p-value*†
PTD based on fetal age	Early (< 34 weeks)	2 (20%)	4 (22%)	1.000
	Late (34–37 weeks)	8 (80%)	14 (78%)	
PTD etiology	Spontaneous labor	7 (70%)	16 (89%)	0.315
	PPROM	3 (30%)	2 (11%)	

Abbreviations: PTD: preterm delivery; PPROM: preterm premature rupture of membrane.
†Fisher Exact test;

Table 3 Comparison of preterm delivery characteristics in patients referred due to spontaneous labor between the two groups

	Aspirin group ($n = 20$)	Control group ($n = 20$)	*p-value*
Betamethasone administration	17 (85%)	20 (100%)	0.231*
Tocolytic agents administration	6 (30%)	8 (40%)	0.507**
PTD	9 (45%)	16 (80%)	0.022**

Abbreviation: PTD: Preterm delivery.
*Fisher Exact test
**Chi-squared test

significantly reduced PTD if the patient experienced spontaneous labor in the current pregnancy.

In a study by Hoffman et al. on pregnant women from low- to middle-income countries, low-dose aspiring showed reduced PTD prior to 37 weeks, in addition to decreased perinatal mortality.[25] In contrast, in a study published in 2022 encompassing 608 pregnant women with a history of spontaneous preterm birth, low-dose aspiring did not demonstrate a significant reduction in preterm birth.[26]

In studies investigating low-dose aspirin to prevent preeclampsia, a decrease in PTL is also reported. Nevertheless,

Table 4 Comparison of neonatal characteristics between the two groups

		Aspirin group ($n = 54$)	Control group ($n = 53$)	*p-value*
Newborn sex	Girl	30 (56%)	35 (66%)	0.276†
	Boy	24 (44%)	18 (34%)	
Apgar 1st minute	≤6	0 (0%)	1 (2%)	0.482‡
	7–8	6 (11%)	8 (15%)	
	9	48 (89%)	44 (83%)	
Apgar 5th minute	≤8	0 (0%)	1 (2%)	0.641‡
	9	5 (9%)	6 (11%)	
	10	49 (91%)	46 (87%)	
NICU admission		10 (19%)	17 (32%)	0.106‡
		Aspirin group ($n = 10$)	Control group ($n = 17$)	*p-value*
NICU admission cause	Prematurity, RDS or TTN	7 (70%)	16 (94%)	0.128‡
	Others	3 (30%)	1 (6%)	
NICU stay	1–2 days	4 (40%)	9 (53%)	0.849‡
	> 3 days	6 (60%)	8 (47%)	

Abbreviations: NICU, neonatal intensive care unit; RDS: respiratory distress syndrome; TTN: transient neonatal. tachypnea
†Fisher Exact test
‡Chi-squared test

the cause of PTL has not been reported generally, and apparently, a decrease in PTL could be due to the decrease in the incidence of pre-eclampsia as one of the important causes of PTL.[27] However, part of the reduction in the incidence of PTD reported in these studies may be attributed to aspirin use. On the other hand, currently published studies on the role of aspirin in the prevention of PTD are mainly secondary analyses of studies and clinical trials on aspirin use for controlling pre-eclampsia, some of which reported beneficial effects of aspirin in the prevention of PTD; other studies did not prove that. Allshouse et al. conducted a reanalysis of data obtained from a clinical trial that investigated the effects of aspirin on women at high risk for pre-eclampsia.[19] They reported that high-risk women with pre-eclampsia who had been receiving aspirin had a reduced rate of PTL due to spontaneous labor or PPROM compared with a placebo group; however, the difference was not statistically significant. Van Vliet et al. conducted a meta-analysis of the data of participants in studies investigating the effect of antiplatelet agents on reducing pre-eclampsia and reported that women who took antiplatelet agents, as compared with a placebo or no treatment group, had a lower risk for PTL in < 37 and 34 weeks of gestation.[20] Although their results indicated the beneficial effects of antiplatelet agents on reducing spontaneous PTL in women at risk for preeclampsia, it may not be effective in cases where such risk factors are not present. Visser et al. also conducted a multicenter randomized clinical trial to determine the effect of low-dose aspirin on preventing spontaneous PTL in women with a history of PTL.[2] Nevertheless, it seems that the clinical results of the mentioned study have not been published yet. Finally, Andrikopoulou et al. conducted a secondary analysis of data obtained from a randomized clinical trial on the effect of low-dose aspirin on the prevention of pre-eclampsia in low-risk nulliparous women and reported a significant reduction in spontaneous PTL in < 34 weeks. However, the incidence of PTL from the 34th to the 37th week and spontaneous PTL in < 37 weeks were not statistically significant.[21]

The results of the aforementioned studies suggest that, in some cases, low-dose aspirin may be effective in preventing spontaneous PTL, although those studies were secondary analyzes in women with risk factors for pre-eclampsia. Although our study, an independent study on women at risk for PTL, was associated with a reduced incidence of PTD in the aspirin group, there was no statistically significant difference. On the other hand, the median duration of prolongation of pregnancy was significantly higher in patients receiving tocolytic agents in the aspirin group. However, because the incidence of PTD was significantly lower in the aspirin group in a subgroup of patients who presented with spontaneous labor in the current pregnancy and were at risk for PTD, it may not be significant in all patients due to the small sample size.

No independent study has been conducted to investigate the effect of low-dose aspirin on the prevention of spontaneous PTL, and studies in this field have been the secondary analyses of research conducted on women with risk factors for pre-eclampsia. The latest recommendations of the American Association of Obstetricians and Gynecologists also indicate that currently, due to lack of sufficient evidence, prophylactic administration of low-dose aspirin has not been approved for the prevention of conditions such as PTL and stillbirth, among others, in the absence of risk factors for pre-eclampsia.[28] Hence, as the strength of our study, it was conducted as an independent randomized clinical trial on the effect of low-dose aspirin for controlling PTD due to

spontaneous labor or PPROM. However, our results showed that low-dose aspirin is not effective in preventing spontaneous PTD in women with a previous history of PTD caused due to spontaneous labor or PPROM.

However, the small sample size, which was the most significant limitation of our study, may have provided statistically insignificant results. In addition, due to not using a placebo in our research, there was no blinding. Therefore, it is recommended to conduct extensive multicenter studies with larger sample sizes and utilize a placebo.

Despite our effort to provide a rationale for using low-dose aspirin in PTL, there were some limitations to the present study. The main limiting factor in the present study is the small sample size, eclipsing its representativeness. Further studies are needed to evaluate the effectiveness of low-dose aspirin in larger populations. Besides, as we were concerned about the term "proven therapy" as defined in the Helsinki declaration, we refused to expose patients in the control group to placebo drugs.[29] Besides, since pregnancy is a very delicate and sensitive issue, most patients would have refused to use a "a not-knowing-what-it-is drug". Recently, there have been some concerns regarding the placebo usage even in the normal population.[29,30] Further studies are needed to assess the placebo effect in a larger population of PTL cases.

Conclusion

The findings of the present study showed that despite the reduction in the incidence of PTD using low-dose aspirin, the reduction rate was not statistically significant. On the other hand, in patients with spontaneous labor prone to PTD, aspirin was effective in reducing the incidence of PTD. Therefore, conducting more extensive studies with larger sample sizes may produce significant results.

Contributions

Mirzamoradi M. contributed to the study design and methodology. Dehghani Z. supervised the whole process and modified it. Bakhtiyari M. contributed to manuscript provision, data analysis, and the submission process. Mohammadi M. and Khavandegar A. contributed to the writing and draft editing. All authors have read and approved the manuscript.

Conflict of İnterests

The authors have no conflict of interests to declare.

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Five-year Contraceptive Use of 52-mg Levonorgestrel Releasing Intrauterine System in Young Women, Menstrual Patterns, and New Contraceptive Choice

Cinco anos de uso contraceptivo do sistema intrauterino liberador de levonorgestrel 52 mg em mulheres jovens, padrões menstruais e nova escolha contraceptiva

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Abstract

Objective To evaluate the continuation rates of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) during the first 5 years of use, reasons for its discontinuation, bleeding patterns, and new contraceptive choice after the 5th year, in adolescents and young women.

Methods The present study was a 5-year prospective cohort conducted in a Family Planning Service of a tertiary hospital in Brazil. We selected 100 healthy women between 15 and 24 years old who used 52-mg LNG-IUS for contraception. The clinical follow-up of these women took place from June 2017 to December 2022. The study evaluated the continuation rates of the method, reasons for its discontinuation, bleeding patterns, and new contraceptive choice after the 5th year. Continuous data were reported as mean ± standard deviation (SD) and range (minimum-maximum). Categorical variables were described as percentages.

Results The continuation rates of LNG-IUS were 89.1% (82/92), 82.9% (72/87), 75.3% (64/85), 70.5% (60/85), and 64.2% (54/84) in the 1st, 2nd, 3rd, 4th, and 5th years of use, respectively. The main reason for discontinuation was acne (11/30). Amenorrhea rates were 50, 54.1, 39, 35.7, and 51.8% at 12, 24, 36, 48, and 60 months, respectively. All patients who completed the study and needed contraception after the 5th year opted for long-acting contraceptive methods (LARC).

Conclusion The LNG-IUS showed high continuation rates in adolescents and young women in the first 5 years of use. Most patients who completed the study chose a LARC method after the 5th year.

Keywords
- levonorgestrel intrauterine system
- adolescents
- amenorrhea
- menstruation
- contraception
- long-acting reversible contraception

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Resumo

Objetivo Avaliar as taxas de continuação do sistema intrauterino liberador de levonorgestrel (SIU-LNG) 52 mg durante os primeiros 5 anos de uso, razões de sua descontinuação, padrões de sangramento e nova escolha contraceptiva após o 5° ano, em adolescentes e mulheres jovens.

Métodos O estudo foi uma coorte prospectiva de 5 anos realizada em um Serviço de Planejamento Familiar de um hospital terciário no Brasil. Selecionamos 100 mulheres saudáveis entre 15 e 24 anos que usaram o SIU-LNG 52 mg para contracepção. O acompanhamento clínico dessas mulheres ocorreu de junho de 2017 a dezembro de 2022. O estudo avaliou as taxas de continuação do método, razões de sua descontinuação, padrões de sangramento e nova escolha contraceptiva após o 5° ano. Os dados contínuos foram relatados como média ± DP e intervalo (mínimo-máximo). As variáveis categóricas foram descritas como porcentagens.

Resultados As taxas de continuação do SIU-LNG foram 89,1% (82/92), 82,9% (72/87), 75,3% (64/85), 70,5% (60/85) e 64,2% (54/84) no 1°, 2°, 3°, 4° e 5° anos de uso, respectivamente. O principal motivo de descontinuação foi a acne (11/30). As taxas de amenorreia foram de 50, 54,1, 39, 35,7 e 51,8% aos 12, 24, 36, 48 e 60 meses, respectivamente. Todas as pacientes que completaram o estudo e necessitaram de contracepção após o 5° ano optaram por métodos contraceptivos de longa duração (LARC).

Conclusão O SIU-LNG apresentou altas taxas de continuação em adolescentes e mulheres jovens nos primeiros 5 anos de uso. A maioria das pacientes que completou o estudo escolheu um método LARC após o 5° ano.

Palavras-chave

- sistema intrauterino de levonorgestrel
- adolescentes
- amenorreia
- menstruação
- contracepção
- contracepção reversível de longa duração

Introduction

Teenage pregnancy is a severe global health problem, especially in low- and middle-income countries.[1] In most countries, the median age at first intercourse is around 17 years old. By 15 years of age, ~ 15% of females had had intercourse; by 18 years, ~ 60%, and by 20 years of age, ~ 80%.[2] In adolescents, contraceptive use and sexual activity can affect the pregnancy rate.[3] Thus, the prescription of contraceptive methods that are acceptable and effective is specially necessary for this group.

The use of long-acting contraceptive methods (LARC) in adolescents could lead to the prevention of pregnancies at an early age and the spacing between them, avoiding unintended pregnancies and abortions.[4] Intrauterine devices (IUDs) are safe for these women, with meager rates of complications such as pelvic inflammatory disease (PID) and uterine perforation.[5,6] Despite the safety of IUDs in adolescents and nulliparous women and recommendations of many different medical societies for their use, they are still underused by women < 20 years old.[7–9] Between 2017 and 2019, 38.7% of women aged 15 to 19 years old in the United States were currently using contraception. The most common contraceptive method used by these women is contraceptive pills, and it was estimated that only 5.8% of young women had used LARC.[10]

Several studies have demonstrated high continuity rates for using the 52-mg levonorgestrel-releasing system (LNG-IUS) among young women.[11–13] Counseling candidates about possible bleeding patterns and adverse effects could lead to lower IUD discontinuation rates.[11] Contraceptive counseling should include anticipatory guidance for adolescents and their parents regarding possible menstrual changes (such as lighter bleeding, spotting, or amenorrhea), side effects (such as acne, headaches, nausea, breast tenderness, and mood changes), and noncontraceptive benefits such as management of irregular or abnormal uterine bleeding and treatment of dysmenorrhea.[14]

Regarding the side effects of LNG-IUS, some studies demonstrated that participants aged between 16 and 35 years old at enrollment were significantly more likely to report new or worsening acne, dyspareunia, pelvic pain, and dysmenorrhea.[15]

Barriers to using LARC by adolescents include patients' lack of familiarity with or understanding of the methods, potentially high cost of initiation, lack of access, low parental acceptance, and obstetrician-gynecologists' and other health care providers' misconceptions about the safety of LARC use in adolescents.[16]

The present study aimed to evaluate continuation rates, bleeding patterns, reasons for its continuation, and new contraceptive choices in the 5th year of use of the 52-mg LNG-IUS in adolescents and young women.

Methods

The present study was a 5-year prospective cohort conducted at the Family Planning Service, Department of Obstetrics and Gynecology, Hospital das Clínicas of the Universidade Federal de Minas Gerais (UFMG, in the Portuguese acronym), Belo Horizonte, state of Minas Gerais, Brazil, from June 2017 to December 2022. The project was approved by the Research Ethics Committee of UFMG (protocol 65138816.8.0000.5149). Participants were women who sought the Family Planning

service for 52-mg LNG-IUS insertion for contraception or treatment of gynecological conditions. All women who agreed voluntarily to participate in the study signed an Informed Consent Form (ICF). Participants < 18 years old provided informed assent, while their parents provided the ICF. The present study is the continuation of a previously published paper with a 5-year follow-up.[17]

The study was conducted with nulliparous or parous women aged between 15 and 24 years old who were eligible for the use of LNG-IUS, according to the World Health Organization (WHO) medical eligibility criteria for contraceptive use. The exclusion criteria were: uterine sounding < 5 cm; cervical cytological abnormalities in the last 18 months; uterine cavity distortion (any congenital or acquired uterine abnormality distorting the uterine cavity in a manner that is incompatible with IUD insertion); current breast cancer, endometrial cancer, or cervical cancer (awaiting treatment); recent history of pelvic inflammatory disease or untreated genitourinary tract infection; abnormal uterine bleeding of unknown cause; < 6 weeks postpartum or postabortion.

Women were applying for the use of LNG-IUS for planning counseling. They accepted the LNG-IUS as a contraceptive method after an explanation of all contraceptive methods available. They answered a questionnaire containing information on education level, parity, previous menstrual pattern, and previous use of contraception. A gynecologist performed a clinical examination. It was not necessary to perform a gynecological ultrasound prior to the insertion of the devices.

The insertion of the 52-mg LNG-IUS was performed up to the 7th day of the menstrual cycle by an obstetric gynecologist and/or a trained resident physician. A urinary or blood pregnancy test was used to exclude pregnancy if the woman was not using an effective contraceptive method. For patients using any effective method of contraception, the LNG-IUS was inserted at any time of the menstrual cycle. According to the service's routine protocol, a transvaginal ultrasound was performed to verify the LNG-IUS positioning 30 days after insertion. The LNG-IUS was considered malpositioned when described as partially expelled, rotated, embedded in the myometrium, or located in the lower uterine segment or cervix.

Follow-up visits occurred every year up to 5 years of use. The continuation rates of the method, reasons for its discontinuation, and bleeding patterns were evaluated. The menstrual pattern was self-reported and classified according to the following definitions. Menstrual cycles within 24-32 days, with bleeding lasting no more than 5 days, were considered regular cycles. Amenorrhea is the absence of uterine bleeding for at least 3 months. Spotting was considered occasional and unpredictable bleeding in small amounts. When it was impossible to return to face-to-face consultations, the women were contacted and questioned via telephone or social networks. At the end of the 5th year of follow-up, patients were contacted by telephone to choose a new contraceptive method since, in Brazil, extended use of the 52-mg LNG-IUS has not yet been approved by the National Health Surveillance Agency (ANVISA).

Continuous data were reported as mean ± standard deviation (SD) and range (minimum-maximum). Categorical variables were described as percentages.

Results

We performed 52-mg LNG-IUS insertion in 100 adolescents and young women. The characteristics of the participants are presented in ►**Table 1**. This group's mean (± SD) age was 22 ± 1.9 years old (range 16 to 24 years old). Most participants were nulliparous (86%). The main reason for the placement of LNG-IUS was contraception (96%). Other reasons for LNG-IUS placement were: treatment of dysmenorrhea (1%), desire for amenorrhea (1%), history of thrombosis (1%), and others (1%). The main contraceptive method previously used by these women was combined hormonal contraceptives (60%). Other contraceptive methods used by these patients were progestin-only pills (4%), combined hormonal injectables (6%), lactational amenorrhea (2%), vaginal rings (1%), condoms (18%), or none (9%).

The only complication observed during the insertion of LNG-IUS was vasa-vagal responses (such as dizziness, nausea, and vomiting) in 7% of women. Major complications, such as uterine perforation or infection, did not occur. Five insertions were guided by ultrasound. Ninety-two LNG-IUS

Table 1 Demographic and gynecological variables ($n = 100$)

Variables	Total
Age (years old)	22.2 ± 1.9
Minimum–Maximum	16.0–24.0
Race	
White	65(65.0)
Not white	35(35.0)
Weight (kg)	60.5 ± 11.3
Height (cm)	1.62 ± 0.1
BMI (kg/m^2)	
Low weight	4 (4.0)
Normal	75 (75.0)
Overweight	14 (14.0)
Obese	5 (5.0)
Parity	
Nulliparous	86 (86.0)
Previous cesarean	1 (1.0)
Previous normal delivery	12(12.0)
Any prior abortion	1 (1.0)
Education	
Less than high school degree	8 (8.0)
High school degree	14 (14.0)
Some college or higher	78 (78.0)
Uterine sounding	7.26 ± 0.74

Abbreviations: BMI, body mass index.
Data are presented as *n* (%) or mean ± SD.

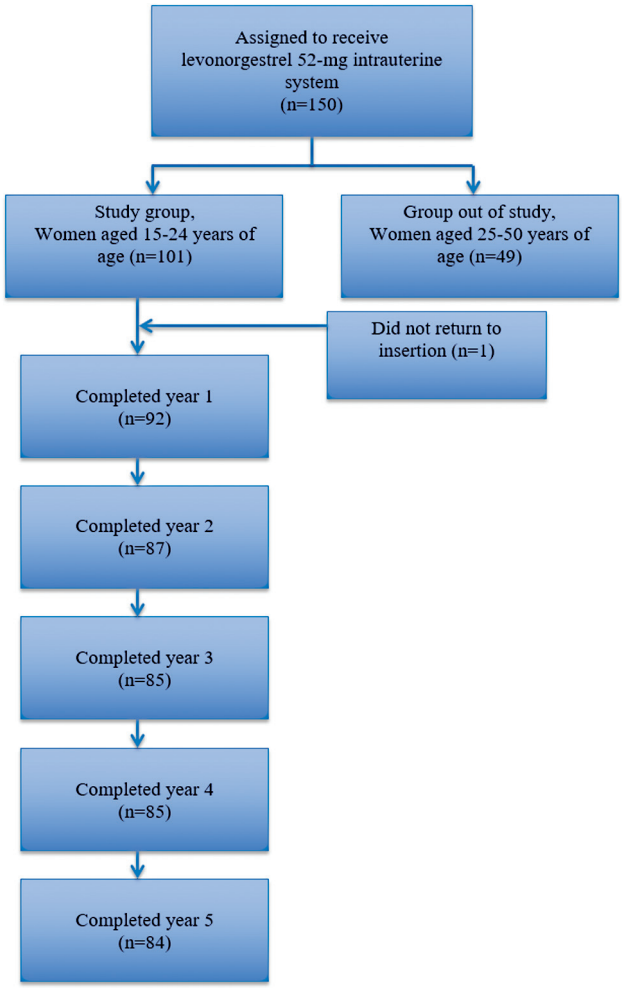

Fig. 1 Participants flowchart.

Table 2 Continuation rates of 52-mg levonorgestrel-releasing intrauterine system in 5-year follow-up of young women ($n = 100$)

Time (years)	Numbers of removals at the end of the year	Losses	Continuation rates (%)
1	10	8	89.1 (82/92)
2	15	13	82.8 (72/87)
3	21	15	75.3 (64/85)
4	24	15	70.5 (60/85)
5	30	16	64.2 (54/84)

were well positioned, 6 were poorly positioned, and 2 patients did not return for reassessment after insertion. Patients with poorly positioned IUS had their IUS repositioned, or a new device was inserted. Participants' follow-up over the first 5 years of the present trial is presented in the Participants Flowchart (►**Fig. 1**).

As shown in ►**Table 2**, among those who were not lost to follow-up, the 52-mg LNG-IUS continuation rates were 89.1% (82/92), 82.8% (72/87), 75.3% (64/85), 70.5% (60/85), and 64.2% (54/84) in the 1st, 2nd, 3rd, 4th, and 5th years of use, respectively.

Menstrual patterns through the 5 years of observation are presented in ►**Figure 2**. Amenorrhea rates were 50, 54.1, 39, 35.7, and 51.8% at 12, 24, 36, 48, and 60 months after insertion. Spotting rates varied during the 5 years of use (20.8, 16.7, 26.6, 21.7, and 14.8%, respectively). Some patients who reported spotting in the 4th year had amenorrhea in the 5th year, and patients with amenorrhea were less likely to discontinue SIU-LNG use in the last year.

Percentage of different bleeding patterns presented by adolescents and young women using 52-mg LNG-IUS during 12, 24, 36, 48, and 60 months of follow-up. In total, 30 participants stopped using LNG-IUS either because of

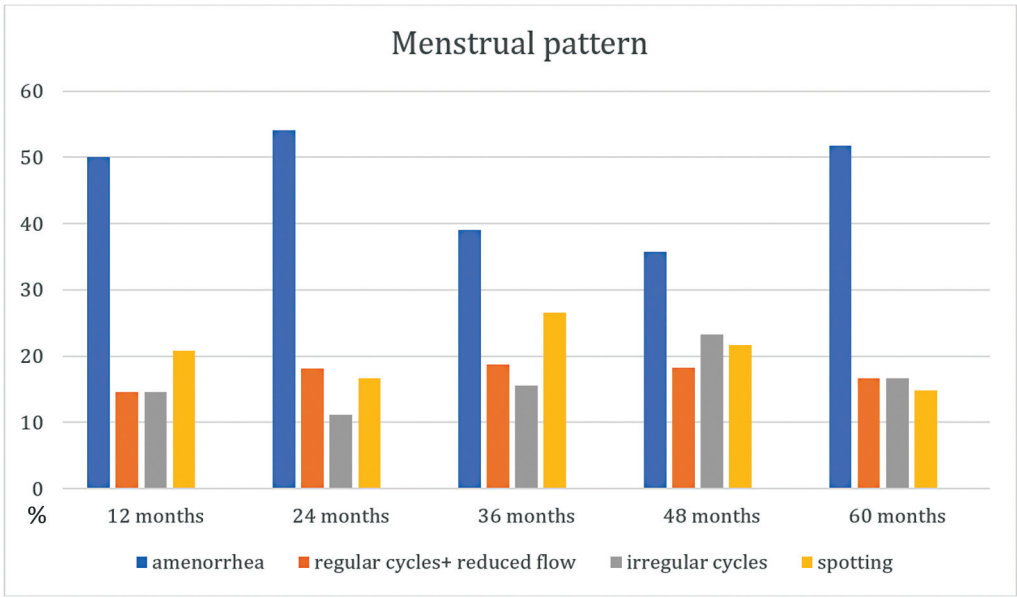

Fig. 2 Menstrual patterns in females using a 52-mg levonorgestrel-releasing intrauterine system at 5-year follow-up.

Table 3 Reasons for discontinuation of the 52-mg levonorgestrel-releasing intrauterine system among young adults in 5 years of follow-up

Time (months)	Reason
1	expulsion
1	bicornuate utero
1	poor positioning of IUS
2	expulsion
4	dyspareunia
5	recurrent candidiasis
5	poor positioning of IUS
6	ruptured ovarian cyst
6	acne
11	acne, loss of hair
15	acne
17	acne
19	dysmenorrhea
21	expulsion
22	irregular uterine bleeding
24	depressive symptoms
27	acne
27	abdominal pain
32	depressive symptoms
32	acne, dysmenorrhea
35	get free of hormones
40	loss of hair; dyspareunia
40	acne
45	previous venous trombosys
46	acne
49	desire to conceive
50	acne
54	acne, loss of hair
54	acne
58	anxiety

Abbreviation: IUS, intrauterine system.

adverse events or a desire to become pregnant. The reasons for the discontinuation of 52-mg LNG-IUS and the time at which they occurred are presented in ►**Table 3**. The main reason for discontinuation was acne (11/30).

At the end of the 5th year, 23 patients chose extended use of 52-mg LNG-IUS, 24 chose to insert a new 52-mg LNG-IUS, three chose to change to 19-mg LNG-IUS, and 2 chose to insert a copper intrauterine device. Two patients chose not to use any contraceptive methods because they were without a male partner (►**Table 4**).

Table 4 Methods selected by young women after the 5th year of using the 52-mg levonorgestrel-releasing intrauterine system ($n = 54$)

Method selected	n
Insertion of new 52-mg levonorgestrel-releasing intrauterine system	24
Extended-use of 52-mg levonorgestrel-releasing intrauterine system	23
19-mg levonorgestrel-releasing intrauterine system	3
Copper intrauterine device	2
None	2

Discussion

The present prospective cohort study describes continuation rates, menstrual patterns, and reasons for discontinuation of 52-mg LNG-IUS among Brazilian adolescents and young adults and new contraceptive choices after the 5th year.

There was no device insertion failure, and in case of difficulty, the devices were inserted guided by ultrasound. The authors believe it is important to emphasize that it is unnecessary to perform an ultrasound prior to device insertion since the incidence of uterine malformations in the population is low. In our study, no patient had a previous ultrasound, and only one patient had a uterine malformation identified on the ultrasound performed after insertion. Similar to several previous studies, there were no serious complications such as ectopic pregnancy, pelvic inflammatory disease, or uterine perforation.[5,6]

Our study found high LNG-IUS continuation rates among young women. Among those women who were not lost to follow-up, the 52-mg LNG-IUS continuation rates were 89.1% (82/92), 82.8% (72/87), 75.3% (64/85), 70.5% (60/85), and 64.2% (54/84) in the 1st, 2nd, 3rd, 4th, and 5th years of use, respectively. Continuation rates for IUDs are generally higher compared with other contraceptive methods for women aged $\leq$ 25 years old. A previous systematic review showed that the 12-month continuation rate of IUD users was 86.5% in adolescents and young women.[18] A retrospective cohort that evaluated continuation rates of the 52-mg LNG-IUS in the general population found continuation rates for the entire group of 85, 77, 70, 64, and 58 per 100 women years at 1, 2, 3, 4, and 5 years after insertion, respectively.[11]

The main reason for the discontinuation of LNG-IUS in this group was acne, which contrasts with previous studies.[6,11,15] Younger patients are more likely to report acne onset or worsening, possibly due to the higher incidences of acne in this age group.[15,19] In addition, our study's patients who had previously used oral contraceptives were more likely to report worsening acne (RR 1.68). Furthermore, progestin contraceptive therapies have also been associated with acne development. As suggested by previous studies, the levonorgestrel intrauterine device may exacerbate inflammatory acne.[20,21] However, there was no questioning or classification of the patient's acne before the insertion of the method.

The discontinuation rate due to irregular bleeding was extremely low (only 1 patient), and most patients had favorable bleeding patterns during the 5-year follow-up. Amenorrhea was the predominant bleeding pattern throughout the 5 years.

Amenorrhea rates were 50, 54.1, 39, 35.7, and 51.8% at 12, 24, 36, 48, and 60 months after insertion. The increase in the amenorrhea rate is justified by the fact that some patients who reported spotting in the 4th year had amenorrhea in the 5th year, and patients who had amenorrhea were less likely to discontinue SIU-LNG use in the last year. This menstrual pattern coincides with descriptions in the literature.[22]

The expulsion rate in our study was 2.2% at 12 months and 3.6% after an overage follow-up of 60 months. This is consistent with other studies supporting that younger women are less likely to experience expulsion than older women.[6,23]

It is important to observe that all women who needed contraception after the 5th year opted to maintain a LARC method. Because of the high risk of unintentional pregnancy, adolescents need highly effective contraceptive methods.

A criticism of the methodology used in the present study is the subjective evaluation of blood loss, so we cannot assure that the menstrual pattern was correctly described. Another problem is that we did not question acne presence before SIU-LNG insertion.

Teenagers and young women are more likely to request premature discontinuation of their IUDs for contraception.[6] Researchers believe that having a trained team capable of answering frequently asked questions from patients, as well as treating side effects, could lead to a reduction in device discontinuation rates. In our study, patients were instructed to contact the main researcher at any time.

The strengths of our study include data collection by a single investigator throughout the five-year follow-up period, as well as lower loss (16%) to follow-up during this period. All patients had a contact telephone number for the main researcher during the entire follow-up period of the research, which may have positively interfered with the low loss of follow-up.

The data from the present study contribute to reaffirming the safety of LNG-IUS in young patients, as well as the high continuation rate during 5-year use. Special attention should be given to counseling and treatment of adverse effects, especially acne.

Conclusion

The LNG-IUS should be routinely offered to young women as a safe and effective contraceptive option. The LNG-IUS showed high continuation rates in adolescents and young women in the first 5 years of use. Most patients had a favorable menstrual pattern with the use of 52-mg LNG-IUS. Young patients should be counseled about side effects, especially acne. Most patients who completed the study chose a LARC method after the 5th year.

Contributions

ECFO conceived the study, performed the experiments, analyzed data, and wrote the paper. ALLR conceived the study, analyzed data, and wrote the paper.

Conflict of Interests

The authors have no conflict of interests to declare.

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Adolescent Female Victims of Sexual Violence: Analysis of Loss of Follow-up after Emergency Care and Outpatient Follow-up

Meninas adolescentes vítimas de violência sexual: Análise da falta de atendimento de emergência e seguimento ambulatorial

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Abstract

Objective To assess the loss to follow-up after emergency care and during 6-months of outpatient follow-up, and the associated variables, among adolescent sexual violence survivors.

Methods This is a retrospective study with review of the medical records of 521 females, aged 10 to 18 years, who received emergency care in a referral service in São Paulo, Brazil. The variables were sociodemographic; personal history; characteristics of abuse, disclosure, and reactions triggered after abuse (physical and mental disorders as well as social changes), psychotropic prescription needs, and moment of abandonment: after emergency care and before completing 6 months of outpatient follow-up. To compare groups of patients lost to follow-up at each time point, we used the Chi-square and Fisher exact tests followed by multiple logistic regression with stepwise criterion for selection of associated variables. We calculated the odds ratio with confidence interval (OR, CI 95%). The level of significance adopted was 5%.

Results A total of 249/521 (47.7%) adolescents discontinued follow-up, 184 (35.3%) after emergency care and 65 (12.4%) before completing outpatient follow-up. The variables of living with a partner (OR = 5.94 [CI 95%; 2.49–14.20]); not having a religion (OR = 2.38 [CI 95%;1.29–4.38)]), having a Catholic religion [OR = 2.11 (CI 95%; 1.17–3.78)]; and not disclosing the abuse [OR = 2.07 (CI 95%; 1.25–3.44)] were associated with loss to follow-up after emergency care. Not needing mental disorder care (OR = 2.72 [CI 95%; 1.36–5.46]) or social support (OR = 2.33 [CI 95%; 1.09–4.99]) were directly associated with loss to outpatient follow-up.

Keywords
- loss to follow-up
- adolescence
- rape
- sexual violence
- retrospective study

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Conclusion Measures to improve adherence to follow-up should be aimed at adolescents who live with a partner and those who do not tell anyone about the violence.

Resumo

Objetivos Avaliar a perda de seguimento de adolescentes vítimas de violência sexual após o atendimento de emergência, durante o seguimento ambulatorial e as variáveis associadas.

Métodos Estudo retrospectivo com a revisão de prontuários de 521 mulheres de 10 a 18 anos, que buscaram atendimento de emergência em um serviço de referência em São Paulo, Brasil. As variáveis foram sociodemográficas; antecedentes pessoais; características do abuso, atitude de revelação e reações desencadeadas após o abuso (distúrbios físicos, mentais e mudanças sociais), necessidades de prescrição de psicotrópicos e momento do abandono: após atendimento de emergência e antes de completar 6 meses de seguimento ambulatorial. Para comparar os grupos de perda de seguimento em cada momento, foram utilizados os testes do qui-quadrado e exato de Fisher, seguidos de regressão logística múltipla com critério *stepwise* para seleção das variáveis associadas. Calculamos a razão de probabilidade com intervalo de confiança (RP, IC 95%). O nível de significância adotado foi de 5%.

Resultados Um total de 249 (47,7%) das adolescentes descontinuaram o acompanhamento, 184 (35.3%) após o atendimento de emergência e 65 (12.4%) antes de completar o seguimento ambulatorial. As variáveis de viver com companheiro [RP = 5,94 (IC 95%; 2,49–14,20]; não ter religião [RP = 2,38 (IC 95%;1,29–4,38)], ter religião católica [RP = 2,11 (IC 95%; 1,17–3,78)] e não revelar o abuso [RP = 2,07 (IC 95%; 1,25–3,44)] foram associadas à perda de seguimento após o atendimento de emergência. Não necessitar de cuidados de saúde mental (RP = 2,72 [IC 95%; 1,36–5,46]) ou apoio social (RP = 2,33 [IC 95%; 1,09–4,99]) foram as variáveis associadas à perda do seguimento ambulatorial.

Conclusão Medidas para melhorar a adesão ao seguimento devem ser direcionadas às adolescentes que vivem com parceiro e às que não revelam a violência sofrida.

Palavras-chave
- perda de seguimento
- adolescência
- estupro
- violência sexual
- e2222ggfthstudo retrospective

Introduction

Global data collected in a systematic review showed that 35.6% of women aged 15 years and older reported having experienced physical and/or sexual partner violence, or sexual violence by a non-partner; this led the World Health Organization (WHO) to declare that "violence against women is a public health problem of epidemic proportions".[1] The WHO highlighted that if the same measures of sexual violence (SV) were measured together, during childhood and adulthood, in all its forms and by all perpetrators (partners and non-partners), the prevalence rates would be much higher.[1] Other publications have shown a high prevalence of SV against girls and female adolescents.[2,3] In Brazil, 179,278 victims of sexual violence aged 0 to 19 years were reported in the period from 2017 to 2020, most of them females.[4]

A couple of outcomes after SV against women are unwanted pregnancy (UP) and sexually transmitted infections (STIs).[1–3] A prospective study with adolescents aged 13 to 17 years described that, after 4 to 5 months of sexual aggression, 4/105 (4%) adolescents had become pregnant, 14/119 (12%) had a STI, and 9/107 (8%) reported new sexual assault.[5] Unwanted pregnancy leads to increased rates of unsafe abortion and its sequelae, and STIs can limit the women's reproductive future.[1–3] Particularly, when abuse occurs at a very young age, long-term complications such as physical and mental disorders and the development of high-risk behaviors are described.[5–7] In the first weeks after abuse, physical pain, and mental disorders—such as posttraumatic stress disorder, depressive and anxious symptoms—are described in most women.[8,9] Studies describe forms of self-harm, such as cutting, and suicidal ideation/behavior.[1–3,9] A study described, in girls aged 12 to 17 years, an association between sexual abuse suffered in childhood and the development of the use of substances, alcohol and other drugs, and aggressive behavior; and supporting the need to address the issue of risk behaviors during the follow-up of survivors of sexual abuse.[7] These situations can decrease women's quality of life. Women survivors of SV describe, in the long term, higher sexual dysfunction scores and lower scores in quality of life.[10]

In order to reduce immediate complications, prophylactic measures have been established in emergency care services, which should be offered within the first 72 hours after SV, by administering emergency contraception, a single dose of antibiotics and postexposure prophylaxis (PEP) against human immunodeficiency virus (HIV) for 28 days.[11,12] Health

services should provide protocols for short and long-term mental health support to survivors of SV, in order to avoid or reduce late complications.[12] Although this care contributes to lessening SV-related harm, studies have described low adherence rates both for treatment in the 1st month and for subsequent outpatient follow-up of up to 6 months.[13–18]

Few studies have specifically evaluated the adherence of surviving adolescents to these protocols.[15,16,19] A study evaluated female survivors of SV aged 12 to 19 years and described that 44/131 (33.6%) completed treatment within the 1st month.[19] The main factors associated with adherence were the victim being white and the aggressor being unknown.[19]

The aim of the present study was to evaluate the loss to follow-up and associated variables among adolescent female survivors of SV who received emergency care in the period from 2011 to 2018 at a university reference service. The analysis was performed after the emergency care and during outpatient follow-up before the standard time predicted of 6 months.

Methods

This was a retrospective cohort study conducted at the Women's Health Care Center, School of Medical Sciences, University of Campinas (UNICAMP). The study was approved by the institutional research ethics committee (REC) under CAAE 20479819.4.0000.5404. Due to the design of this study, we asked the REC to waive the application of the consent form for this research, which was accepted. We followed all items in the strengthening of the communication of observational studies in epidemiology (STROBE).

Our university hospital is a regional reference for the care of female survivors of SV in the city of Campinas, SP, Brazil, which provides services to a coverage area for approximately 4.0 million inhabitants. Since the late 1990s, care for survivors of SV and its injuries has been standardized and must be dispensed by the Unified Health System (SUS, in the Portuguese acronym).[20,21] Our service takes care of female survivors in the first 6 months after SV, providing emergency care and outpatient 6-month follow-up with a multidisciplinary team, as provided for in the Technical Standard.[21]

All women seeking the service in the first 72 hours after SV receive the prophylaxis for bacterial and viral STI, as well as emergency contraceptive; those that arrive between 72 hours and 5 days receive emergency contraception. After emergency care, outpatient consultations are scheduled to follow 6 months with a multidisciplinary team. The loss to follow-up after emergency care was defined when adolescents performed emergency care after SV and never returned to the service. The loss of outpatient follow-up was defined for adolescents who underwent emergency care after SV and returned for outpatient follow-up but did not complete 6 months of multidisciplinary care.

This study was conducted exclusively with data from the review of electronic and physical medical records of female survivors of SV aged 10 to 18 years, who underwent emergency care from January 1st, 2011, to December 31st, 2018. We collected data from emergency care and outpatient follow-up performed by the multidisciplinary team during the 6 months. The last adolescent included had her medical record reviewed until July 1st, 2019, when data collection was completed.

The variables were sociodemographic (age group [10–14 years old; 15–18 years old]), self-reported ethnicity (white/non-white); education ($\leq$ 8 years/$>$ 8 years); intellectual disability (ID) (yes/no); marital status (single/cohabitating with partner), occupation (student/employee/without occupation), and religion (Pentecostal-Evangelical tradition/Catholic/no religion/other religion)]; personal background (history of initiated sexual life (yes/no); previous SV; history of mental disorders [psychiatric disorder/other disorder/suicidal behavior/no disorder]); characteristics of the SV (acute abuse [an event that is not repeated] or chronic abuse [when the aggression is repeated over time and is perpetrated by the same aggressor/aggressors]; aggressor (known/unknown); number of aggressors (single/multiple); type of violence suffered (vaginal/oral/anal); suffered some intimidation (yes/no); *blackout* during the aggression (yes/no); psychoactive substance (PAS) consumption before the event (alcohol; other PAS); SV perception (yes/no/she does not know/she lied about the violence); disclosure about SV (yes/no); received support from someone (yes/no) and time passed until emergency care in hours.

To assess the loss of outpatient follow-up before 6 months, we used the previous variables and those that measured the *reactions triggered after abuse*: physical disorders (sleep disturbs/appetite disturbs/others disturbs [physical disposition, gastrointestinal and urinary symptoms]); mental disorders (anxious symptoms/depressive symptoms/suicidal behavior/suicide attempt/flashbacks); social reactions (social avoidance/changes in daily routine [irregular bedtime/wake up and meal times/missed school/work/other activities; not being home alone at home/not going go out alone]/change of address/change of city/change of school); and psychotropic prescription needs during follow-up.

To compare categorical variables between lost to follow-up and non-lost to follow-up groups, we used the Chi-square or Fisher exact test. We used univariate and multiple logistic regression analysis with stepwise selection criteria to determine the variables associated with loss to follow-up at two times: after emergency care and before the end of the 6-month outpatient follow-up. We calculated the odds ratio (OR) for loss to follow-up with a 95% confidence interval (CI). The significance level was 5%. We used the Statistical Analysis System for Windows, version 9.2 (SAS Institute Inc, 2002–2008, Cary, NC, USA).

Results

During the period from January 1st, 2011, to December 31st, 2018, 1,174 women survivors of SV received emergency care at our service, 534 (45.5%) of whom were adolescents aged 10 to 18 years. Thirteen (2.4%) adolescents were excluded due to a lack of data recorded in the medical records (►**Fig. 1**).

►**Table 1** shows some sociodemographic characteristics of the 521 adolescents who made up this sample. More than half of the adolescents (53.5%) were aged between 15 to

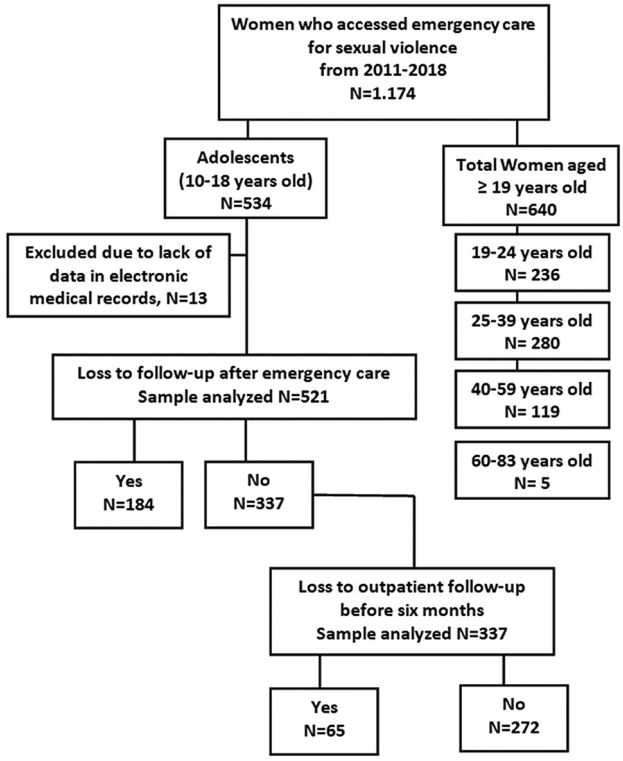

Fig. 1 Flowchart of emergency care digitized from the hospital database according to the age characteristics of the women treated between 2011 and 2018.

18 years, 64.2% self-reported white ethnicity, and were equally distributed between ≤ 8 and > 8 years of formal education. Most of the adolescents (92.1%) were single, 85.3% studying, and 4.6% had ID. Less than 10% of them lived with their partner, were employed; or had no occupation, that is, they were not studying or working at the time they suffered SV (►**Table 1**). Of the 521 adolescents, 249 (47.7%) were lost to follow-up at some point during the follow-up; 184/521 (35.3%) adolescents were lost to follow-up after emergency care, and 65/521 (12.4%) adolescents who started the outpatient follow-up were lost to follow-up before completing 6 months (►**Table 1**).

►**Table 2** shows the results of the regression analysis for abandonment of follow-up after emergency care. The univariate regression analysis showed that cohabiting with a partner, not having a religion or having a Catholic religion, not having experienced a blackout during the assault, not having initiated sexual life before the SV, having no history of previous SV, not having disclosed the violence to anyone, and not having received support from someone were characteristics associated with loss to follow-up after receiving emergency care (►**Table 2**). After multiple logistic regression, adolescents who lived with a partner remained associated with a higher risk of loss to follow-up after emergency care, with OR 5.94 (95% CI; 2.49–14.20) in relation to those who did not. The risk of loss to follow-up after emergency care was also higher for adolescents who reported not having a religion (OR 2.38 [95% CI; 1.29–4.38]) and having a Catholic religion (OR 2.11 [95% CI; 1.17–3.78]) in relation to those who had a Protestant religion; and those who reported not having disclosed the aggression to anyone had twice the risk (OR 2.07 [95% CI; 1.25–3.44]) in relation to those who had told (►**Table 2**). No other variables were associated with loss to follow-up after emergency care (data not shown).

The variables associated with abandonment of outpatient follow-up before 6 months after regression analysis are shown in ►**Table 3**. The univariate analysis showed that the variables that increased the chances of loss to follow-up were lying about the SV suffered, not having disclosed the aggression to anyone, not having received support from someone, not having presented the need to prescribe psychotropic drugs, and not having presented reactions of physical disorders, sleep disorders, mental disorders, anxiety symptoms, social changes and social avoidance behaviors triggered after the violence (►**Table 3**). After multiple logistic

Table 1 Sociodemographic characteristics of adolescent victims of sexual violence who received emergency care in the period from 2011 to 2018 and frequency of loss to follow-up soon after emergency care and outpatient follow-up loss < 6 months

Sociodemographic characteristics	n	%
Age group (n = 521)		
10–14 years old	242	46.4
15-–18 years old	279	53.5
Self-reported ethnicity (n = 517)		
White	332	64.2
Non-White	185	35.8
Education (n = 517)		
≤ 8 years	260	50.3
> 8 years	257	49.7
Intellectual disability (n = 521)		
Sim	24	4.6
Nao	497	95.4
Marital status (n = 521)		
Single	480	92.1
Cohabiting with a partner	41	7.8
Occupation (n = 491)		
Student	419	85.3
Employee	31	6.3
No occupation	41	8.3
Religion		
Pentecostal-Evangelical tradition	199	41.4
Catholic	149	31.0
No religion	104	21.6
Other religion	28	5.8
Loss to follow-up (n = 521)		
After emergency care	184	35.3
Before completing 6 months	65	12.4
Completed follow-up	272	52.2

Table 2 Comparison of adolescents who lost or not follow-up after emergency care and variables associated with discontinuing according to sociodemographic characteristics, personal history, type of violence suffered, attitudes after the event and time until emergency care

Variables	Loss to follow-up after emergency care						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (IC 95%)	P[d]	OR (IC 95%)
Age group (n = 521)			0.315[a]				
10–14 years old	80 (43.4)	162 (48.0)			Ref.		
15–18 years old	104 (56.5)	175 (51.9)		0.315	1.20 (0.84–1.73)	NS	
Self-reported ethnicity (n = 517)			0.634[a]				
White	120 (65.5)	212 (63.4)			Ref.		
Non-white	63 (34.4)	122 (36.5)		0.634	0.91 (0.63–1.33)	NS	
Education (n = 517)			0.996[a]				
≤ 8 years	92 (50.2)	168 (50.3)			Ref.		
> 8 years	91 (49.7)	166 (49.7)		0.996	1.00 (0.70–1.44)	NS	
Intellectual disability (n = 521)			0.505[a]				
No	174 (94.5)	323 (95.8)			Ref.		
Yes	10 (5.4)	14 (4.1)		0.506	1.33 (0.58–3.05)	NS	
Marital status (n = 521)			< 0.001[a]				
Single	155 (84.2)	325 (96.4)			Ref.		Ref.
Cohabiting with a partner	29 (15.7)	12 (3.5)		< 0.001	5.07 (2.52–10.20)	< 0.001	5.94 (2.49–14.20)
Occupation (n = 491)			0.347[a]			NS	
Student	142 (84.5)	277 (85.7)			Ref.		
Employee	14 (8.3)	17 (5.2)		0.207	1.61 (0.77–3.35)	NS	
No occupation	12 (7.1)	29 (8.9)		0.550	0.81 (0.40–1.63)	NS	
Religion (n = 480)			< 0.001[a]				
Protestant	52 (30.0)	147 (47.9)			Ref.		Ref.
Catholic	68 (39.3)	81 (26.4)		< 0.001	2.37 (1.51–3.73)	0.013	2.11 (1.17–3.78)
No religion	44 (25.4)	60 (19.5)		0.004	2.07 (1.26–3.42)	0.005	2.38 (1.29–4.38)
Other religion	9 (5.2)	19 (6.2)		0.503	1.34 (0.57–3.15)	0.558	0.67 (0.18–2.53)
Sexual activity initiated (n = 506)			0.034[a]				
Yes	43 (24.1)	109 (33.2)			Ref.		
No	135 (75.8)	219 (66.7)		0.034	1.56 (1.03–2.36)	NS	
History of mental disorder (n = 428)			0.249[a]				
No	100 (90.1)	272 (85.8)			Ref.		

(*Continued*)

Table 2 (*Continued*)

Variables	Loss to follow-up after emergency care						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (IC 95%)	P[d]	OR (IC 95%)
Yes	11 (9.9)	45 (14.2)		0.252	0.67 (0.33–1.34)	NS	
Previous mental disorder (n = 56)			0.308[b]				
No disorder			–		Ref.		
Psychiatric disorder	5 (45.4)	24 (53.3)		0.261	0.57 (0.21–1.53)	NS	
Suicidal behavior	2 (18.1)	10 (22.2)		0.437	0.54 (0.12–2.53)	NS	
Other disorder	4 (36.3)	11 (24.4)		0.985	0.99 (0.31–3.18)	NS	
History of sexual violence (n = 511)			0.033[a]				
Yes	22 (12.2)	65 (19.6)			Ref.		
No	158 (87.8)	266 (80.3)		0.035	1.75 (1.04–2.96)	NS	
Abuse (n = 521)			0.240[a]				
Single abuse	177 (96.2)	316 (93.7)			Ref.		
Chronic abuse	7 (3.8)	21 (6.2)		0.245	0.60 (0.25–1.43)	NS	
Known aggressor (n = 520)			0.687[a]				
Yes	96 (52.4)	183 (54.3)			Ref.		
No	87 (47.5)	154 (45.7)		0.687	1.08 (0.75–1.55)	NS	
Number of aggressors (n = 520)			0.215[a]				
Single	162 (88.5)	285 (84.5)			Ref.		
Multiple	21 (11.4)	52 (15.4)		0.161	0.67 (0.38–1.17)	NS	
Some intimidation (n = 491)			0.381[a]				
No	17 (10.4)	32 (9.7)			Ref.		
Yes	135 (82.8)	283 (86.2)		0.735	0.90 (0.48–1.67)	NS	
Does not know	11 (6.7)	13 (3.9)		0.359	1.59 (0.59–4.31)	NS	
Vaginal aggression (n = 521)			0.985[a]				
No	67 (36.4)	123 (36.5)			Ref.		
Yes	117 (63.6)	214 (63.5)		0.985	1.00 (0.69–1.46)	NS	
Oral aggression (n = 521)			0.154[a]				
No	149 (80.9)	289 (85.7)			Ref.		
Yes	35 (19.0)	48 (14.2)		0.156	1.41 (0.88–2.28)	NS	
Anal aggression (n = 521)			0.209[a]				
No	162 (88.0)	283 (83.9)			Ref.		

Table 2 (*Continued*)

Variables	Loss to follow-up after emergency care						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (IC 95%)	P[d]	OR (IC 95%)
Yes	22 (11.9)	54 (16.0)		0.210	0.71 (0.42–1.21)	NS	
Alcohol use before aggression (n = 469)			0.277[a]				
No	149 (87.6)	251 (83.9)			Ref.		
Yes	21 (12.3)	48 (16.0)		0.055	0.56 (0.31–1.01)	NS	
PAS use before aggression (n = 420)			0.236[a]				
No	152 (97.4)	251 (95.0)			Ref.		
Yes	4 (2.5)	13 (4.9)		0.233	0.56 (0.22–1.45)	NS	
Blackout during the aggression (n = 515)			0.009[a]				
Yes	28 (15.4)	85 (25.4)			Ref.		
No	153 (84.5)	249 (74.5)		0.029	1.70 (1.05–2.74)	NS	
Sexual violence perception (n = 521)			0.061[b]				
Yes	172 (93.5)	293 (86.9)			Ref.		
No	5 (2.7)	28 (8.3)		0.016	0.30 (0.12–0.80)	NS	
She does not know	4 (2.1)	7 (2.1)		0.966	0.97 (0.28–3.37)	NS	
She lied about the violence	3 (1.6)	9 (2.6)		0.401	0.57 (0.15–2.13)	NS	
Disclosure about sexual violence (n = 414)			< 0.001[a]				
Yes	58 (50.8)	222 (74.0)			Ref.		Ref.
No	56 (49.1)	78 (26.0)		< 0.001	2.75 (1.75–4.30)	0.005	2.07 (1.25–3.44)
Received support from someone (n = 361)			0.023[a]				
Yes	48 (64.0)	220 (76.9)			RRef.		
No	27 (36.0)	66 (23.0)		0.023	1.88 (1.09–3.24)	NS	
Time until emergency care			0.871[a]				
≤ 72 hours	123 (69.1)	237 (70.5)			Ref.		
> 72h––5 days	15 (8.4)	27 (8.0)		0.842	1.07 (0.55–2.09)	NS	
> 5 days–6 months	40 (22.4)	72 (21.4)		0.764	1.07 (0.69–1.67)	NS	

Abbreviations: CI, confidence interval; NS, not significant; OR, odds ratio; Ref, reference level.
[a]Chi-squared test.
[b]Fisher exact test.
[c]Univariate logistic regression analysis (*n = 521*; loss to follow-up after emergency care no, *n = 337*; loss to follow-up after emergency care yes, *n = 184*).
[d]Multivariate logistic regression analysis with stepwise variable selection criteria (*n = 337*; loss to follow-up after emergency care no, *n = 271*; loss to follow-up after emergency care yes, *n = 107*).

Rev Bras Ginecol Obstet Vol. 45 No. 11/2023

Table 3 Comparison between adolescents who were lost and those who were not to outpatient follow-up before 6 months and variables associated with dicontinuity according to sociodemographic characteristics, personal history, type of violence suffered, attitudes after the event, time until emergency care, and physical and mental disorders as well as social reactions triggered after abuse

Variables	Loss to follow-up before 6 months						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (CI 95%)	P[d]	OR (CI 95%)
Age (n = 337)			0.447[a]				
10–14 years old	34 (52.3)	128 (47.0)			Ref.		
15–18 years old	31 (47.7)	144 (52.9)		0.447	0.81 (0.47–1.39)	NS	
Self-reported ethnicity (334)			0.857[a]				
White	40 (62.5)	172 (63.7)			Ref.		
Non–white	24 (37.5)	98 (36.3)		0.857	1.05 (0.60–1.85)	NS	
Education (n = 334)			0.290[a]				
≤ 8 years	36 (56.2)	132 (48.9)			Ref.		
> 8 years	28 (43.7)	138 (51.1)		0.291	0.74 (0.43–1.29)	NS	
Intellectual disability (n = 337)			0.485[b]				
No	61 (93.8)	262 (96.3)			Ref.		
Yes	4 (6.1)	10 (3.6)		0.374	1.72 (0.52–5.66)	NS	
Marital status (n = 337)			0.474[b]				
Single	64 (98.4)	261 (95.9)			Ref.		
Cohabiting with a partner	1 (1.5)	11 (4.0)		0.346	0.37 (0.05–2.92)	NS	
Occupation (323)			0.826[a]				
Student	51 (87.9)	226 (85.2)			Ref.		
Employee	3 (5.1)	14 (5.2)		0.540	0.71 (0.24–2.13)	NS	
No occupation	4 (6.9)	25 (9.4)		0.937	0.95 (0.26–3.43)	NS	
Religion (307)			0.303[a]				
Catholic	19 (31.6)	62 (25.1)			Ref.		
Pentecostal-Evangelical tradition	30 (50.0)	117 (47.3)		0.592	0.84 (0.44–1.61)	NS	
No religion	10 (16.6)	50 (20.2)		0.326	0.65 (0.28–1.53)	NS	
Other religion	1 (1.6)	18 (7.3)		0.107	0.18 (0.02–1.45)	NS	
Sexual activity initiated (n = 328)			0.227[a]				
No	38 (60.3)	181 (68.3)			Ref.		
Yes	25 (39.6)	84 (31.7)		0.228	1.42 (0.80–2.50)	NS	
History of mental disorder (317)			0.106[a]				

Table 3 (*Continued*)

Variables	Loss to follow-up before 6 months						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (CI 95%)	P[d]	OR (CI 95%)
No	51 (92.7)	221 (84.3)			Ref.		
Yes	4 (7.2)	41 (15.6)		0.115	0.42 (0.15–1.23)	NS	
Previous mental disorder (317)			0.506[b]				
None					Ref.		
Psychiatric disorder	2 (50.0)	22 (53.6)		0.802	0.87 (0.28–2.65)	NS	
Suicidal behavior	–	10 (24.4)		0.131	0.20 (0.01–3.55)	NS	
Other disorder	2 (50.0)	9 (21.9)		0.113	0.19 (0.01–3.23)	NS	
History of sexual violence (n = 331)			0.842[a]				
No	52 (81.2)	214 (80.1)			Ref.		
Yes	12 (18.7)	53 (19.8)		0.842	0.93 (0.47–1.87)	NS	
Abuse (337)			0.572[b]				
Single abuse	60 (92.3)	256 (94.1)			Ref.		
Chronic abuse	5 (7.7)	16 (5.8)		0.589	1.33 (0.47–3.78)	NS	
Known aggressor (337)			0.846[a]				
Yes	36 (55.3)	147 (54.0)			Ref.		
No	29 (44.6)	125 (45.9)		0.846	0.95 (0.55–1.63)	NS	
Number of aggressors (337)			0.711[a]				
Single	54 (83.0)	231 (84.9)			Ref.		
Multiple	11 (16.9)	41 (15.0)		0.615	1.21 (0.58–2.51)	NS	
Some intimidation			0.652[a]				
No	8 (12.7)	24 (9.0)			Ref.		
Yes	53 (84.1)	230 (86.8)		0.397	0.69 (0.29–1.62)	NS	
Does not know	2 (3.1)	11 (4.1)		0.486	0.55 (0.10–3.00)	NS	
Vaginal aggression (337)			0.621[a]				
No	22 (33.8)	101 (37.1)			Ref.		
Yes	43 (66.1)	171 (62.8)		0.621	1.15 (0.65–2.04)	NS	
Oral aggression (337)			0.198[a]				
No	59 (90.7)	230 (84.5)			Ref.		
Yes	6 (9.2)	42 (15.4)		0.203	0.56 (0.23–1.37)	NS	
Anal aggression (337)			0.551[a]				

(*Continued*)

Table 3 (*Continued*)

Variables	Loss to follow-up before 6 months						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (CI 95%)	P[d]	OR (CI 95%)
No	53 (81.5)	230 (84.5)			Ref.		
Yes	12 (18.4)	42 (15.4)		0.551	1.24 (0.61–2.52)	NS	
Alcohol use before aggression (299)			0.270[a]				
No	41 (78.8)	210 (85.0)			Ref.		
Yes	11 (21.1)	37 (14.9)		0.671	0.84 (0.39–1.85)	NS	
PAS use before aggression (264)			0.460[b]				
No	41 (93.1)	210 (95.4)			Ref.		
Yes	3. (6.8)	10 (4.5)		0.418	1.56 (0.53–4.54)	NS	
Blackout about the aggression (n = 334)			0.387[a]				
No	45 (70.3)	204 (75.5)			Ref.		
Yes	19 (29.7)	66 (24.4)		0.927	1.03 (0.55–1.92)	NS	
Sexual violence perception (n = 337)			0.004[b]				
Yes	50 (76.9)	243 (89.3)			Ref		
No	7 (10.7)	21 (7.7)		0.298	1.62 (0.65–4.02)	NS	
She does not know	2 (3.0)	5 (1.8)		0.435	1.94 (0.37–10.30)	NS	
She lied about the violence	6 (9.23)	3 (1.1)		0.002	9.72 (2.35–40.17)	NS	
Disclosure about sexual violence (n = 300)			0.009[a]				
Yes	31 (59.6)	191 (77.0)			Ref		
No	21 (40.4)	57 (23.0)		0.010	2.27 (1.21–4.25)	NS	
Received support from someone (n = 286)			0.009[a]				
Yes	30 (62.5)	190 (79.8)			Ref		
No	18 (37.5)	48 (20.1)		0.011	2.38 (1.22–4.62)	NS	
Time until emergency care (n = 336)			0.764[b]				
$\leq$ 72 hours	50 (76.9)	187 (69.0)			Ref.		
$>$ 72 hours–5 days	3 (4.6)	24 (8.8)		0.230	0.47 (0.14–1.62)	NS	
$>$ 5 days–6 months	12 (18.4)	60 (22.1)		0.412	0.75 (0.37–1.50)	NS	
Reactions triggered after abuse (n = 302)							
Some physical disorder (n = 302)			0.011[a]				
Yes	17 (32.1)	128 (51.4)			Ref		
No	36 (67.9)	121 (48.6)		0.012	2.24 (1.20–4.20)	NS	

Table 3 (*Continued*)

Variables	Loss to follow-up before 6 months						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (CI 95%)	P[d]	OR (CI 95%)
Sleep disorders (n = 302)			0.043[a]				
Yes	15 (28.3)	108 (43.3)		–	Ref		
No	38 (71.7)	141 (56.6)		0.045	1.94 (1.02–3.71)	NS	
Appetite disorder (n = 302)			0.117[a]				
No	46 (86.8)	192 (77.1)			Ref.		
Yes	7 (13.2)	57 (22.9)		0.123	0.51 (0.22–1.20)	NS	
Other physical disorder (n = 302)			0.544[b]				
No	51 (96.2)	232 (93.1)			Ref.		
Yes	2 (3.7)	17 (6.8)		0.291	0.45 (0.10–1.98)	NS	
Some mental disorder (n = 302)			< 0.001[a]				
Yes	22 (41.5)	174 (69.8)			Ref		Ref
No	31 (58.5)	75 (30.1)		< 0.001	3.27 (1.78–6.02)	0.005	2.72 (1.36–5.46)
Anxiety symptoms (n = 302)			0.013[a]				
Yes	15 (28.3)	117 (47.0)			Ref		
No	38 (71.7)	132 (53.0)		0.014	2.25 (1.18–4.29)	NS	
Depressive symptoms			0.140[a]				
No	48 (90.5)	205 (82.3)			Ref.		
Yes	5 (9.4)	44 (17.6)		0.147	0.49 (0.18–1.29)	NS	
Suicide attempt			0.415[b]				
No	50 (94.3)	241 (96.8)			Ref.		
Yes	3 (5.6)	8 (3.2)		0.394	1.81 (0.46–7.05)	NS	
Suicidal behavior (n = 302)			0.589[b]				
No	50 (94.3)	227 (91.1)			Ref.		
Yes	3 (5.6)	22 (8.8)		0.450	0.62 (0.18–2.15)	NS	
Flashbacks (n = 302)			0.047[a]				
No	48 (90.5)	196 (78.7)			Ref.		
Yes	5 (9.4)	53 (21.3)		0.054	0.39 (0.15–1.02)	NS	
Some social change (n = 302)			< 0.001[a]				
Yes	33 (62.2)	213 (85.5)			Ref		Ref
No	20 (37.7)	36 (14.4)		< 0.001	3.59 (1.86-6.93)	0.029	2.33 (1.09–4.99)

(*Continued*)

Table 3 (*Continued*)

Variables	Loss to follow-up before 6 months						
	Comparative analysis			Univariate analysis[c]		Multivariate logistic regression analysis[d]	
	Yes	No	P	P[c]	OR (CI 95%)	P[d]	OR (CI 95%)
Social avoidance (n = 302)			0.009[a]				
Yes	7 (13.2)	77 (30.9)		–	Ref		
No	46 (86.8)	172 (69.1)		0.006	2.79 (1.34–5.81)	NS	
Changes in daily routine (n = 302)			0.477[a]				
No	45 (84.9)	201 (80.7)			Ref.		
Yes	8 (15.1)	48 (19.2)		0.478	0.75 (0.33–1.68)	NS	
Changes of address (n = 302)			1.000[b]				
No	49 (92.4)	227 (91.1)			Ref.		
Yes	4 (7.5)	22 (8.8)		0.762	0.84 (0.28–2.55)	NS	
Changes of school (n = 302)			0.719[b]				
No	50 (94.3)	238 (95.5)			Ref.		
Yes	3 (5.6)	11 (4.4)		0.697	1.30 (0.35–4.82)	NS	
Changes of city or state (n = 302)			0.540[b]				
No	52 (98.1)	246 (98.8)			Ref.		
Yes	1 (1.9)	3 (1.20)		0.695	1.58 (0.16–15.47)	NS	
Psychotropic prescription needs (n = 282)			0.007[a]				
Yes	9 (18.7)	92 (39.3)			Ref		
No	39 (81.2)	142 (60.7)		0.009	2.81 (1.30–6.07)	NS	

Abbreviations: CI, confidence interval; NS, not significant; OR, odds ratio; ref, reference level.
[a]Chi-square test.
[b]Fisher exact test.
[c]Univariate logistic regression analysis (*n = 337;* loss to follow-up before 6 months no, *n = 272*; loss to follow-up before 6 months yes, *n = 65*).
[d]Multivariate logistic regression analysis with stepwise variable selection criteria (*n = 277*; loss of outpatient follow-up no, *n = 230*; loss of outpatient follow-up yes, *n = 47*).

regression analysis, only two variables remained associated with loss to outpatient follow-up before 6 months: adolescents who did not have mental disorders and did not report social changes were more likely to discontinue this follow-up before 6 months, (OR 2.72 [95% CI; 1.36–5.46]) and (OR 2.33 [95% CI; 1.09–4.99]), respectively, in relation to the adolescents who presented these reactions (►**Table 3**). No other variables were associated with loss to follow-up before the end of the 6 months (data not shown).

Discussion

Almost half of the adolescents, 249/521 (47.7%), who received emergency care did not complete the proposed outpatient follow-up. Of 521 adolescents, 184 (35.3%) discontinued after emergency care and did not start outpatient follow-up; another 65 (12.4%) adolescents were lost to outpatient follow-up before 6 months. We consider these loss-to-follow-up rates to be high, especially for the age group studied.

Other studies of survivors of SV have shown higher rates of discontinuation before the age of 6 months.[13–18] A prospective study carried out from 1988 to 1990 in a university service in Vancouver, Canada, with women aged over 16 years treated in emergency care after SV reported that only 61/296 (21%) could be traced to 6 months.[13] A retrospective study analyzed data from 1,695 adult victims of sexual abuse treated in emergency care in Barcelona during the period from 2006 to 2015 and reported that, among the 883 who received prophylactic treatment for HIV, only 284 (32%) completed the 6-month follow-up.[17] One study conducted in Brazil evaluated survivors of SV who received emergency care from 2001 to 2013 and described that 110/199 (55.2%) discontinued outpatient follow-up before 6 months.[14] Another Brazilian retrospective study, conducted between 2007 and 2016, that aimed to assess the care provided to female survivors of SV aged 11 to 77 years reported that 167/444 (37.6%) women did not return within the 1st month, and 284/444 (64%) discontinued before completing the follow-up of 90 days.[18]

The lower loss to follow-up found in our study compared to those mentioned was probably due to differences between the samples. While our study included only adolescent females up to 18 years of age, the others included populations of survivors of different ages. It is important to highlight that the Brazilian legislation determines that the legal guardian of minors under 19 years of age be held accountable when the rights linked to public policies are not fulfilled, including the treatment and monitoring of victims of SV.[21] Therefore, by virtue of the law, the adolescent population usually complies with the care provided more frequently, at the risk of legal measures that may be proposed by the Guardianship Council and executed by the Judge of Childhood and Adolescence.[21] In addition, our service routinely makes phone calls to teenagers who have missed appointments to reschedule them before reporting the absence to the Guardianship Council, which also increases the frequency of appointments. We found a single prospective study of sexually assaulted female adolescents who received emergency care at 18 hospital centers in Ontario, Canada, and that assessed adherence to PEP treatment.[22] The results showed that 131/307 (42.7%) adolescents agreed to use the treatment, and only 44/131 (33.6%) completed the planned 28-day treatment.[22] Other clinic-based studies in Zimbabwe and Kenya with victims seen in the emergency room, and which included the description of frequency of adolescents and females, described even lower adherence rates, of 8% and 1.4%, respectively, for follow-up periods of up to 60 days.[15,16]

Our results show that the loss to follow-up was higher right after emergency care. We do not have information regarding whether the adolescents who did not return completed the prophylaxis or if they became pregnant. However, as our service is the regional reference and no adolescent returned pregnant, we believe that this complication did not occur in the adolescents in this sample. The multivariate regression analysis showed that the chance of not starting outpatient follow-up was six times increased in adolescents who lived with a partner and twice as high in cases of non-disclosure. Although intimate partner violence is described as a contributing factor to discontinuation of care,[16] in our results, having a known aggressor was not associated with loss to follow-up at any of the studied time points.

However, the opinion of the partner and/or family members may have influenced adherence to care, as described by other authors, including possible added fear due to the proximity of living with the aggressor.[22] Studies carried out in Vancouver, Canada (1992), and Mombasa (2019) and Nairobi (2022), in Kenya, showed that both family interference and proximity to the aggressor can influence adherence to follow-up.[13,16,22] The study carried out in Nairobi with 28 multidisciplinary health professionals, experienced in providing care to children and adolescents who have survived SV, sought to assess the difficulties and challenges of providing quality care.[22] Professionals described that family interference was a barrier for adolescents to disclose SV and to have access to health care and justice; in addition, family interference influenced the quality of care and loss to follow-up.[22]

In patriarchal cultures such as Brazil, women are socially stigmatized after suffering SV, which certainly favors non-disclosure on the part of survivors about the violence. Moreover, they do not want to remember the event, reducing the chance that they will attend the outpatient follow-up. Adolescents who reported not having a religion and having a Catholic religion were twice as likely to be lost to follow-up compared to those who had a Protestant religion. Although the majority of the Brazilian population calls itself Catholic, it is known that this affiliation is associated with considerable flexibility in religious practice and in the feeling of belonging, which comes close to having no religion.[22,23] On the contrary, in Protestant denominations, in general, members attend services more frequently and share values in the family nucleus.[23,24] Thus, it is possible that the association between the variables not having a religion/being Catholic and non-

adherence to outpatient follow-up may be due to a less effective support network.

The loss of outpatient follow-up was less frequent and considered by the authors to have less impact on treatment, since only two variables were shown to be associated with loss of outpatient follow-up: not having a mental illness and not reporting social reactions. We conclude that the adolescents who discontinued the outpatient follow-up before 6 months were those who no longer needed mental health support and those who were not forced to change their life routine, that is, they did not feel threatened, frightened, or rejected in the social environment. On the other hand, we consider it possible that the more intense situations of suffering favored adherence and the need to persist in the follow-up, while the need to help to change schools, housing or to achieve protective actions may have contributed to increasing the bond with the team and adherence to the follow-up until the 6th month. These results agree with a study describing that survivors who received at least one psychological consultation were more likely to finish treatment in the first month and to remain in follow-up for 6 months.[14] It also agreed with a study carried out only with female adolescents, which described that being moderately or very anxious, the attitude of encouragement given by the provider and being a student were factors associated with acceptance of care.[22]

At the time of SV, just under 10% of the adolescents lived with their partner, were employed; or had no occupation, which means that they neither studied nor worked. These characteristics increase the vulnerability of the individual to suffer SV. An early age for both marriage and paid employment can decrease the conditions for better educational preparation and to develop social skills, and, moreover, increases susceptibility to intimate partner violence[3]; the lack of occupation can predispose to the risk of suffering SV both inside and outside the space of the household and predispose to the development of higher risk behaviors.[22] In this sample, the rate of 4.6% of adolescents with ID was higher than that described in the general population, around 1%,[25] but it was not associated with a greater loss to follow-up, as described by other authors.[13]

We consider the retrospective nature of this study to be its main limitation. Certainly, we have a lot of missing information not collected in during appointments and added to the retrospective data analysis, which may have induced some bias in the results. During the consultations, we did not ask in detail about religion and its practice, nor have we evaluated the possible interference of family members/close people in the adolescents' attitudes and in their health care. Another limitation of this study was the lack of data on family income and social status of the adolescents followed up at our service. On the other hand, to our knowledge, this is the 1st study to assess the abandonment of follow-up in adolescent females during a 6-month follow-up period.

Conclusion

Prospective studies should be carried out to better understand the individual factors that may lead to loss to follow-up in adolescent female survivors of SV. Particularly, adolescents who live with their partner and those who report not having anyone to whom to disclose the abuse should receive specific care in the emergency room to increase adherence to follow-up.

Contributions

ASBT: project development, data collection, data analysis, manuscript and editing; OPA, ACA and ALT: data collection and manuscript writing; RCSA and AF: project development, data analysis, manuscript writing and revision.

Conflict of Interests

The authors have no conflict of interests to declare.

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Endometrial Progesterone and Estrogen Receptors in Relation to Hormonal Levels in Women with Unexplained

Receptores endometriais de progesterona e estrogênio em relação aos níveis hormonais em mulheres com aborto recorrente inexplicável

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Abstract

Objective Recurrent miscarriage has been linked to hormonal disturbance due to dysregulation of its receptors rather than to the availability of the hormone. We aimed to investigate endometrial expression of progesterone and estrogen receptors in relation to serum and endometrial hormonal levels in unexplained recurrent miscarriage.

Methods The present case control study included 20 cases with unexplained recurrent miscarriage and 20 parous women as controls. Ovulation was confirmed using an ovulation kit and 10 to 12 days after detecting the urinary luteinizing hormone surge, all women were subjected to a blood sample and to an endometrial biopsy. Progesterone and estrogen levels were measured in serum and in endometrial tissue and receptor concentrations were in the endometrial sample.

Results Women with recurrent miscarriage showed significantly lower concentration of receptors in both the cytoplasm and the nucleus of endometrial tissue compared with controls. The nuclear/cytoplasm ratio of progesterone receptor was significantly higher in cases compared with controls, implicating that recurrent miscarriage is probably linked to nongenomic activity of the hormone; this was also significant for estrogen receptor. Serum progesterone and estrogen hormonal levels were comparable between groups while both hormones were significantly reduced in the endometrium of recurrent miscarriage cases. Receptors significantly correlated with endometrial hormonal level but not to serum level.

Conclusion Recurrent miscarriage might be linked to reduced endometrial progesterone and estrogen receptors and appears to be more related to nongenomic activity of progesterone. Endometrial receptors expression correlates to tissue hormonal level rather than to serum hormonal level.

Keywords
- Pregnancy loss
- Receptor
- Recurrent miscarriage
- Estrogen
- Progesterone

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Introduction

Recurrent miscarriage (RM) refers to "3 or more consecutive miscarriages."[1] However, a diagnosis of RM could be considered after 2 consecutive miscarriages[2,3] on the basis that the incidence of a subsequent miscarriage does not significantly rise after the third compared to the second miscarriage.[2] Parental genetic abnormalities, uterine anatomical factors as well as antiphospholipid syndrome are agreed as direct causes for RM. Several other factors have been proposed but remain controversial and the existing evidence is either limited or inconclusive.[1–3] Cases presenting with RM are challenging because of the wide range of the proposed etiology and the diverse workup required for assessment; nevertheless, in $>50\%$ of these, the cause remains unidentified.

Progesterone is one of the ovarian sex hormones which was demonstrated to play a crucial role for successful reproduction.[4] The interaction between progesterone and its receptors has been reported to initiate a paracrine effect preparing the endometrium for implantation as well as supporting the developing embryo and maintaining uterine quiescence throughout pregnancy.[5]

Empirical use of progesterone has been proposed to address unexplained RM.[6] This practice was based on the assumption that insufficient hormonal level may be the cause of RM, but such management has yielded conflicting results. In a meta-analysis assessing the role of progesterone supplementation in prevention of RM, Haas et al.[7] concluded that a subsequent miscarriage may be reduced with progesterone therapy in women with unexplained RM. The PROMISE study,[8] on the other hand, demonstrated the ineffectiveness of progesterone in cases with RM. This might lead to hypothesize that the defect might be inadequate response of the receptors despite sufficient serum progesterone.

The objective of the present study is to investigate the endometrial expression of progesterone receptors (PR) and estrogen receptors (ER) in relation to serum and endometrial hormonal levels in women with unexplained RM.

Methods

The present case control study was conducted between April 2018 and May 2020. The study protocol agreed with the Helsinki Declaration for ethical medical research and it was approved by the council of the obstetrics and gynecology department. After thorough explanation of the study, 40 women aged between 20 and 40 years old, having regular menstrual cycles for at least 3 months, signed an informed consent form and were enrolled in the present study. The sample size was calculated using G* power which showed that a sample of 20 cases per group with an allocation ratio of 1:1 is required to achieve an effect size of 1.09 with an α error $= 0.05$ and the study power was set at 0.9. The effect size was estimated from the results of a previous study.[9]

The cases group included 20 women with unexplained RM defined as ≥ 3 prior spontaneous first trimester miscarriages with the last miscarriage within 6 months and prior investigations did not identify any cause for miscarriage. Prior workup in the course of management included normal hormonal levels, negative screening for antiphospholipid antibodies, exclusion of anatomical abnormalities by either 3D ultrasound, hysteroscopy or hysterosalpingography and normal karyotyping for both partners. Women with known genetic, anatomical, endocrine, autoimmune, or infectious disorders were excluded. The control group included 20 fertile women with at least 1 term birth presenting for unrelated conditions, women receiving hormonal treatment for any reason, and women with any known condition that may be related to miscarriage were excluded. The included women were instructed to avoid sexual intercourse or to use barrier contraception for the study duration (not to disturb an ongoing pregnancy during endometrial sampling) and to monitor their ovulation using a commercially available ovulation kits (Planny; DKT LLC) and they were scheduled for a return visit 10 to 12 days after detecting the urinary LH surge. They were subjected to an endometrial biopsy obtained using a pipelle curette and it was frozen in liquid nitrogen until the time of analysis. On the same day, a 5 cc blood sample was withdrawn and was left to clot in room temperature, then it was centrifuged and the serum was separated and frozen until the time of assay.

Assessment of ER and PR in the Endometrial Sample

Total receptors concentration was assessed in the endometrial sample using the technique described in a previous study.[9] The tissue was homogenated at 4°C then it was centrifuged for 60 minutes to obtain the supernatant (cytosol fraction). The 'raw' button was dissolved in buffer and incubated for 1 hour, during which the pellet was dissolved every 15 minutes. The solubilized proteins were obtained by centrifugation (nucleosol fraction). The ER was measured incubating the cytosol and the nucleosol (200 ml) in several concentrations (0.25–5.0 mM) of 3H-estradiol during 18 to 20 hours at 4°C. The nonspecific union was analyzed using diethylstillbestrol in excess (200). The PR was determined using 3H-ORG-2058 (0.25–10 mM) for 18 to 20 hours at 4°C. Both receptors were quantified using a Scatchard analysis and the proteins values were determined in the cytosol and in the nucleosol using the Lowry method. The sensitivity limits of this method were 1.0 to 75 and 1.0 to 50 fmol/mg-protein for ER and PR, respectively. The intra- and interassay relative standard deviation (SD) for the ER and PR were $<6\%$.

Assessment of Endometrium and Serum Hormonal Level

Estradiol and progesterone concentrations in the collected endometrial biopsy and serum were measured by a high-performance liquid chromatography method performed with an Agilent Series 1050 quaternary gradient pump, Series 1050 auto sampler, Series 1050 UV Vis detector (Agilent co., Germany), and HPLC 2D Chemstation software (Hewlett-Packard, Les Ulis, France) following a previously described technique.[10]

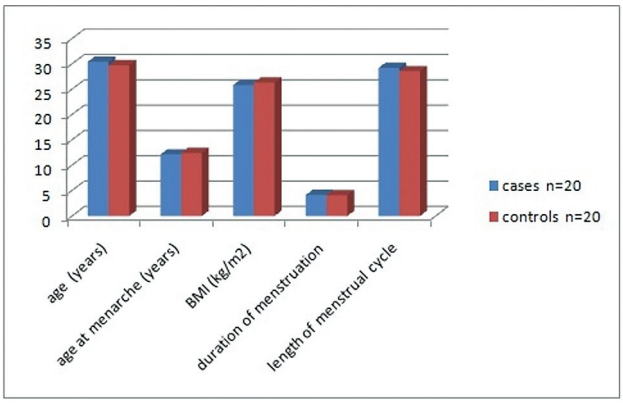

Fig. 1 Baseline demographics and background history.

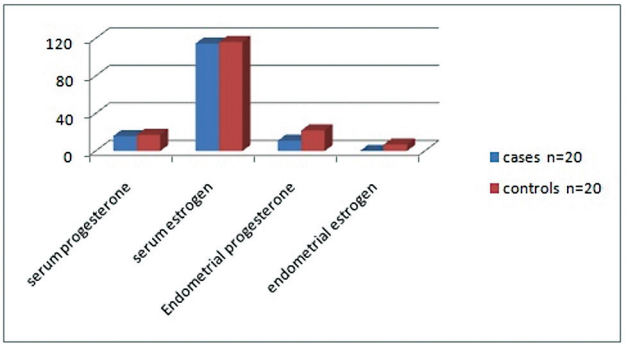

Fig. 3 Comparison between serum and endometrial hormonal levels among cases and controls.

Results

The cases group included 12 women (60%) with a history of prior 3 miscarriages and 8 women (40%) with 4 previous miscarriages; background history was comparable between groups (►**Fig. 1**).

The concentration of PR and ER was measured in the cytoplasm as well as in salt extracted nucleus. Compared with controls, women with RM showed a significantly lower concentration of PR in the cytoplasm (3.61 ± 1.52 versus 29.46 ± 10.56 fmol/mg protein; $p < 0.001$) and in the nucleus (6.61 ± 1.63 versus 40.43 ± 9.35 fmol/mg protein; $p < 0.001$). Estrogen receptor concentration was also significantly reduced in the cytoplasm (5.17 ± 1.9 versus 36.42 ± 12.8 fmol/mg protein; $p < 0.001$) and in the nucleus (12.78 ± 4.08 versus 59.88 ± 19.69 fmol/mg protein; $p < 0.001$) among women with RM compared with controls. In both groups, PR and ER were more expressed in the nucleus more than in the cytoplasm (►**Fig. 2**).

It was also noticed that the receptor concentration is more reduced in the cytoplasmic compartment. The nuclear/cytoplasm ratio of PR was significantly higher in cases (2.15 ± 0.92) compared with controls (1.54 ± 0.65; $p = 0.02$); this ratio was also significant for ER (2.56 ± 0.62 in cases versus 1.78 ± 0.68 in controls; $p = 0.001$). Regarding the PR/ER ratio, neither the cytoplasm nor the nuclear compartment was significantly different between cases and controls ($p > 0.05$). Progesterone and estrogen serum levels were comparable between groups while both hormones were significantly reduced in the endometrium of cases with RM (►**Fig. 3**). The mean of serum progesterone was 15.79 ± 2.94 ng/ml in cases compared with 17.22 ± 3.02 ng/ml in controls while serum estrogen was 114.56 ± 7.35 pg/ml in cases compared with 116.1 ± 7.88 pg/ml in controls; this difference was statistically not significant ($p > 0.05$). Endometrial progesterone was 10.86 ± 3.11 versus 21.85 ± 3.3 ng/ml among cases and controls respectively ($p < 0.001$), and endometrial estrogen level was 0.0437 ± 0.03 compared with 6.77 ± 3.55 ng/ml in cases and controls,

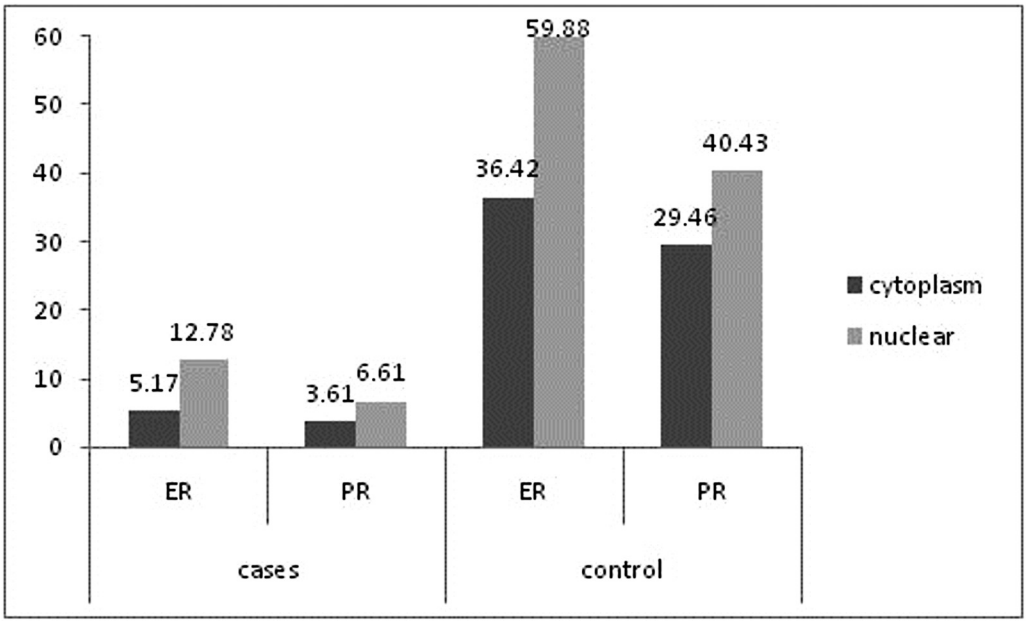

Fig. 2 Comparison between cytoplasm and nuclear concentration of progesterone and estrogen receptors among cases and controls.

respectively ($p < 0.001$). Correlations between receptors and hormonal levels are demonstrated in ►**Charts 1** and **2**. Both receptors were positively correlated with the endometrial level of its hormone and inversely related to each other, and these correlations were statistically significant. Both receptors significantly correlated positively with the endometrial level of its hormone while correlation to the serum level was not significant. These observations were found in cases as well as in controls.

Discussion

The present case control study compared 20 women with unexplained RM with 20 parous controls. Compared with controls, women with RM showed a significantly lower concentration of receptors in the cytoplasm as well as in the nuclear compartments of endometrial tissue. The nuclear/cytoplasm ratio of both PR and ER was significantly higher in cases compared with controls, which implicates that RM seems linked to nongenomic activity of the hormones. Serum hormonal levels were comparable between groups while both hormones were significantly reduced in the endometrium of cases with RM and receptors significantly correlated positively with the endometrial hormonal level but not with serum level.

Progesterone receptors are expressed in 2 isoforms; PR-A and PR-B, with other PR isoforms of uncertain physiological relevance. Both isoforms are expressed during the proliferative phase and increase with rising estrogen level, then PR-B remains constant while PR-A declines in the late secretory phase.[11] A defect in progesterone function has been attributed to dysregulation of PR rather than the availability of the hormone and disturbed receptor expression has been linked to pregnancy loss, although the exact mechanism is poorly understood.[12] Dysregulation of PR may be associated with reduced receptor expression or linked to genetic polymorphisms of PR affecting its response to progesterone.[13,14] Furthermore, RM may be linked to progesterone resistance as a result of epigenetic modification; this has been reported in a baboon model of endometriosis.[15]

Estrogen hormone has also been linked to miscarriage. Estrogen binds to its receptors to stimulate uterine cells to express PR thus promoting the endometrial response to progesterone.[11] Estrogen receptors are expressed in 2 isoforms, alpha and beta, which promote endometrial priming for pregnancy. During the proliferative phase, ERα expression is at its greatest, then it declines in the secretory phase.[16] A significant reduction of ER expression in decidua has been reported in women with early spontaneous miscarriage compared with women presenting for elective termination of pregnancy[17] and ER dysregulation has also been demonstrated to alter the expression of PR.[15]

Isoforms expression of both PR and ER can be assessed using biochemical, real-time RT-PCR or immunohistochemical methods. The common sequence of the isoforms limits the quantification of individual receptor isoform.[11] It has been demonstrated that there is unequal efficacy of the different antibodies used for immunohistochemical tests in recognizing

Chart 1 Correlations between receptor concentrations and hormonal levels among cases

	PR (cytoplasm)	PR (nuclear)	ER (cytoplasm)	ER (nuclear)	Serum progesterone	Endometrial progesterone	Serum estrogen	Endometrial estrogen
PR (cytoplasm)	—	0.373 (0.11)	- 0.924* (< 0.001)	- 0.874* (< 0.001)	0.326 (0.16)	0.791* (< 0.001)	- 0.312 (0.18)	- 0.692* (0.001)
PR (nuclear)	0.373 (0.11)	—	- 0.46* (0.04)	- 0.359 (0.12)	0.085 (0.72)	0.412 (0.07)	- 0.096 (0.69)	- 0.276 (0.24)
ER (cytoplasm)	- 0.924* (< 0.001)	- 0.46* (0.04)	—	0.838* (< 0.001)	- 0.218 (0.36)	- 0.728* (<0.001)	0.195 (0.41)	0.804* (< 0.001)
ER (nuclear)	- 0.874* (< 0.001)	- 0.359 (0.12)	0.838* (< 0.001)	—	- 0.396 (0.08)	- 0.64* (0.002)	0.37 (0.11)	0.599* (0.005)
Serum progesterone	0.326 (0.16)	0.085 (0.72)	- 0.218 (0.36)	- 0.396 (0.08)	—	0.377 (0.1)	- 0.344 (0.14)	- 0.214 (0.36)
Endometrial progesterone	0.791* (< 0.001)	0.412 (0.07)	- 0.728* (< 0.001)	- 0.64* (0.002)	0.377 (0.1)	—	- 0.367 (0.11)	- 0.55* (0.01)
Serum estrogen	- 0.312 (0.18)	- 0.096 (0.69)	0.195 (0.41)	0.37 (0.11)	- 0.344 (0.14)	- 0.367 (0.11)	—	0.319 (0.17)
Endometrial estrogen	- 0.692* (0.001)	- 0.276 (0.24)	0.804* (< 0.001)	0.599* (0.005)	- 0.214 (0.36)	- 0.55* (0.01)	0.319 (0.17)	—

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
Analysis done using the Pearson correlation test; data presented as r value (*p*-value).
*statistically significant

Chart 2 Correlations between receptor concentrations and hormonal levels among controls

	PR (cytoplasm)	PR (nuclear)	ER (cytoplasm)	ER (nuclear)	Serum progesterone	Endometrial progesterone	Serum estrogen	Endometrial estrogen
PR (cytoplasm)	—	0.185 (0.43)	- 0.926* (< 0.001)	- 0.742* (< 0.001)	- 0.182 (0.44)	0.639* (0.002)	0.144 (0.54)	- 0.536* (0.02)
PR (nuclear)	0.185 (0.43)	—	- 0.054 (0.82)	- 0.038 (0.87)	0.133 (0.58)	0.141 (0.55)	0.249 (0.29)	- 0.537* (0.02)
ER (cytoplasm)	- 0.926* (< 0.001)	- 0.054 (0.82)	—	0.613* (0.004)	0.126 (0.6)	- 0.526* (0.02)	0.125 (0.6)	0.396 (0.08)
ER (nuclear)	- 0.742* (< 0.001)	- 0.038 (0.87)	0.613* (0.004)	—	0.332 (0.15)	- 0.577* (0.008)	0.085 (0.72)	0.572* (0.008)
Serum progesterone	- 0.182 (0.44)	0.133 (0.58)	0.126 (0.6)	0.332 (0.15)	—	0.035 (0.88)	- 0.094 (0.69)	0.061 (0.8)
Endometrial progesterone	0.639* (0.002)	0.141 (0.55)	- 0.526* (0.02)	- 0.577* (0.008)	0.035 (0.88)	—	- 0.148 (0.44)	- 0.437 (0.05)
Serum estrogen	0.144 (0.54)	0.249 (0.29)	0.125 (0.6)	0.085 (0.72)	- 0.094 (0.69)	- 0.148 (0.44)	—	- 0.258 (0.27)
Endometrial estrogen	- 0.536* (0.02)	- 0.537* (0.02)	0.396 (0.08)	0.572* (0.008)	0.061 (0.8)	- 0.437 (0.05)	- 0.258 (0.27)	—

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
Analysis done using the Pearson correlation test; data presented as r value (*p*-value),
*statistically significant

receptor isoforms.[18] The present study evaluated the total concentration of the receptors and did not account for the different receptor isoforms due to technical limitations in accurately quantifying separate isoforms and derived by the consideration that the endometrial response to hormones represents the combined activities of its isoforms.

The present study shows that compared with fertile women, individuals with unexplained RM had significantly lower PR and ER concentrations in the nuclear and cytoplasmic compartment. In agreement with our findings, Rahnama et al.[19] demonstrated that PR expression was significantly lower in women with RM and the authors suggested that this difference may be linked to RM. Also in line with the present results, Salazar et al.[20] reported a significantly lower PR and ER in cases with RM compared with fertile women.

In another study, Carranza-Lira et al.[9] reported that cytoplasmic PR was significantly lower in women with RM but, contrary to our results, that nuclear PR was significantly lower in controls. However, that study agreed with the present results in that ER in cytoplasmic and nuclear compartment were lower in women with RM but it did not reach significance. The differences from the present results may be attributed to the small sample of that study as it only included 5 women with RM and 6 controls.

Also in agreement with the present results, Liang et al.[21] studied the expression of PR in decidual tissue of women with unexplained RM in comparison with normal pregnant women subjected to induced abortion using immunohistochemistry and they reported significant down regulation of PR expression in the RM group (0.1632 ± 0.007 versus 0.2122 ± 0.01; $p = 0.0003$).

As noted from previous studies,[11,16] there is a physiological variation throughout the menstrual cycle in endometrial expression of both PR and ER, but the present study evaluated the status of the receptors in the midluteal phase which represents the most relevant period for establishing and maintenance of pregnancy.

Currently, progesterone is demonstrated to function through a genomic activity mediated via the nuclear receptors and a nongenomic activity mediated via the extranuclear receptors.[22] Contrary to our results, nuclear receptors are hypothesized to be the primary mechanism for progesterone action in the human female reproductive system.[11] The present study demonstrates that the cytoplasmic fraction of PR is significantly more reduced than the nuclear fraction in women with RM, thus implicating the nongenomic activity in the pathophysiology of RM. Further studies are needed to explore this observation.

The physiology of female reproduction is regulated by ovarian steroids which coordinate to produce a favorable environment required for embryo implantation and progression of pregnancy. This is established by modulation of maternal immune system and although no clear mechanism has been reported implicating progesterone in this action,[11] it has been reported that decidualization of the endometrium depends on adequate progesterone level together with endometrial expression of PR to mediate its effect.[23] A decline in

serum progesterone and estrogen has also been reported in women with early spontaneous miscarriage compared with women presenting for elective termination of pregnancy.[24]

Currently, there is no agreement on a cutoff for serum progesterone level that best defines ovulatory cycles or may predict pregnancy outcome. Several levels for midluteal progesterone have been suggested to confirm ovulation. Only two retrospective studies reported on hormonal levels in cycles ending up with pregnancy.[17,25] Takaya et al.[17] reported that a minimum of 5.6 ng/ml serum progesterone and 70.2 pg/ml estrogen is required to achieve pregnancy. A higher value was reported in an earlier study in which Sallam et al.[25] reported that a minimum of 10.83 ng/ml is required to achieve pregnancy; however, they assessed women who underwent induction of ovulation with human menopausal gonadotrophin which is known to increase progesterone levels.

The mean serum hormonal level in the present population was comparable to that of parous women and it was above the previously demonstrated cutoffs required for favorable pregnancy outcome. The adequate serum hormones in the current population rules out serum progesterone decline as the sole cause of RM outside the context of luteal phase deficiency. In addition, it might provide explanation for the heterogeneous evidence regarding empiric progesterone supplementations in women with RM.

On the other hand, tissue concentration seems to have a role in the pathophysiology of RM according to the present results, which showed that progesterone and estrogen concentrations were significantly lower in the endometrial sample of women with unexplained RM compared with fertile women. Variation in blood concentration of sex steroids has been demonstrated to influence the endometrial expression of PR and ER[26] and it was suggested that both receptors change in line to blood or endometrial changes of sex steroids.[27,28] This in part agrees with the present results as both PR and ER were found to significantly correlate with endometrial hormonal concentration but not to serum levels.

In agreement with our results, Li et al.[29] reported no significant difference between serum estrogen in RM compared with normal fertile women. Also, Salazar et al.[20] reported a significant reduction in endometrial progesterone concentration in RM women but in disagreement with our results, they reported a comparable estrogen concentration and significantly lower serum progesterone.

A limitation of the present study is the evaluation of the total concentration of the receptor without assessing if there is a difference in different isoforms expression, but this point can be argued by the technical difficulty in quantifying receptor isoforms and also by the consideration that progesterone action represents the combined activities of the isoforms. Another limitation is the retrospective nature of the study. A strength of the present study is the evaluation of the hormonal function as a unit with assessment of the hormones at serum and tissue combined with receptor expression. This highlighted a subgroup with a normal serum hormonal level but with a suboptimal response related to aberrant receptor expression, also explaining in part the heterogeneous response to empirical progesterone supplementations in RM excluding a subgroup which obviously will not benefit from such treatment.

Conclusion

Recurrent miscarriage might be linked to reduced endometrial progesterone and estrogen receptors and appears to be more related to nongenomic activity of progesterone. Endometrial receptors expression correlates to tissue hormonal level rather than to serum hormonal level.

Contributions

Gomaa I: study conception, project development, protocol development, data analysis. Sabry A: protocol development, data collection, manuscript drafting. Allam IS: study conception, data analysis. Ashoush S: project development, data collection. Reda A: data interpretation, manuscript writing. All authors critically revised the manuscript and approved the final version.

Conflict of Interests

The authors have no conflict of interest to declare.

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The Role of Thyroid Hormones, Vitamins, and Microelements in Female Infertility

O papel dos hormônios da tiroide, das vitaminas e dos microelementos na fertilidade feminina

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Abstract

Objective It is well known that female infertility is multifactorial. Therefore, we aimed to compare the effects of thyroid dysfunction, vitamin deficiency, and microelement deficiency in fertile and infertile patients.

Materials and Methods Between May 1st, 2017, and April 1st, 2019, we conducted a retrospective case-control study with of 380 infertile and 346 pregnant patients (who normally fertile and able to conceive spontaneously). The fertile patients were selected among those who got pregnant spontaneously without treatment, had a term birth, and did not have systemic or obstetric diseases. The levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), anti-thyroid peroxidase (anti-TPO), vitamin D, vitamin B12, folic acid, ferritin, and zinc of both groups were compared.

Results There was no difference between patients in the infertile and pregnant groups in terms of low normal and high serum T3 and T4 levels ($p = 0.938$; $p > 0.05$) respectively, nor in terms of normal and high anti-TPO levels ($p = 0.182$; $p > 0.05$) respectively. There was no significant difference regarding patients with low, insufficient, and sufficient vitamin D levels in the infertile and pregnant groups ($p = 0.160$; $p > 0.05$) respectively. The levels of folic acid, ferritin, and zinc of the infertile group were significantly lower than those of the pregnant group.

Conclusion The serum levels of folic acid, ferritin, and zinc in infertile patients presenting to our outpatient clinic were lower than those o the fertile patients.

Keywords
- infertility
- vitamin B12
- vitamin D
- folic acid
- ferritin
- zinc
- thyroid hormones

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Resumo

Objetivo Sabe-se que a infertilidade feminina é multifatorial. Portanto, nosso objetivo foi comparar os efeitos da disfunção tireoidiana, deficiência de vitaminas e deficiência de microelementos em pacientes férteis e inférteis.

Materiais e Métodos Entre 1° de maio de 2017 e 1° de abril de 2019, realizamos um estudo retrospectivo caso-controle com 380 pacientes inférteis e 346 grávidas (normalmente férteis e capazes de conceber espontaneamente). As pacientes férteis foram selecionadas entre aquelas que engravidaram espontaneamente sem tratamento, tiveram parto a termo e não apresentavam doenças sistêmicas ou obstétricas. Os níveis de hormônio estimulante da tireoide (TSH), triiodotironina (T3), tiroxina (T4), antitireoide peroxidase (anti-TPO), vitamina D, vitamina B12, ácido fólico, ferritina e zinco de ambos os grupos foram comparados.

Resultados Não houve diferença entre as pacientes dos grupos inférteis e gestantes em relação aos níveis altos de sérumT3 e T4 normais baixos e altos ($p = 0{,}938$; $p > 0{,}05$), respectivamente nem aos níveis normais e altos de anti-TPO ($p = 0{,}182$; $p > 0{,}05$), respectivamente. Não houve diferença significativa em relação aos pacientes com níveis baixos, insuficientes e suficientes de vitamina D nos grupos inférteis e gestantes ($p = 0{,}160$; $p > 0{,}05$), respectivamente. Os níveis de ácido fólico, ferritina e zinco do grupo infértil foram significativamente menores do que os do grupo grávida.

Conclusão Os níveis de sérum de ácido fólico, ferritina e zinco nas pacientes inférteis atendidas em nosso ambulatório foram menores do que nas pacientes férteis.

Palavras-chave

- infertilidade
- vitamina b12
- vitamina D
- ácido fólico
- ferritina
- zinco
- hormônios da tireoide

Introduction

Infertility is a public health problem affecting 15% of couples of childbearing age,[1] and it has a negative impact on psychological well-being in both developed and underdeveloped societies. Studies[2] have shown that the level of psychological stress of infertile couples is comparable to that of patients with a cancer diagnosis or heart disease. It is known that the male factor of cases ranges from 20% to 35%, the female factor, also from 20% to 35%, and the unexplained group, from 10% to 20%.[3]

Many factors can influence female infertility, and one of the most important is undiagnosed and untreated thyroid disease. In primary hypothyroidism, high levels of thyrotropin-releasing hormone (TRH) are secreted to increase the levels of thyroid-stimulating hormone (THS), resulting in hyperprolactinemia, oligomenorrhea, and anovulation.[4] Hypothyroidism can cause miscarriage, premature birth, and neuro- developmental disorders.[5] Thyroid antibodies spontaneously lead to negative results in in vitro fertilization (IVF) because their molecular mimicry interferes with the interaction between the zona pellucida and the sperm cell.[6] Therefore, intracytoplasmic sperm injection (ICSI) is preferred in women with positive thyroid autoantibodies.[7] Moreover, thyroid autoantibodies negatively affect the embryo and lead to early pregnancy loss.[8] It is known that TSH levels in euthyroid patients do not affect the results of intrauterine insemination.[9]

Vitamin B12, as a cofactor, can normalize high levels of homocysteine by converting homocysteine into methionine with the help of the enzyme folic acid methionine synthetase.[10] High homocysteine levels, which occur in patients with folic acid and B12 deficiency, impair oocyte maturation and embryo quality.[11] In patients with normal blood cobalamin and folic acid levels, it results in low homocysteine levels and, thus, better embryo quality.[12]

Vitamin D plays a role in the expression of the *HOXA-10* gene in endometrial stromal cells; it also regulates immune responses during implantation, and may lead to implantation failure or embryo immune rejection if deficient.[13,14] In addition, vitamin D has been shown to increase the expression of 3b-hydroxysteroid dehydrogenase and progesterone production by inhibiting follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH) gene receptors in granulosa cells.[15] Therefore, studies[16] advocate keeping serum vitamin D concentrations within normal limits in infertile patients.

Zinc is well known to be a cofactor of ~ 200 enzymes, and it regulates DNA replication and meiosis.[17] When zinc is deficient, meiotic division occurs in oocytes at metaphase 2.[18] In addition, a relationship between zinc and low birth weight has been demonstrated.[19]

There are studies[20] advocating that unexplained infertility is associated with low ferritin levels, that it leads to recurrent miscarriage in infertile patients, that it should become routine in infertile patients, and that substitution should be performed in infertile cases before treatment.

In light of this information, we aimed to investigate the relationship involving the serum levels of TSH, triiodothyronine (T3), thyroxine (T4), vitamin B12, folic acid, zinc, vitamin D, and ferritin in infertile patients and infertility.

Materials and Methods

Between May 1st, 2017 and April 1st, 2019, in the Department of Gynecology and Obstetrics, Ankara University, we

conducted a retrospective case-control study with pregnant and infertile patients aged between 18 and 40 years. The infertile group was composed of 380 patients who had presented to the reproductive health outpatient clinic for the first time (and had not been previously treated for infertility), and the pregnant group was composed of 346 patients who were followed up in the clinic, had given birth spontaneously, had not received any treatment or medical support, had had no obstetric or systemic problems during their pregnancy, and whose first-trimester blood parameters could be determined. The pregnant group was accepted as the fertile group, and their blood results from weeks 7 to10 were obtained and studied. The exclusion criteria for the infertile patients were: severe oligospermia or azoospermia, uterine abnormalities (septate, unicornuate, bicornuate, and didelphis uterus, and others), and submucosal myoma or endometrial polyps. The hysterosalpingography of all infertile patients included was examined, and those with tubal junction anomalies and hydrosalpinx were excluded.

In the pregnant group, we included patients whose blood results from weeks 7 to 10 of gestation were available. In both groups, we selected patients who had not taken any vitamin or food supplements in the previous six months. The exclusion criteria for the pregnant group were patients with a diagnosis of infertility and pregnancy for as treatment, patients diagnosed with habitual abortion, patients with a history of thrombophilia, patients with endocrine, metabolic, hematologic, or genetic diseases, epilepsy patients, those who had received high-dose folic acid therapy due to an abnormality in the previous pregnancy, and those who had taken vitamin or food supplements in the previous six months.

The groups were compared based on serum levels of TSH, T3, T4, anti-thyroid peroxidase (anti-TPO), vitamin D, B12, folic acid, ferritin, and zinc.

We defined infertile couples as those for whom pregnancy had not occurred despite regular sexual intercourse for 1 year if the woman was younger than 35 years and for 6 months if the woman was older than 35 years.

We obtained written approval from the institutional Ethics Committee (number I-4–149–19).

The data collected for the statistical analysis were recorded using the IBM SPSS Statistics for Windows software (IBM Corp., Armonk, NY, United States). The Shapiro-Wilk normality test was used to evaluate the distribution of the data. In line with the results of this test, the Student *t*-test or the Mann-Whitney U test were used to compare the continuous variables, and the Chi-squared test was used to assess the distribution of the categorical variables.

Results

We included a total of 726 patients, 380 in the infertile group and 346 in the pregnant group. The mean age of the infertile group was of 30.57 years ($p = 0.000$), and that of the pregnant group was o 28 years ($p < 0.001$). In the infertile group, 67 (17.9%) patients had secondary infertility, and 308 (82.1%) had primary infertility. There was no difference between subjects in the infertile and fertile groups in terms of smoking status ($p = 0.088$; $p > 0.05$ respectively). The body mass index (BMI) of the infertile group was significantly higher than that of the pregnant group ($p = 0.001$) (►**Table 1**).

The standard reference range was of 1.0 nmol/mL to 2.9 nmol/mL for T3, of 50 nmol/mL to 150 nmol/L for T4, and > 30 IU/mL for anti-TPO positivity. According to TSH levels, the patients were divided into 3 subgroups: < 2.5 mIU/mL, 2.5–4.5 mIU/mL, and > 4.5 mIU/mL. There was no difference between patients in the infertile and pregnant groups in terms of low normal and high serum T3 and T4 levels ($p = 0.938$; $p > 0.05$) respectively. A significant difference was found between pregnant and infertile patients in all TSH level subgroups: while there were more patients with TSH < 2.5 mIU/mL in the pregnant group, a higher proportion of patients with TSH levels between 2.5 mIU/mL and 4.5 mIU/mL and > 4.5 mIU/mL were found in the infertile group. Subclinical hypothyroidism was found in ~ 3.3% of patients in the pregnant group and in ~ 13% of patients in the infertile group. There was no difference between the pregnant and infertile groups in terms of normal and high anti-TPO levels ($p = 0.182$; $p > 0.05$) respectively. In total, 95.8% of patients in the pregnant serum T3 group, 96.1% of patients in the infertile group, and in the pregnant serum T4 group, 99.7% of patients were found to be normal in 98.3% of patients in the infertile group (►**Table 2**).

In line with many previous studies, in the present study, we classified vitamin D levels > 30 ng/mL as adequate, levels between 20 30 ng/mL and 30 ng/ml, as inadequate, and levels < 20 ng/mL as low. There was no significant difference regarding patients with low, insufficient, and sufficient levels of vitamin D in the infertile and pregnant groups (►**Table 3**) ($p = 0.160$; $p > 0.05$ respectively). Vitamin D levels were considered sufficient in 5.4% of the patients in the infertile group and in 8.9% of the patients in the pregnant patient group. Considering the whole sample, vitamin D levels were sufficient in 7.1% of the patients.

Low vitamin D levels were found in 76.1% of the infertile group and in 75.6% of the pregnant group. Deficiency was

Table 1 Characteristics of the study sample

	Infertile group (n = 380)	Pregnant group (n = 346)	*p*-value
Mean age (years)	30,57 ± 6,503	28,07 ± 5,189	< 0.001
Mean body mass index (kg/m^2)	26.227 ± 4.38086	25.0476 ± 4.48651	0.001
Smoker: n (%)	75 (20.7)	47(15.6)	0.088

Table 2 Comparison of the results of the thyroid function test between infertile and pregnant patients

		Infertile group: n (%)	Pregnant group: n (%)	P-*value*
T3	Low	1 (0.3)	2 (0.6)	> 0.05
	Normal	345 (96.1)	321 (95.8)	
	High	13 (3.6)	12 (3.6)	
T4	Low	1(%0.3)	0	> 0.05
	Normal	354 (98.3)	339 (99.7)	
	High	5 (1.4)	1 (0.3)	
TSH	< 2.5 mIU/L	221 (59.7)	296 (87.3)	< 0.001
	2.5–4.5mIU/L	101 (27.3)	32 (9.3)	
	> 4.5 mIU/L	48(%13)	11(%3.3)	
Anti-TPO	Normal	266 (82.7)	256 (86.5)	> 0.05

Abbreviations: Anti-TPO, anti-thyroid peroxidase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Table 3 Comparison of vitamin D values

Group	Vitamin D			Total
	Low	Insufficient	Sufficient	
Infertile group: n (%)	255 (76.1)	62 (18.5)	18 (5.4)	335 (100)
Pregnant group: n (%)	239 (75.6)	49 (15.5)	28 (8.9)	316 (100)
Total: n (%)	494 (75.9)	111 (17.1)	46 (7.1%)	651 (100)

Table 4 Comparison of the levels of vitamin B12, folic acid, ferritin, and zinc in the infertile and pregnant groups

		Infertile group: n (%)	Total sayı: n	Pregnant group: n (%)	Total sayı: n	*p*-value
Vitamin B12	Low	66 (17.7)	372	73 (21.5)	339	> 0.05
	Normal	306 (82.3)		266 (78.5)		
Folic acid	Low	95 (26)	366	26 (7.8)	333	< 0.001
	Normal	271 (74)		307 (92.2)		
Ferritin	Low	155 (45.5)	341	98 (29.2)	336	< 0.001
	Normal	186 (54.5)		238 (70.8		
Zinc	Low	39 (23.9)	163	17 (13.1)	130	< 0.001
	Normal	124 (76.1)		113 (86.9)		

defined as following serum levels: vitamin B12 < 200 pg/mL; folic acid < 5.9 ng/mL; zinc < 76 mg/mL; and ferritin < 11 ng/mL. Serum vitamin B12 levels were found in 17.7% of the infertile group and in 21.5% of the pregnant group, with no significant difference between the groups. In the infertile group, the levels of folic acid, ferritin, and zinc were significantly lower than those of the pregnant group. Miscarriage was observed in 26 patients (0.78%) of 333 the patients in the folic acid pregnant group and in 95 (0.25%) of the 366 patients in the infertile group. Ferritin levels were low in 155 (45.5%) out of 341 infertile patients and in 98 (29.2%) out of 336 pregnant women. The levels of zinc were assessed in 130 pregnant women and in 163 infertile patients, and it was low in 13.1% of the pregnant group and in 23.9% of the infertile group (►**Table 4**).

Discussion

In the present study, we found no significant differences between the infertile and pregnant groups in terms of the levels of T3, T4, anti-TPO, vitamin D and vitamin B12, and the serum levels of ferritin, folic acid, and zinc were significantly lower in the infertile patient group compared with the pregnant group.

A study on the effect of vitamin D on infertility and endometriosis found that adequate vitamin D levels ($\geq$ 30 ng/mL) should be ensured in women undergoing IVF treatment. Studies[21] show that vitamin D supplementation regulates serum lipid levels in patients with polycystic ovary syndrome, and it reduces the risk of endometriosis.

In another study,[21] although the authors noted that vitamin D and its metabolites play an important role in embryo implantation and immunologic protection of the embryo and that couples with serum vitamin D concentrations higher than 50 nmol/L have a higher chance of becoming pregnant, they stated that this is not true for all patients.[22] The reason why this study[22] does not support the results of the present study might be because both studies were conducted with different populations. Studies[23] have shown that vitamin D deficiency (< 10 ng/mL) is also associated with the presence of thyroid antibodies, and that TSH levels tend to have a direct relationship with vitamin D status in women with thyroid autoimmunity as opposed to those without.

In the present study, although the rate of patients with serum TSH levels < 2.5 mIU/mL was significantly lower in the infertile group compared with the pregnant group, no significant relationship was found between both groups in terms of the levels of T3, T4, and anti-TPO. Similar to the results of the present study, in a large retrospective study[24] with 11,254 patients from Denmark, the authors found that infertility and subclinical hypothyroidism were associated. Another study[25] stated that the levels of T3 and T4 were not associated with conception; however, anti-TPO might reduce the quality of the oocyte. In the present study, the rate of patients with TSH levels between 2.5 mIU/mL and 4.5 mIU/mL and > 4.5 mIU/mL was higher in the infertile group, which is in line with previous studies[26] investigating the same parameters in infertile patients. In addition, the prevalence of thyroid autoimmune diseases was higher in women with polycystic ovary syndrome and idiopathic subfertility. Therefore, women with hypothyroidism should be treated until their serum levels of TSH reach < 2.5 mIU/mL before undergoing therapy with assisted reproductive techniques (ARTs). Euthyroidism should be restored and maintained several months before starting the ART therapy. Fertilization rates and embryo quality may deteriorate in women with TSH > 4.0 mIU/mL.[26] Meta-analysis studies[26] mainly including women with TSH levels > 4.0 mIU/mL have shown that the rates of live birth increase after hypothyroidism treatment. However, autoimmune thyroid disease with euthyroidism increases the live birth rate in women with the disease.[27]

Similarly, in a study published in 2017 by Irene La Vecchia et al.,[28] the levels of vitamin A, vitamin E, folic acid, vitamin B12, and ferritin were investigated among infertile patients. This study[28] differed from ours in the sense that the infertile patients were not compared with fertile patients. Vitamin B12 levels were low in 66% of 269 patients, and folic acid levels were low in 22%[28] In the present study, low levels of vitamin B 12 were detected in 17.7% of the infertile and 21.5% of the pregnant group. Folic acid was observed to be low in 26% of the infertile group, similar to the result found by La Vecchia et al.[28] Ferritin levels were adequate in more than 80% of patients assessed by La Vecchia et al.[28] In the present study, we observed low levels of ferritin r45.5% of the infertile patients. In similar studies,[29] the levels of folic acid increased the success of the ART treatment by decreasing serum homocysteine levels, especially in patients with unexplained infertility. High serum levels of vitamin D and folic acid increase oocyte quality and the release of follicular estradiol, thus positively affecting fertility.[30] Another study[31] stated that IVF success was higher because more metaphase II (MII) oocytes were obtained from patients who took vitamin B12 supplements. In addition, low serum levels of ferritin were associated with recurrent pregnancy loss.[32] A study[33] conducted at an infertility center in the United States revealed that normal plasma antioxidant (zinc, selenium, and vitamin E) levels within normal reference ranges do not benefit male fertility. Studies[32,34] on ferritin and zinc in infertility have generally focused on male infertility. However, in the present study, we found a relationship involving serum levels of zinc and ferritin and female infertility. Nevertheless, there is a need for prospective multicentric studies with larger samples. In a study with polycystic ovarian patients,[34] the authors found no correlation between the serum levels of zinc in the case and control groups In addition, another study[32] found that ferritin levels were significantly lower in patients with recurrent pregnancy loss compared with the control group.[32]

Although the present study is not on a new subject, it can be considered an extension of previous studies with large samples that investigated the association of vitamin D, vitamin B12, folic acid, ferritin, zinc, and thyroid hormones with infertility. In addition, the fact that the present study was conducted in a different population may have caused our data to differ from previously reported data. The sample size of the present study is sufficient to identify vitamin D, B12, folic acid, ferritin, zinc, and thyroid hormones in infertility. We only included white patients to ensure the study's homogeneity. Still, in terms of mean age, the infertile group was older than the pregnant group. A limitation of the present study is that it did not consider the lifestyles, eating habits, socioeconomic status, or practice of physical activities of the patients. Thus, there may be differences in certain serum blood levels, especially in those of vitamins and microelements.

Conclusion

In the present study, we found that the serum levels of vitamin D and vitamin B12 of the infertile patients were as low as those of fertile patients. The levels of folic acid, ferritin, and zinc were also lower in infertile patients. In addition, subclinical hypothyroidism was observed more frequently in infertile patients. Prospective studies with larger samples are needed.

Contributors
All authors were involved in the design and analysis, contributed to the writing of the manuscript, and read and approved the final manuscript.

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

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Risk Profile of High-grade Cervical Lesions and Cervical Cancer Considering the Combination of Cytology, HPV Genotype, and Age among Women Undergoing Colposcopy

Perfil de risco de lesões cervicais de alto grau e câncer cervical considerando a combinação de citologia, genótipo do HPV e idade entre mulheres submetidas a colposcopia

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Abstract

Objective The present study aims to establish a risk profile for high-grade cervical lesions and cervical cancer (CIN2 +) in women undergoing colposcopy at the Hospital do Câncer de Barretos, through the analysis of Human Papillomavirus (HPV) infection, cervical cytology, and patient's age.

Methods Retrospective cross-sectional study based on a computerized database of women aged ≥ 18 years old who underwent colposcopy at the Prevention Department of the Hospital do Câncer de Barretos from 2017 to 2019.

Results A total of 3,411 women were included, 58.0% were positive for high-risk-HPV test, with a higher prevalence of CIN2+ for HPV16 (30.3%) and other HPV (45.0%). Cytological findings that suggest invasive cervical cancer (squamous cells or adenocarcinoma), regardless of the status of HPV test, showed 100% diagnosis of CIN2 + , while atypias that suggest high-grade lesions, HSIL and ASC-H, positive for HPV test, showed in 86 and 55.2%, respectively, diagnosis of CIN2 + . ASC-H cytological results among women aged > 40 years old and negative HPV were mainly associated with benign findings. We observed that ≤ CIN1 has a higher prevalence among older women with negative HPV, while for high-grade lesions there is an increase among young women HPV16- and/or 18-positive. In cancer diagnosis, we observed a predominance of HPV 16/18 regardless of the age group.

Conclusion The highest risks of precursor lesions and cervical cancer were found among women with positive HPV 16/18 tests and severe cytological atypia in

Keywords
- squamous intraepithelial lesions of the cervix
- uterine cervical neoplasms
- papillomavirus infections
- colposcopy
- risk

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population screening tests. In addition, cytological findings of ASC-H HPV negative in women > 40 years old usually represent benign findings in histological investigation.

Resumo

Objetivo Estabelecer um perfil de risco de lesões intraepiteliais de alto grau e câncer do colo do útero (NIC2 +) em mulheres submetidas a colposcopia considerando-se a infecção pelo papilomavírus humano (HPV), citologia cervical e idade.

Métodos Estudo retrospectivo transversal em banco de dados informatizado de mulheres com idade ≥ 18 anos que realizaram colposcopia no departamento de Prevenção de Câncer no Hospital do Câncer de Barretos/SP no período de 2017 a 2019.

Resultados Foram incluídas 3.411 mulheres, sendo 58,0% positivas para HPV de alto risco, e maior prevalência de NIC2+ para HPV16 (30,3%) e outros HPV (45,0%). Resultados citológicos sugestivos de lesões invasivas (epidermoide ou adenocarcinoma), independente do teste de HPV, apresentaram 100% de diagnóstico NIC2 +, enquanto atipias sugestivas de lesões de alto grau, HSIL e ASC-H, associados a HPV positivo, apresentaram 86 e 55,2%, respectivamente. Resultados citológicos de ASC-H entre mulheres > 40 anos e HPV negativo foram associados principalmente a achados benignos. Observamos que ≤ NIC1 apresenta uma maior prevalência entre mulheres mais velhas com HPV negativo, enquanto para lesões de alto grau, há um aumento entre mulheres mais jovens positivas para HPV16/18. Para diagnóstico de câncer, observamos que há um predomínio de HPV16/18 independente da faixa etária.

Conclusão Foi identificado maior risco de lesões precursoras e câncer entre mulheres com HPV 16/18 positivo e atipias citológicas graves em testes de rastreio populacional. Além disso, resultados citológicos de ASC-H quando associados a HPV negativo com idade > 40 anos habitualmente representam achados benignos em investigação histológica.

Palavras-chave
- lesão escamosa intraepitelial cervical
- neoplasias do colo do útero
- infecções por papillomavirus
- colposcopia
- risco

Introduction

Cervical cancer is one of the most frequent types of cancer among women worldwide, being the fourth in incidence and mortality, with an estimated 604,127 new cases in 2020.[1] Among the countries with the highest incidence of this disease, Brazil is fourth (17,743) in absolute numbers after India, China, and Indonesia.[1,2] According to data from the National Cancer Institute (INCA, in the Portuguese acronym), cervical cancer is the third most common cancer among Brazilian women (7.0%).[3]

Persistent infection by human papillomavirus (HPV) is the leading cause of cervical cancer, with 14 types considered oncogenic (hrHPV). Types 16 and 18 together are responsible for ~ 70% of squamous cell carcinomas, followed by types 31, 33, 45, 52, and 58.[4–6]

The early detection of precursor lesions through population screening programs and the expansion of HPV vaccination coverage can minimize the impact of cervical cancer.[7,8] In Brazil, cervical cytology is recommended for women aged between 25 and 64 years old. Tests for the detection of HPV are not available for women assisted by the public health system; however, regional strategies and some population-based studies have been used.[9–12]

The initiatives to implement molecular tests in population screening are justified because there is evidence that the presence of hrHPV infection, even among women with normal cytology, increases the risk of CIN2+ and may contribute to bringing the diagnosis forward by more than a decade depending on the case.[11–15] In addition, HPV16/18 coinfection is related to high rates of high-grade lesions (56.7%) and cancer (71.1%),[16] which demonstrates the importance of tests based on the polymerase chain reaction (PCR) technique with genotyping of the viral types.

The association of viral type with the age of the infected woman may also represent an increased risk factor for precursor lesions. Positivity for HPV16 in CIN2+ cases showed an increased risk among English women aged 24 to 44 years old, and for the group aged from 45 to 64 years old, there was a greater association with viral types other than 16/18.[17]

Considering the cytological findings, the association of moderate to severe atypia and hrHPV infection among patients referred for colposcopy represents a high risk for histological diagnosis of high-grade and invasive lesions.[18] The presence of severe atypia among women infected with types 16/18 indicates a high risk of CIN2 +, with results varying between 60.2 and 83.6%.[19]

Therefore, cytological results, HPV testing, and age have demonstrated their potential in the stratification of risk for precursor lesions and cervical cancer.[18,20] At the Hospital do Câncer de Barretos (HCB, in the Portuguese acronym), all patients performed hr-HPV test in the colposcopy; therefore, the objective of the present study was to stratify the risk of precursor lesions and cancer among women undergoing colposcopy at the Hospital do Câncer de Barretos in São Paulo, state of São Paulo, Brazil.

Methods

Women $\geq$ 18 years old who underwent colposcopy at the Cancer Prevention Unit of the HCB from 2017 to 2019 were included. Patients undergoing colposcopy were previously screened by cervical cytology, and HPV tests were performed as a cotest on the same sample of screening cytology or collected during the colposcopy examination. Inconclusive results or findings related to other sites (vagina, vulva, and endometrium) were disregarded.

This was a retrospective cross-sectional study based on a computerized database of the Department of Cancer Prevention of the HCB.

The cervical cancer screening program includes conventional cervical smear and liquid based cytology (LBC, BD SurePath). Samples were sent to the Pathology laboratory for preparation of slides according to the manufacturer's instructions using BD PrepMate and BD PrepStain.

For the detection of HPV DNA, the Cobas HPV Test X480TM (Roche Molecular Systems, Pleasanton, CA, USA) was used. This test detects 14 types of HPV, with HPV 16 and 18 alone and HPV-others encompassing the oncogenic types in a grouping: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.[21]

Women are referred for colposcopy due to abnormal cervical screening at the HCB. During colposcopy, biopsy is performed when the gynecologist identifies a lesion in the examination. Biopsy was not performed when squamocolumnar junction (SCJ) was visualized and no lesion was identified by the gynecologist. Finally, when SCJ was not visualized and no lesion was identified by the gynecologist, an endocervical curettage (ECC) was performed.

The gold standard considered was the combination of colposcopic examination and anatomopathological results for cases undergoing biopsies or excisional therapeutic procedures (excision of the transformation zone of the cervix [TZE]). The final histological diagnosis was established according to the most severe result obtained.

Analyses of comparisons of proportions were performed using the chi-squared test, considering that the differences between the groups were statistically significant when the *p*-value was < 0.05. A confidence interval (CI) of 95% was considered. IBM SPSS Statistics for Windows version 27 (IBM Corp., Armonk, NY, USA) was used for data storage and statistical analysis.

The present study was conducted in accordance with the guidelines for good clinical practice and was approved by the Ethics Committee of the HCB under CAAE number 50357321.9.0000.5437.

Results

A total of 3,411 women aged from 18 to 93 years old (mean 42.5 years old) who underwent colposcopy between March 2017 and December 2019 were included; 27.4% of the participants were tested for HPV at the time of screening (associated with cytology), and 72.6% were tested during colposcopy. The positivity rate for HPV was 58.0% (1,979 women), with 802 positive for HPV16/18 (40.5%) and 1,177 positive for other HPV types (59.5%). HPV16 alone was detected in 19.6% of the cases. Among the women positive for types 16/18, there was a higher prevalence (38.4%) of CIN3. Among the women positive for other viral types than 16/18, 52.8% had no intraepithelial lesions or cancer. In the group of women who tested negative for HPV, 86% had benign findings on colposcopy associated with pathological findings. Our findings show the evidence of false positives in DNA-HPV results since we find $\sim$ 5% of CIN2+ findings in HPV-negative cases, which could be explained by the possibility of a few cases of cervical cancer not being caused by HPV (►**Fig. 1**).

Regarding cytology, the presence of atypical squamous cells of undetermined significance, which cannot rule out a high-grade lesion (ASC-H), was the most frequent finding (40.8%) and the cytological classification that most commonly pushes the patient to the complementary examination of colposcopy. The mean ages of the women diagnosed with high-grade intraepithelial lesions were 36.4 years old and, for cases of cervical cancer, 43.8 years old (►**Table 1**).

Considering the diagnoses of CIN2/3 and cervical cancer, the HPV positivity rates were 90.8% and 94.5%, respectively. Types 16 and 18 were detected in 50.8% of the women with CIN2/3 and in 81.7% of the patients diagnosed with cancer. HSIL and ASCH were the types of cytological atypia most frequently associated with the diagnosis of CIN2+ (►**Table 2**).

For the analysis of HPV positivity in the CIN2+ and CIN3+ populations, there was greater positivity in the group of other HPVs (45 and 41.5%, respectively) and HPV16 alone (30.3 and 34%, respectively). The most frequent combination was observed in the combined HPV16 and other HPV groups, namely, 14.4% for CIN2+ and 14.0% for CIN3+ (►**Fig. 2**).

Positivity for HPV 16 and 18 was associated with a higher prevalence of diagnosis of CIN2, CIN3 and cancer (8.4, 39.3, and 12.5%, respectively), while other HPV types and negative HPV showed higher prevalence of diagnosis of $\leq$ CIN1 (67.4 and 94.6%, respectively). Regarding cytology, the diagnoses of benign and low-grade intraepithelial lesions were more frequent among women with cytology showing ASCUS, LSIL or NILM. CIN2/3 was more frequent among women with AIS, IA, SCC, HSIL (invasive) or HSIL cytology (►**Table 3**).

Patients classified as ASCH were the most frequent finding in cytology (►**Table 1**). In total, 54.0% of these patients are $\geq$ 40 years old. We observe in this group 64.6% negative HPV associated with 61.8% of diagnosis as benign/CIN1.

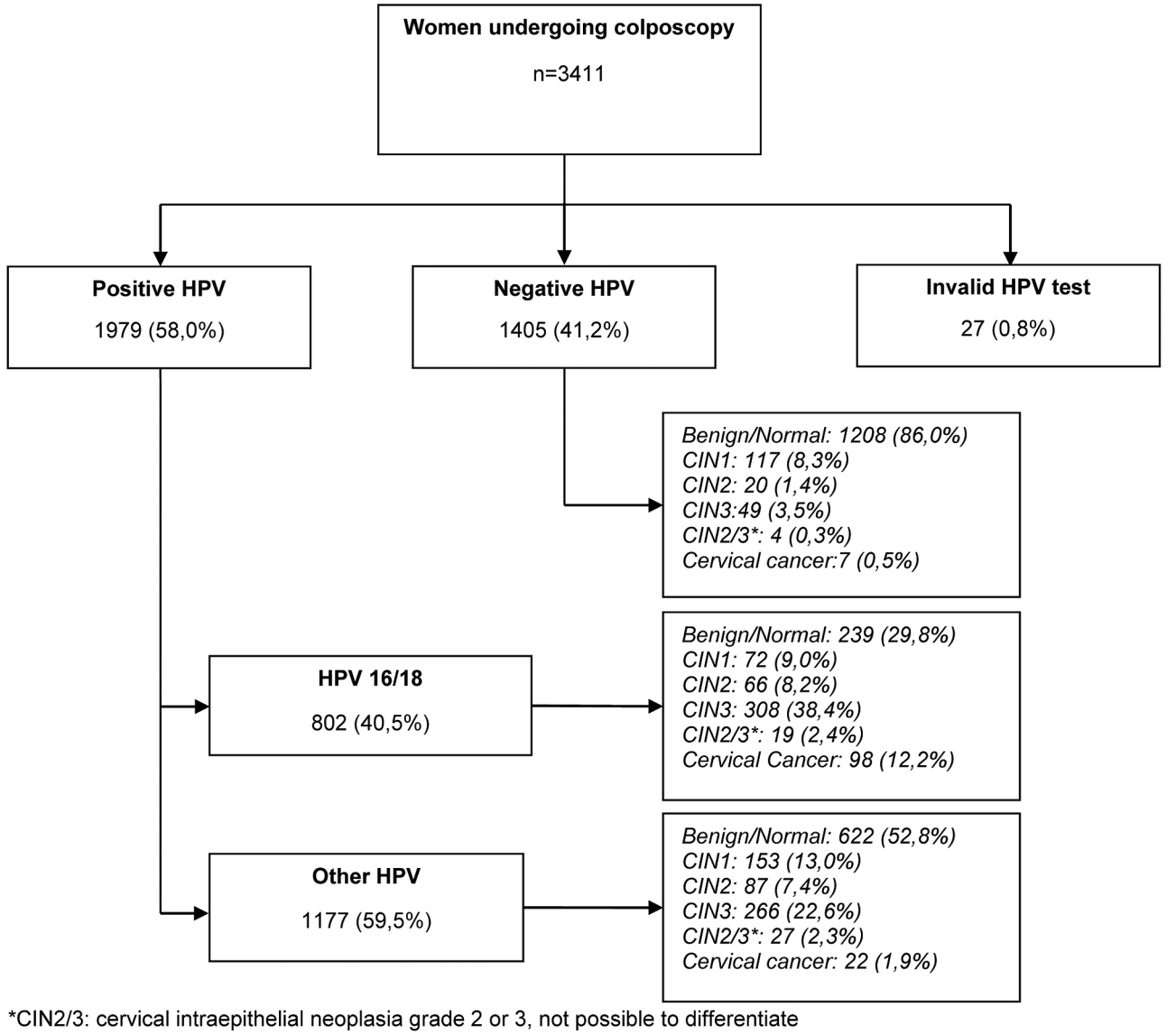

Fig. 1 Women undergoing colposcopy in relation to the HPV test and final diagnosis.

Otherwise, women < 40 years old showed a positivity for HPV in 67,2%. In this group, 44,5% had the diagnosis of CIN2+ (►**Fig. 3**).

►**Fig. 4** shows the risk of CIN2+ according to the combination of cytological results and HPV tests.

There was a higher prevalence of infection by type 16/18 among younger women diagnosed with CIN2/3 and the involvement of the other viral types increased proportionally with increasing age. Among women diagnosed with cancer, a higher incidence of infection by type 16/18 was also found in all age groups, but there was a tendency for other viral types to increase beginning at 35 years old (►**Fig. 5**).

Discussion

The present study aimed to stratify the risk of precursor lesions and cervical cancer among women who were attended at a reference center for colposcopy, considering age, the cytological test result, and HPV genotype.

The possibility of molecular tests associated with colposcopic and cytological evaluation increases the accuracy of diagnosis, and the high negative predictive value of HPV tests confers a low risk of relevant tissue damage among women who test negative. In our study, 41.19% of the women were negative for hrHPV, of which 86% were negative for intraepithelial lesions and cervical cancer. Other studies have demonstrated the association between colposcopic and histological findings and HPV infection status.[18,20,24] Among women referred for colposcopy, a large group showed cytological results of mild atypia or undetermined findings; for these cases, some groups of low-risk HPV (not identified by the method used in the study) and some results related to tissue repair, inflammation, and atrophy are expected.

In the qualitative evaluation of the composition of viral types among women who tested positive, it was observed

Table 1 Study population according to HPV test, age, cytology, and final diagnosis

				Mean age (years old)
			n (%)	
HPV genotyping	Positive		1979 (58.0)	40.1
		HPV16	388 (19.6)	38.3
		HPV18	101 (5.1)	40.0
		Other HPV	1177 (59.5)	41.6
		HPV16 and HPV18	12 (0.6)	30.4
		HPV16 and other HPV	214 (10.8)	37.3
		HPV18 and other HPV	68 (3.4)	40.2
		HPV16, HPV18, and other HPV	19 (1.0)	28.4
	Negative		1405 (41.2)	45.7
	Invalid		27 (0.8)	44.9
Cytology	ASC-H		1392 (40.8)	42.3
	AGC		480 (14.1)	43.8
	ASC-US		418 (12.3)	42.8
	HSIL		393 (11.5)	37.9
	LSIL		362 (10.6)	42.0
	NILM		165 (4.8)	45.0
	HSIL (inv)		43 (1.3)	43.9
	Atypical cells of undefined origin		80 (2.3)	46.7
	Endometrial cells[a]		28 (0.8)	52.7
	Unsatisfactory		24 (0.7)	51.2
	AIS		14 (0.4)	43.1
	SCC		9 (0.3)	49.1
	IA		3 (0.1)	47.7
Final Diagnosis	Benign		2089 (61.2)	45.7
	CIN1		344 (10.1)	38.4
	CIN2		174 (5.1)	35.4
	CIN3		627 (18.4)	36.4
	CIN2/3[b]		50 (1.5)	35.6
	Adenocarcinoma in situ		41 (1.2)	39.6
	Invasive adenocarcinoma		7 (0.2)	47.3
	Squamous cell carcinomas		79 (2.3)	43.8
Total			3411 (100)	42.5

Abbreviations: AGC-US, atypical glandular endocervical cells[23]; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high grade squamous intraepithelial lesion; HSIL (inv), high grade squamous intraepithelial lesion cannot exclude invasion[22]; IA, Invasive adenocarcinoma; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; SCC, squamous cell carcinoma.
[a]Endometrial cells (in a woman $\geq$ 45 years old.
[b]CIN2/3: cervical intraepithelial neoplasia grade 2 or 3, not possible to differentiate.

Table 2 Characterization of the study population according to the final diagnosis

Final diagnosis	Total	Positive HPV	hrHPV genotyping		Cytology						
			HPV 16/18	Other HPV	SCC	IA	AIS	HSIL (inv)	HSIL	ASC-H	Others*
Benign	2089	861 (41.2)	239 (27.8)	622 (72.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	70 (3.4)	822 (39.4)	1195 (57.2)
CIN1	344	225 (65.4)	72 (32.0)	153 (68.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (6.1)	142 (41.3)	181 (52.6)
CIN2/3	851	773 (90.8)	393 (50.8)	380 (49.2)	2 (0.2)	1 (0.1)	1(0.1)	29 (3.4)	266 (31.2)	394 (46.3)	158 (18.6)
Cervical cancer	127	120 (94.5)	98 (81.7)	22 (18.3)	7 (5.5)	2 (1.6)	13 (10.2)	12 (9.5)	36 (28.4)	34 (26.8)	23 (18.1)

Abbreviations: AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; HPV, human papillomavirus; HSIL (inv), high grade squamous intraepithelial lesion cannot exclude invasion[22]; IA, Invasive adenocarcinoma; SCC, squamous cell carcinoma.
*Others: AGC/ASC-US/ Atypical cells of undefined origin /LSIL/endometrial cells/unsatisfactory/NILM.

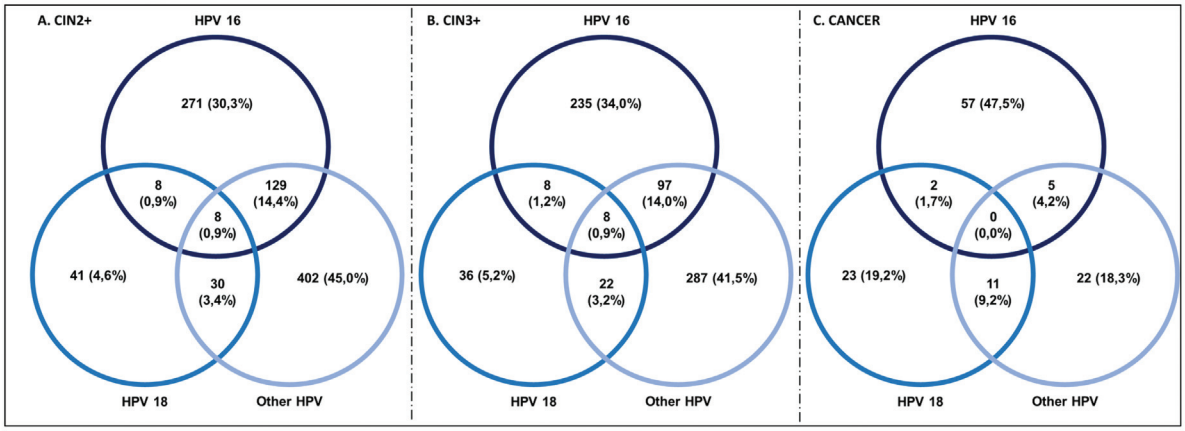

Fig. 2 HPV genotyping for CIN2 +, CIN3 +, and cancer.

Table 3 Prevalence of HPV genotyping and cytology according to final diagnosis

	≤ CIN1	CIN2	CIN3	Cancer	*p-value*
	n (%; 95%IC)	n (%; 95%IC)	n (%; 95%IC)	n (%; 95%IC)	
hrHPV genotyping					
HPV 16/18	311 (39.7%; 36.3–43.2)	66 (8.4%; 6.6–10.6)	308 (39.3%; 35.9–42.9)	98 (12.5%; 10.3–15.0)	0.00*
Other HPV	775 (67.4%; 64.6–70.1)	87 (7.6%; 6.1–9.2)	266 (23.1%; 20.7–25.7)	22 (1.9%; 1.2–2.9)	0.00*
Negative HPV	1325 (94.6%; 93.3–95.7)	20 (1.4%; 0.9–2.2)	49 (3.5%; 2.6–4.6)	7 (0.5%; 0.2–1.0)	0.00*
Cytology					
ASC-H	964 (70.5%; 68.0–72.9)	97 (7.1%; 5.8–8.6)	273 (20.0%; 17.9–22.2)	34 (2.5%; 1.7–3.5)	0.000*
AGC	433 (91.2%; 88.2–93.6)	1 (0.2%; 0.0–1.2)	29 (6.1%; 4.1–8.7)	12 (2.5%; 1.3–4.4)	0.000*
ASC-US	364 (87.3%; 83.7–90.3)	16 (3.8%; 2.2–6.2)	34 (8.2%; 5.7–11.2)	3 (0.7%; 0.2–2.1)	0.000*
HSIL	91 (24.0%; 19.8–28.6)	34 (9.0%; 6.3–12.3)	218 (57.5%; 52.4–62.6)	36 (9.5%; 6.7–12.9)	0.000*
LSIL	315 (88.0%; 84.2–91.2)	21 (5.9%; 3.7–8.8)	21 (5.9%; 3.7–8.8)	1 (0.3%; 0.0–1.6)	0.000*
NILM	150 (91.5%; 86.1–95.3)	3 (1.8%; 0.4–5.3)	10 (6.1%; 3.0–11.0)	1 (0.6%; 0.0–3.6)	0.000*
Atypical cells of undefined origin	63 (78.8%; 68.2–87.1)	0 (0.0%; 0.0–4.5**)	12 (15.0%; 8.0–24.7)	5 (6.3%; 2.1–14.0)	0.085
HSIL (inv)	2 (4.8%; 0.6–16.2)	2 (4.8%; 0.6–16.2)	26 (61.9%; 45.6–76.4)	12 (28.6%; 15.7–44.6)	0.000*
AIS	0 (0.0%; 0.0–23.2**)	0 (0.0%; 0.0–23.2**)	1 (7.1%; 0.2–33.9)	13 (92.9%; 66.1–99.8)	0.000*
SCC	0 (0.0%; 0.0–33.6**)	0 (0.0%; 0.0–33.6**)	2 (22.2%; 2.8–60.0)	7 (77.8%; 40.0–97.1)	0.000*
IA	0 (0.0%; 0.0–70.8**)	0 (0.0%; 0.0–70.8**)	1 (33.3%; 0.8–90.6)	2 (66.7%; 9.4–99.2)	0.002

Abbreviations: AGC-US, atypical glandular endocervical cells[23]; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high grade squamous intraepithelial lesion; HSIL (inv), high grade squamous intraepithelial lesion cannot exclude invasion[22]; IA, Invasive adenocarcinoma; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; SCC, squamous cell carcinoma.
*p-value < 0.01.
**One-sided 97.5% confidence interval.

that the majority (59.5%) was infected with non-16/18 types. However, there is a clear trend toward benign findings and low-grade intraepithelial lesions in this group of women, whereas type 16/18 increases the risk of CIN3 +. The ESTAMPA study conducted in Latin American countries also found an association between HPV16/18 positivity and the severity of tissue lesions (30.6% CIN2, 56.7% CIN3, and 71.1% cancer).[16] The impossibility of individual genotyping of HPV types other than 16/18 is a limitation of the present study because it could stratify, for example, the importance of types 31, 33, and 45 that have been demonstrated in other publications.[25–30]

Cytological atypia classified as ASCH was the most frequent, and in 40.8% of the cases, the need for colposcopic

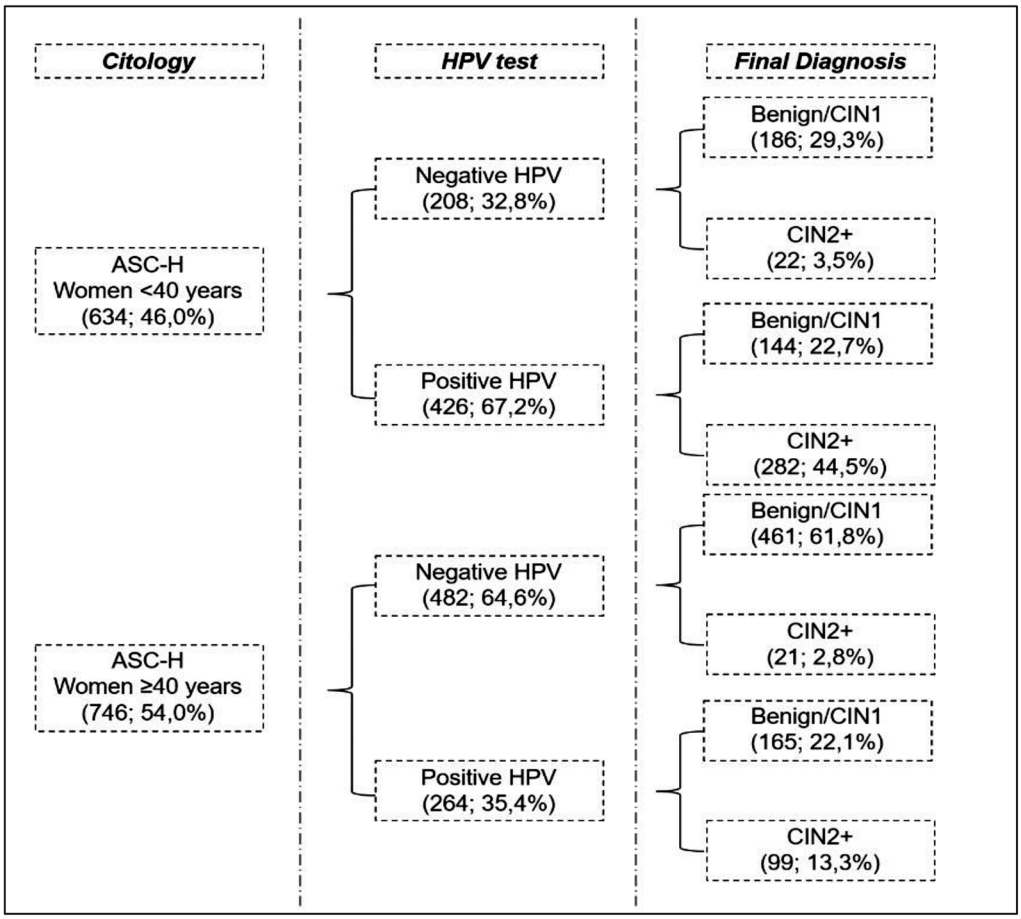

Fig. 3 Characterization of patients with ASC-H cytology.

examination was justified. Among the women who received this cytological report, 50% tested positive for HPV, and a trend of CIN2/3 diagnoses was observed for the group of younger women. Other studies demonstrated the association of ASCH with precursor lesions and cancer according to HPV status.[19,31–33]

There is a clear association of ASCH results with factors of atrophy of the cervical epithelium among postmenopausal women, and when associated with negative HPV > 40 years old, they usually represent benign findings in histological investigation.

Women with SCC and AI cytology, regardless of the HPV test status, had a 100% diagnosis of CIN2 +/CIN3 +, which reflects the high specificity of cytology directly associated with the degree of atypia. When associated with positive HPV, the cytology HSIL and ASCH presented a diagnosis of CIN2+ in 86 and 55.2% of patients, respectively. In the absence of HPV infection, CIN2+ detection decreases to < 50% for these same cytological results. These results agree with those of another study that reported a specificity of 86.6% in the diagnosis of CIN2+ among women with HSIL and positive HPV16/18.[18]

In view of the risks of developing precursor lesions and cervical cancer, the detection of HPV has shown great benefits, especially due to the increased sensitivity in detecting CIN3 +.[33–35] Several studies have implemented the use of HPV tests in population screening of precursor lesions and cervical cancer in place of cytology, which makes it possible to extend the interval of repetition of the exams to periods of 5 years.[36,37] In Brazil, HPV testing is not available for population screening in the public health system, which is still based on cytological tests.[10] Some isolated and regional initiatives have proposed the use of HPV tests with results that endorse its applicability, including positive results in cost-effectiveness evaluations among Brazilian women.[11,38]

Our study did not aim to evaluate the primary screening of cervical lesions by molecular tests but focused on the importance of stratifying the risk of women previously screened by cytological tests, considering age and the results of the investigation for HPV by genotyping. The results demonstrate the importance of additional molecular tests, especially among women with cytological tests classified as inconclusive changes and atypia of undetermined significance.

In addition, the possibility of partial HPV genotyping may indicate the need for clinical procedures and personalized follow-up protocols for each patient with individual risk stratification. Although it was not the focus of the present study, the HPV vaccinated populations may also be an additional benefit with HPV genotyping for those viral types that are not protected by the vaccine.

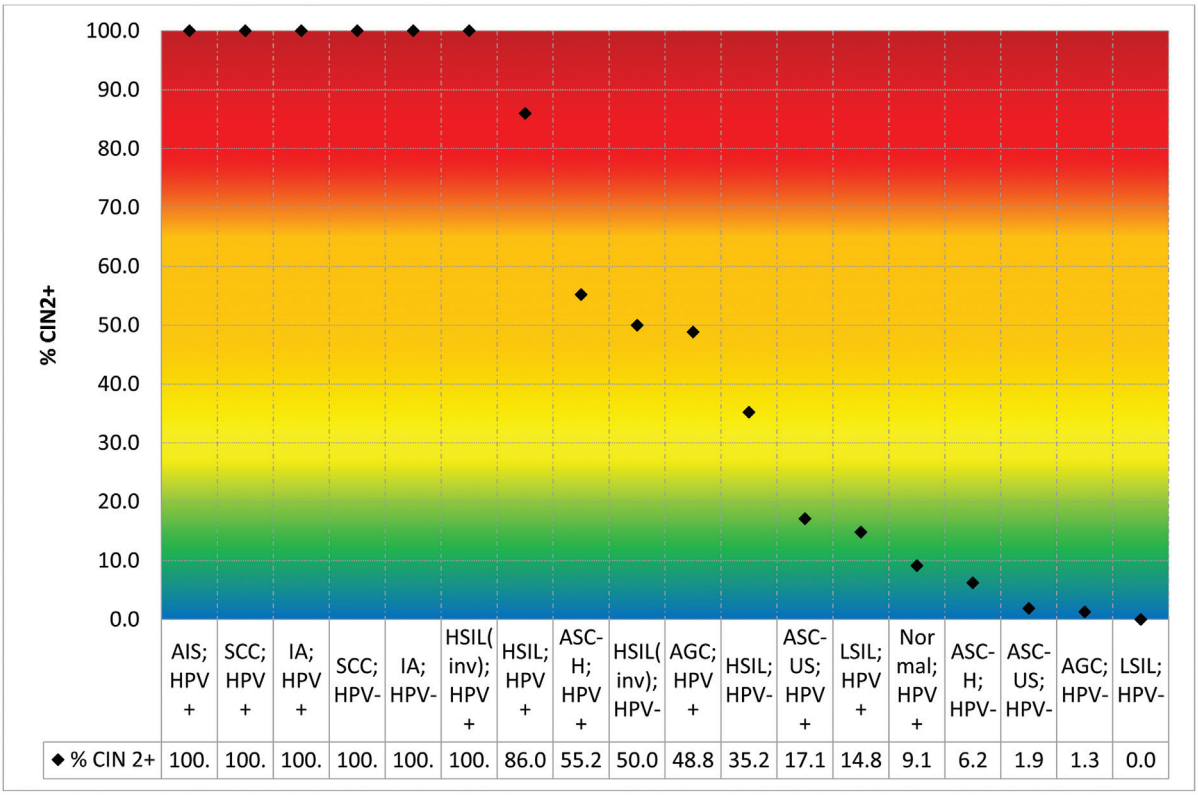

Fig. 4 Prevalence of CIN2+ according to cytology and HPV test results.

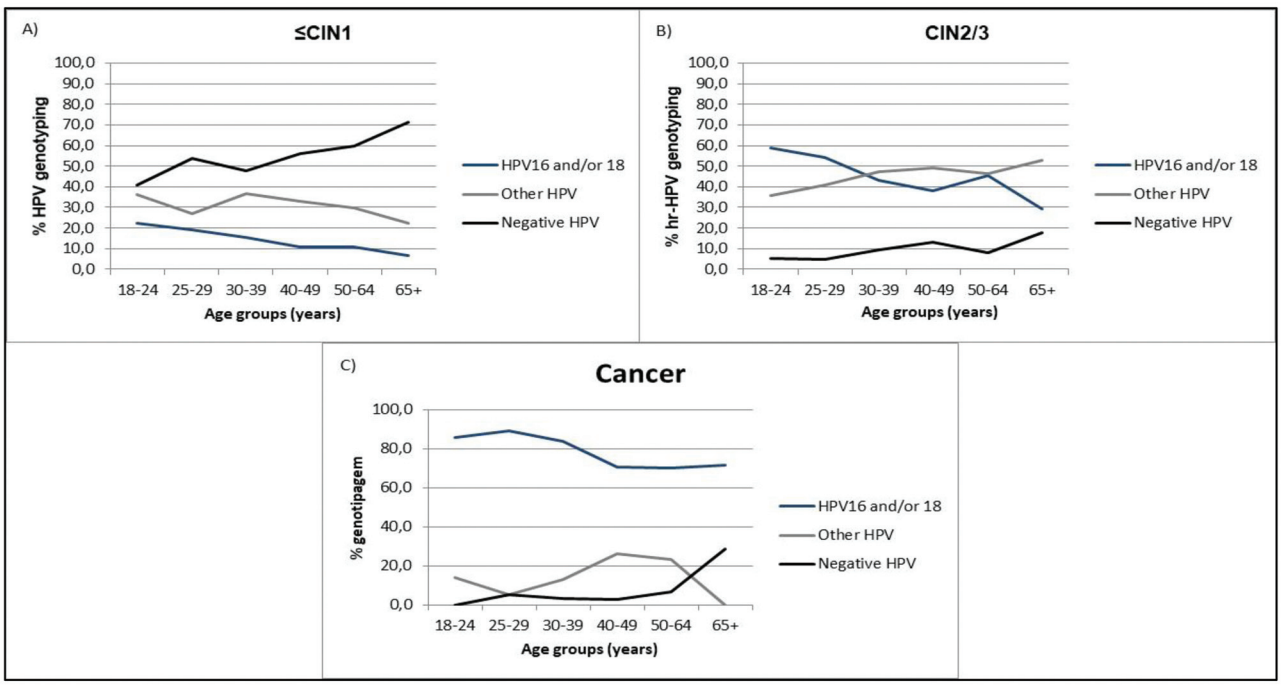

Figure A shows a p-value < 0,01. Figure B shows a p-value < 0,01. C. Figure C shows a p-value 0,16. Invalid HPV was disregarded

Fig. 5 Association between HPV genotype and age at final diagnosis.

The results described here reinforce the importance of types 16/18 in the carcinogenesis of cervical cancer and add evidence regarding the participation of other viral types in a large proportion of women diagnosed with precursor lesions.

Conclusion

The highest risks of precursor lesions and cervical cancer were found among women with positive HPV 16/18 tests and severe cytological atypia in population screening tests. Patients with cytology classified as ASCH may have a risk of CIN2+ stratified by the HPV test, and the number of positive tests will be higher among younger women < 40 years old.

Contributors

All authors were involved in substantial contributions to conception and design, data collection, data analysis and interpretation; article writing, relevant critical review of the intellectual content; and final approval of the version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

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Effectiveness of an Educational Intervention with Guidelines from the Total Acceleration of Postoperative Recovery Project (ACERTO) in Gynecology

Efetividade de uma intervenção educativa com diretrizes do projeto Aceleração da Recuperação Total Pós-operatória (ACERTO) na ginecologia

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Abstract

Objective To evaluate the effectiveness of an educational intervention among gynecologists about recommendations of the Total Acceleration of Postoperative Recovery (ACERTO, in the Portuguese acronym) project derived from the solid foundations of Enhanced Recovery After Surgery (ERAS) guidelines to optimize hospital care for surgical-gynecological patients.

Methods Educational intervention through monthly 1-hour long meetings (3 months), with the application of an objective questionnaire about specific knowledge of the ACERTO project between before and after educational intervention phases, for gynecologists, after approval by the ethics committee and signature of informed consent by participants, in a federal university hospital.

Results Among the 25 gynecologists who agreed to participate, the educational intervention could be effective with a statistically significant difference between the phases before and after the intervention for the main recommendations of the ACERTO project, such as abbreviation of preoperative fasting ($p = 0.006$), venous thromboembolism prophylaxis ($p = 0.024$), knowledge and replication of ACERTO ($p = 0.034$), and multimodal analgesia ($p = 0.021$).

Conclusion An educational intervention, through clinical meetings with exposition and discussion of the recommendations of the ACERTO project based on the ERAS protocol can be effective for the knowledge and possibility of practical application of the main measures, such as abbreviation of preoperative fasting, multimodal analgesia, and prophylaxis of thrombosis among gynecologists.

Keywords
- preoperative care
- perioperative care
- surgical procedures in gynecology
- enhanced recovery after surgery

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Resumo

Objetivo Avaliar a efetividade de uma intervenção educativa entre ginecologistas de um hospital universitário a fim de capacitar o conhecimento científico das recomendações do projeto Aceleração da Recuperação Total Pós-operatória ACERTO, derivado das bases sólidas do protocolo *Enhanced Recovery After Surgery* (ERAS) para otimizar a assistência hospitalar de pacientes cirúrgico-ginecológicas.

Métodos Intervenção educativa por meio de reuniões mensais por 3 meses, com duração de 1 hora, com aplicação de questionário objetivo com questões de conhecimentos específicos do projeto ACERTO com fases antes e depois da intervenção, para profissionais ginecologistas, após aprovação do comitê de ética em pesquisas (CEP) e assinatura do termo de consentimento livre e esclarecido (TCLE) pelos participantes.

Resultados Dentre os 25 ginecologistas que aceitaram participar, a intervenção educativa se mostrou eficaz com diferença estatisticamente significante entre as fases antes e depois da intervenção para as principais recomendações do projeto ACERTO, como abreviação de jejum pré-operatório ($p = 0.006$), profilaxia de tromboembolismo venoso ($p = 0.024$), conhecimento e replicação do conhecimento do ACERTO ($p = 0.006$) e analgesia multimodal ($p = 0.006$).

Conclusão Uma intervenção educativa, por meio de reuniões clínicas com exposição e discussão das recomendações do projeto ACERTO baseadas em evidências e derivadas do ERAS é eficaz para o conhecimento e possibilidade de aplicação prática de medidas como abreviação de jejum pré-operatório, analgesia multimodal e profilaxia de trombose entre ginecologistas.

Palavras-chave

- cuidados pré-operatórios
- cuidados perioperatórios
- procedimentos cirúrgicos em ginecologia
- recuperação melhorada após a cirurgia

Introduction

The Acceleration of Total Postoperative Recovery (ACERTO) project is a program that aims to optimize the postoperative recovery time in patients who undergo surgical procedures.[1] The program brings together pre, intra, and postoperative measures that favor the surgical outcome in several areas such as abdominal, bariatric, pediatric, orthopedic, and also in the gynecological area. Derived from the solid foundations of the Enhanced Recovery After Surgery (ERAS), the ACERTO project, in Brazil and other Latin American countries, prioritizes evidence-based medicine in addition to being an educational program.[1–3]

Currently, several medical societies, including the International Federation of Gynecology and Obstetrics (FIGO),[4] American College of Obstetricians and Gynecologists (ACOG),[5] the European Society for Clinical Nutrition and Metabolism (ESPEN),[6] and the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO),[7] among others, are engaged in the development of clinical guidelines and protocols that improve the quality of perioperative care through ERAS. Mastery of the surgical technique is important; however, perioperative care favors positive surgical results, in addition to maximizing recovery, minimizing unpleasant symptoms such as pain, reducing complications such as thrombosis, and decreasing hospitalization time and hospital costs.[1–7]

The term ACERTO was an acronym developed in Latin America for ERAS with the purpose of favoring the understanding and adherence of the ERAS recommendations with local adaptations.[1] The ACERTO project, just like ERAS guidelines, focuses on clear information to the patient about the surgery, abbreviation of preoperative fasting, early postsurgical patient ambulation, thrombosis prophylaxis, early oral refeeding, optimization of the use of drains and probes to avoid unnecessary use, hyperhydration prevention, and facilitatation of analgesia to stimulate the recovery of patients undergoing surgical treatment.[1–7]

Despite the scientific support of the ACERTO Project's recommendations, few hospitals or services apply its guidelines in practice due to lack of knowledge and adherence of health professionals. Given this scenario, the objective of the present study was to evaluate the effectiveness of an educational intervention in the gynecology department of a university hospital on the main recommendations of the ACERTO project to foster the knowledge and adherence of professionals in the practical applicability of standardized measures, such as the abbreviation of the preoperative fasting, prophylaxis for thromboembolic events, and multimodal and humanized analgesia approach to enable postoperative recovery in gynecological surgeries.

Methods

The study is quantitative and prospective, with a before and after design of an educational intervention (►**Figure 1**). It was carried out only after approval by the Research Ethics Committee (REC) of Universidade Federal de Uberlândia (UFU), with a favorable opinion CAAE: 57830922.5.0000.5152, in the department of gynecology of the Hospital de Clínicas da Universidade Federal de Uberlândia (HCUFU), a regional

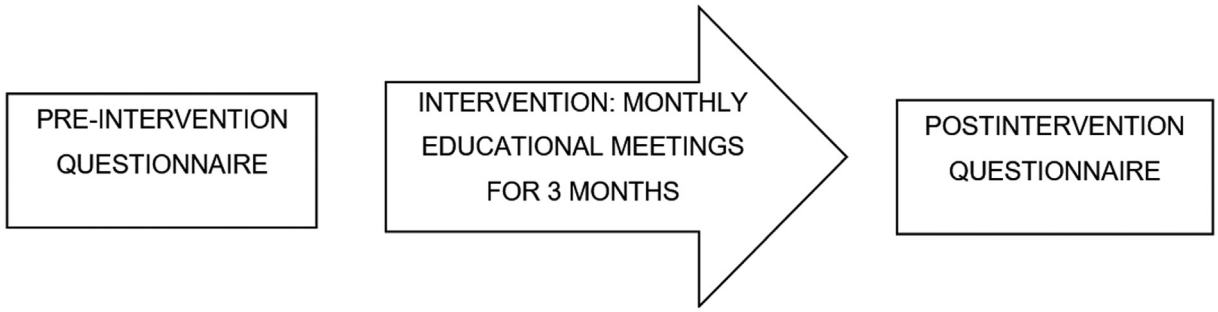

Fig. 1 Schematic design of the study.

university hospital managed by Empresa Brasileira de Serviços Hospitalares (EBSERH). The methodology consisted of an educational intervention to medical professionals invited to participate in the study, from the area of gynecology, through scientific meetings that addressed the main recommendations of the ACERTO project in perioperative care for surgical-gynecological patients. The inclusion criteria were gynecologists from the gynecology sector of HCUFU who agreed to participate in the research and signed the informed consent form (ICF). The exclusion criteria were: Not accepting to participate in the research, not signing the ICF, or not belonging to the HCUFU gynecology sector.

All teaching gynecologists, residents and preceptors were invited, and only those who voluntarily met the inclusion criteria, participated in the sample. After clarifying the project and signing the ICF, they filled out a knowledge assessment questionnaire of the main recommendations of the ACERTO project (attached). The questionnaire was standardized with 30 questions, 10 of which were YES or NO, 10 with simple justification and 10 multiple-choice, with a completion time of approximately 5 to 10 minutes on knowledge of abbreviation of preoperative fasting, prophylaxis for thromboembolic events, knowledge about multimodal analgesia and surgical metabolism. This questionnaire was approved by the REC of the institution as a data collection instrument, delivered to the participating gynecologists, with confidentiality of the names of the participants, with only the sample number identification for later construction of the database, containing questions about knowledge, applicability, and development of the ACERTO project, as well as the advantages for the patient in the postoperative period and the safety in applying it. The same questionnaire was applied after the educational intervention.

- Application of the printed questionnaire and delivery to the gynecologists before the educational intervention or preintervention (PRE) phase on the recommendations of the ACERTO project.
- Educational explanation about the benefits of the ACERTO project parameters to research participants. The educational intervention consisted of monthly meetings of 30 to 40 minutesfor 3 months, with at least 20 minutes of open time for discussions and suggestions to encourage adherence to effective measures to accelerate the patients' recovery.
- Application of the printed questionnaire and delivery to the gynecologists after the educational intervention, or postintervention phase (POST), on the recommendations of the ACERTO project (►**Figure 1**).

To calculate the sample size, the following formula was used, described by Fontenelle et al.[8] where: $z\alpha/2 =$ Alpha error value (two-tailed); $z\beta =$ Beta error value; s = standard deviation; d = Minimum difference to be detected. The sample size was determined so that it could identify, with 95% confidence (α error = 0.05), a difference, if any, of at least 5 participants between the before and after groups who would possibly adhere or not to the ACERTO project, among the averages. The power of the test was considered to be 80% (error $\beta = 0.20$). Therefore, through this calculation, a sample of at least 20 participants from the gynecology department was suggested. This would be the minimum number of participants for the survey not to be terminated. The Chi-square or Fisher test was used to analyze categorical variables. Results were expressed as mean, followed by standard deviation (SD) or mean standard error or median. Data were analyzed using the IBM SPSS Statistics for Windows, version 20.0 software (IBM Corp., Armonk, HY, USA), with license granted to the department of mathematics at UFU. The data were analyzed quantitatively, with data protection, academic secrecy, until the publication of the results, with the objective of evaluating whether the educational intervention proved to be effective in obtaining a significant response regarding the characterization of the scientific knowledge of gynecologists about the ACERTO project derived from of ERAS at HCUFU.

Results

The data analyzed after applying the methodology described above are expressed below. ►**Table 1** shows a homogeneous sample between phases, with a total of 25 participants from 38 professional gynecologists in the department (65.78%), the majority being female, with a mean age of 27 years and less than 5 years since graduation. According to the data in ►**Table 2**, there was effectiveness of the educational intervention carried out to promote knowledge of the ACERTO project among the analyzed sample, with a statistically significant difference between the phases of before, or preintervention (PRE), and after, or postintervention (POST).

Table 1 Descriptive Statistics: Demographic data of the sample

	PHASE	Mean	Standart deviation Min	Max
AGE	PRE	27.1	2.90	25 34
	POST	27.1	2.90	25 34
GENDER*		Female N (%)	Male N (%)	
	PRE	20 (80.0%)	5 (20.0%)	
	POST	20 (80.0%)	5 (20.0%)	
TIME OF GRADUATION (y)		Less than 5y N (%)	Greater than 5y N (%)	
	PRE	22 (88.0%)	3 (12.0%)	
	POST	22 (88.0%)	3 (12.0%)	

Abbreviation: y, years.
Chi-square: $p = 0.248$.
*self-definition of gender identity.

Table 2 Knowledge of the ACERTO project and/or Mendelson syndrome and the ability to replicate and apply it in care practice

Knowledge of the ACERTO project and/or Mendelson syndrome			
PHASE	YES	NO	TOTAL
PRE	12 (48.0%)	13 (52.0%)	25 (100.0%)
POST	25 (100.0%)	0 (0.0%)	25 (100.0%)
Total	12 (75.0%)	4 (25.0%)	25 (100.0%)
Chi-square: $p = 0.021$			
The ability to replicate and apply it in care practice.			
PHASE	YES	NO	TOTAL
PRE	4 (16.0%)	21 (84.0%)	25 (100.0%)
POST	25 (100.0%)	0 (0.0%)	25 (100.0%)
Total	29 (58.0%)	21 (42.0%)	50 (100.0%)

Chi-square: $p = 0.034$.

Knowledge was consolidated in the POST phase in relation to the abbreviation of fasting, one of the priority guidelines of the ACERTO project, with clarification that the ingestion of clear liquid, enriched with carbohydrate and protein, without residues, up to 2 hours before surgery, does not predispose to the risk of pulmonary aspiration of gastric contents (Mendelson syndrome).[9] The effectiveness of the educational intervention was confirmed by the willingness to reproduce and apply knowledge in practice among gynecologists, as analyzed in ►**Table 2**.

According to the data in ►**Tables 3** and **4**, the educational intervention on prophylaxis recommendations for venous thromboembolism (VTE) aligned with the ACERTO project and ERAS among the evaluated gynecologists. These measures proved to be effective between the PRE and POST phases, both through criteria for mechanical and drug prophylaxis ($p = 0.024$) as well as encouraging early walking in the postoperative period ($p = 0.006$).

Table 3 Cited criteria for deep venous thromboembolism prophylaxis in the pre and postintervention phases

Criteria described	PHASE	
	PRE	POST
	N (%)	N (%)
Caprini	3 (12.0%)	23 (92.0%)
BMI, history of DVT	1 (4.0%)	0
Previous history, pathologies, surgical size	1 (4.0%)	0
Did not specify	13 (52.0%)	1 (4.0%)
Did not answer	7 (28.0%)	1 (4.0%)
TOTAL	25 (100%)	25 (100%)

Abbreviations: BMI, body mass index; DVT, deep venous thromboembolism.
Chi-square: $p = 0.024$.

Table 4 Comparison of early walking recommendation between the pre and post intervention phases

Time to stimulate early ambulation	PHASE	
	PRE	POST
	N (%)	N (%)
After recovery from spinal anesthesia	14 (56%)	22 (88.0%)
2 H	3 (12.0%)	0
4 H	1 (4.0%)	2 (8.0%)
6 H	1 (4.0%)	0
12 H	2 (8.0%)	0
Did not answer	4 (16%)	1 (4.0%)
TOTAL	25 (100.0%)	25 (100.0%)

Chi-square: $p = 0.006$.

Table 5 Prescription of opioids within multimodal analgesia

PHASE	YES	NO	TOTAL
PRE	13 (52.0%)	12 (48.0%)	25 (100.0%)
POST	0 (0.0%)	25 (100.0%)	25 (100.0%)
Total	13 (26.0%)	37 (74.0%)	50 (100.0%)

Chi-square: $p = 0.021$.

According to the ACERTO project criteria, multimodal analgesia involves pharmacological and non-pharmacological measures to minimize pain. However, the use of opioids is not recommended due to side effects. According to the data in ►**Table 5**, the educational intervention was effective in consolidating this knowledge among the studied sample.

The same outcome can be observed in relation to the concept of abbreviation of fasting for solids and liquids PRE and POST intervention, in which gynecologists consolidated with statistical difference the recommendation that fasting for solids can be established for up to 6 hours and for liquids without residues up to 2 hours before surgery (►**Table 6**).

Table 6 Comparison between knowledge of preoperative fasting time for solids and liquids without residues before and after the intervention

Preoperative fasting time for clear liquids without residues	PHASE	
	PRE	POST
	N (%)	N (%)
2H	13 (52.0%)	25 (100%)
6 H	8 (32.0%)	0 (0.0%)
8H	3 (12.0%)	0 (0.0%)
Did not answer	1 (4.0%)	0 (0.0%)
TOTAL	25 (100.0%)	25 (100.0%)
Preoperative fasting time for solids	**PHASE**	
	PRE	POST
	N (%)	N (%)
6 H	8 (32.0%)	25 (100.0%)
12 H	16 (64.0%)	0 (0.0%)
Did not answer	1 (4.0%)	0 (0.0%)
TOTAL	25 (100.0%)	25 (100.0%)

Chi-square: $p = 0.0098$.

Discussion

The results of the present study indicate that the perioperative care recommendations consolidated by the ERAS, despite being published and endorsed by several medical societies, are not always adhered to in practice, as observed in the statements of the questionnaire about such recommendations before a didactic explanation. On the other hand, the efforts to adapt the main recommendations such as abbreviation of preoperative fasting, prophylaxis of VTE, and stimulation of multimodal, as occurred with the ACERTO project, are commendable initiatives to bring evidence-based medicine from practice.[1–7,10]

In addition to projects adapted to the local reality, efforts to produce scientific discussions, training courses or educational interventions, such as the methodology used in this study, can be effective in disseminating knowledge and adherence to medical approaches such as paradigm shifts. The process of changing behavior occurs progressively with individual response; however, education provides the basis for the security of the practical application of new technologies.[8,9,11,12] According to recent studies on ERAS recommendations, barriers to implementation were analyzed, and the authors concluded that successful implementation requires a multidisciplinary team, a willingness to change, and a clear understanding of the protocol. Additionally, the difficulty in accomplishing necessary compliance to all protocol items calls for new implementation strategies, such as educational intervention.[11–13]

In perioperative care, an educational intervention provided greater knowledge and possible adherence to measures, such as abbreviation of preoperative fasting.[1] This measure promotes a positive modulation of insulin resistance, with a lower risk of rebound hyperglycemia in the postoperative period, with a lower chance of complications derived from a diabetogenic state provided by prolonged fasting.[12–15] Other authors have already demonstrated the positive modulation of trauma response metabolism by ingestion of clear liquid enriched with carbohydrate (ERAS) and added protein (ACERTO) up to 2 hours before gynecological surgery, without putting the patient at risk of pulmonary aspiration.[9,12–19] The understanding of the physiology of fasting abbreviation in the positive modulation of surgical metabolism favors adherence to this measure.[9,12–18]

Regarding pain management, the ACERTO project, aligned with ERAS, does not recommend the prescription of intraoperative and postoperative opioid analgesics, due to possible side effects such as drowsiness, dizziness, nausea, vomiting, and even respiratory depression. In addition to these effects being unpleasant for the patient, they make it difficult to approach early refeeding and walking, so encouraged by both projects.[12–16]

The ERAS and ACERTO protocols recommend the standardization of criteria for prescribing mechanical and/or drug prophylaxis according to Caprini's parameters, enshrined in the literature. However, before the educational intervention, such criteria were not established in the choice of antithrombotic therapy for the gynecological patient.[20,21]

According to the data from the present study, the educational intervention can be effective in consolidating concepts about antithrombotic therapy in perioperative care, previously not very well established among the sample of gynecologists evaluated. In addition, the simple early ambulation, recommended by the ERAS protocol and the ACERTO project, sometimes, unfortunately, of poor reinforcement in practice, is one of the pillars for the prevention of VTE, one of the most feared surgical complications in surgical procedures.[20–29]

In university hospitals with standardized management, where basic measures of the recommendations of the ACERTO project were implemented, the process took place in an educational way, with the adherence of professionals after scientific knowledge of the solid, practical and reliable bases of the ACERTO project, with satisfactory results both as an improvement in the assistance such as resource optimization.[1] In Latin America, these data were observed at Hospital Universitário Júlio Muller of Universidade Federal do Mato Grosso and Hospital de São Paulo of Escola Paulista de Medicina, among others.[1]

Challenges to the ERAS implementation may be encountered in other countries, regardless of the level of socioeconomic development. Health services from Canada, point out that the development of training sessions for health care professionals across the continuum of care (preoperative and admissions, operating room and postanesthesia care unit, and postoperative care) and the encouragement of their feedback can start an ERAS program.[30]

The authors point out that the initial results remain under follow-up to assess the long-term adherence to the perioperative measures discussed and accepted by the majority of the body of gynecologists.

The positive point of the present study refers to the most recommended topic of perioperative care according to evidence-based medicine, with a methodologically rigorous, prospective study of practical analysis of adherence to these recommendations. In addition, it demonstrates a possibility of reproducibility that is easy to perform in any hospital care service to optimize surgical results and reduce hospitalization time and consequent hospital costs. Educational intervention can be the basis for the practical application of evidence-based medicine. Taking standardized scientific knowledge of measures such as abbreviation of preoperative fasting, pulmonary thromboembolism (PTE prophylaxis, and multimodal analgesia to the professional who is in the service practice can make a difference in the quality of hospital care.

Another positive point was the approval of the project by the hospital management where the study was carried out with financial and scientific support to serve as a pilot for other areas in order to reduce complications, optimize hospitalizations and reduce hospital costs.

The main difficulty in the project was recruiting the sample, as these are professional gynecologists with a workload who showed up for meetings during off-duty hours, which limited the sample size. However, the authors believe that this fact was overcome due to the engagement of voluntary, spontaneous participants, without recruitment or call, favoring the execution of the project within the sufficient number of sample according to the initial statistical calculation. Thus, the educational intervention methodology can be stimulated and reproduced in other hospital services with the expectation of favorable results, as in the present study.

Conclusion

Educational intervention for gynecology professionals can consolidate scientific concepts of perioperative care endorsed by medical societies worldwide. This simple, low-cost, and highly reproducible methodology can be encouraged in other hospital services to align evidence-based medicine such as the ERAS-derived ACERTO project, with perioperative care in practice. Therefore, it is concluded that the perioperative recommendations for accelerating the patient's recovery, such as abbreviation of preoperative fasting, multimodal analgesia, and prophylaxis of thrombosis, complement and consolidate, as a fitting, after an educational intervention to an exceptional and humane quality of evidence-based care in gynecological surgery. The authors point out that this educational project, despite addressing a set of standardized perioperative recommendations, does not overcome the individualized decision of conduct based on the free exercise of medicine.

Contributions

Marra J: Project development, data collection, writing/proofreading/editing of the manuscript. Samper I: Project development, data collection, writing/proofreading/editing of the manuscript. Xavier L: Project development, data collection, writing/proofreading/editing of the manuscript. Anelvoi R: Project development, data collection, writing/proofreading/editing of the manuscript. Uyeda MG: Project development, data collection, writing/proofreading/editing of the manuscript. Sartori M: Project development, data collection, writing/proofreading/editing of the manuscript. Marquini G: Project development, data collection, writing/proofreading/editing of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Fetal Macrosomia and Postpartum Hemorrhage in Latin American and Caribbean Region: Systematic Review and Meta-analysis

Macrossomia fetal e hemorragia pós-parto na região da América Latina e Caribe: Revisão sistemática e metanálise

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Abstract

Objective To determine the association between fetal macrosomia (FM) and postpartum hemorrhage (PPH) in Latin American and Caribbean (LAC) women.

Data Sources Studies evaluating the association between FM and PPH ($\geq$ 500 ml) and severe PPH ($\geq$ 1,000 ml) until November 4, 2021, indexed in CINHAL, Scopus, Embase, Cochrane Library, MEDLINE, LILACS, and SciELO.

Selection of Studies Inclusion criteria were cohort and case-control studies that provided the number of PPH and FM cases. Exclusion criteria were studies lacking information about the number of cases, with a population of women who were not from LAC; published in a language other than English, Spanish, or Portuguese, and with a different design.

Data Collection Data extraction was performed independently by two authors, and discrepancies were resolved with a third author. Data regarding FM and PPH cases were retrieved.

Data Synthesis Of the 1,044 articles evaluated, 5 studies were included, from 6 different countries: Argentina and Uruguay (multi-country), West Indies, Antigua and Barbuda, French Guyana, and Suriname. The pooled odds ratio (OR) for FM and PPH in the meta-analysis (five studies) was 2.10 (95% confidence interval [CI]: 1.79–2.47; I^2: 0%), with estimates within this 95% CI in the sensitivity analysis. The combined OR for severe PPH (3 studies) was 1.61 (95% CI: 0.40–6.48; I^2: 91.89%), showing high heterogeneity.

Keywords
- postpartum hemorrhage
- fetal macrosomia
- systematic review
- meta-analysis
- Latin America

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Conclusion There was a positive association between FM and PPH in the LAC, increasing the risk of the presence of this event 2-fold. The high heterogeneity of the studies that measured severe PPH does not allow drawing conclusions about the estimates obtained.

Resumo

Objetivo Determinar a associação entre macrossomia fetal (FM) e hemorragia pós-parto (HPP) em mulheres da América Latina e Caribe (ALC).

Fontes de dados Estudos avaliando a associação entre FM e HPP ($\geq$ 500 ml) e HPP grave ($\geq$ 1.000 ml) até 4 de novembro de 2021, indexados no CINHAL, Scopus, Embase, Biblioteca Cochrane, MEDLINE, LILACS e SciELO.

Seleção de estudos Os critérios de inclusão foram estudos de corte e caso-controle que forneceram o número de casos de HPP e FM. Os critérios de exclusão foram estudos sem informação sobre o número de casos, com uma população de mulheres que não eram da ALC; publicado em um idioma diferente do inglês, espanhol ou português e com um design diferente.

Coleta de dados A extração de dados foi realizada independentemente por dois autores, as discrepâncias foram resolvidas com um terceiro autor. Os dados relativos aos casos de FM e HPP foram recuperados.

Síntese dos dados Dos 1.044 artigos avaliados, foram incluídos 5 estudos, de 6 países diferentes: Argentina e Uruguai (multipaíses), Índias Ocidentais, Antígua e Barbuda, Guiana Francesa e Suriname. O *odds ratio* agrupado (OR) para FM e HPP na meta-análise (cinco estudos) foi de 2,10 (intervalo de confiança de 95% [IC]: 1,79–2,47; I2: 0%), com estimativas dentro deste IC de 95% no análise sensitiva. O OR combinado para HPP grave (3 estudos) foi de 1,61 (95% CI: 0.40–6.48; I2: 91.89%), mostrando alta heterogeneidade.

Conclusão Houve associação positiva entre FM e HPP na ALC, aumentando em 2 vezes o risco da presença desse evento. A alta heterogeneidade dos estudos que mediram a HPP grave não permite tirar conclusões sobre as estimativas obtidas.

Palavras-chave
- hemorragia pós-parto
- macrossomia fetal
- revisão sistemática
- metanálise
- América latina

Introduction

Postpartum hemorrhage (PPH) is a public health problem. It is traditionally defined as blood volume loss greater than 500 ml after vaginal delivery or 1,000 ml after cesarean delivery. Recently, the American College of Obstetricians and Gynecologists has defined PPH as a cumulative blood volume loss $\geq$ 1,000 ml or blood loss associated with clinical manifestations of hypovolemia (such as hypotension and tachycardia), regardless of the route of delivery.[1] Globally, PPH is the leading cause of maternal mortality, with over 80,000 deaths in 2015, with low and middle-income countries presenting more than 30 times the number of maternal deaths compared with high-income ones.[2] Additionally, the global prevalence of PPH ($\geq$ 500 ml) exceeds 10% of women giving birth, with the highest rates being found in Africa (25.7%), North America (13.1%), and Europe (12.7%). Furthermore, Africa (5.1%), North America (4.3%), and Latin America and the Caribbean (LAC, 3.3%) present the highest prevalence rates of severe PPH ($\geq$ 1,000 ml).[3]

Globally, the main causes of PPH are uterine atony (more than 70%), obstetric lacerations (20%), retained placental tissue (10%) and clotting factor deficiencies (less than 1%).[1] In turn, fetal macrosomia (FM, gestational weight $\geq$ 4,000 g) is recognized as a risk factor for the occurrence of PPH in several regions of the world,[4–6] being mainly associated with preexisting diabetes, maternal obesity before pregnancy, gestational diabetes, excessive weight gain during gestation, abnormal fasting and postprandial glucose levels, dyslipidemia, history of a macrosomic fetus, and postterm pregnancy.[7] Proper identification of the predictors of PPH, as well as active management of stage 3 of labor, is crucial for the prevention of this health problem, which is still the leading cause of maternal death in low- and middle-income countries.

The countries that make up the LAC region have high fertility rates, high levels of poverty, and poor health care coverage and quality, which have resulted in a maternal mortality rate in this region of 88 maternal deaths per 100,000 live births.[8] The prevalence of FM in LAC varies between 4.5 and 5.4%.[9] An increase in obesity and diabetes in women has been described in this region,[10] which could explain the increase in the prevalence of FM.[9] Despite the

knowledge about PPH and FM in various regions of the world, there is still little evidence about its association in LAC. Therefore, the aim of the present study was to determine the association between FM and PPH in women from LAC through a systematic review with meta-analysis of the published scientific literature.

Methods

The systematic review protocol was registered in the Prospective International Registry of Systematic Reviews (PROSPERO) (CRD42021233589). This study followed the Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA) 2020 guidelines.[11] This systematic review with meta-analysis focused on studies conducted in populations from LAC.

On November 14, 2021, a comprehensive search for studies that made estimates of the association between FM and PPH in women from LAC was conducted using seven electronic bibliographic databases: CINHAL, Scopus, Embase, Cochrane Library, MEDLINE, LILACS, and SciELO. The search terms focused on postpartum hemorrhage, fetal macrosomia, Latin America, and Caribbean Region. The countries considered as part of LAC in this study are those included on the Pan-American Health Organization (PAHO) list.[12] The electronic search did not require additional language, time, or design filters and was complemented by a manual review of the references of the included articles (►**Chart 1**). The records found in the electronic search were imported to the Mendeley (Elsevier, Amsterdam, Netherlands) reference management software, and all duplicate records were removed.

Inclusion criteria were: (a) case–control studies, and (b) cohorts that provided the number of PPH and FM cases. Articles were excluded if they: (a) lacked information on the number of cases with PPH and/or FM; (b) included a population of women who were not from LAC; (c) were not published in English, Spanish, or Portuguese; and (d) included articles with a different design (i.e., editorials, review articles).

All studies identified in the search and that met the inclusion criteria underwent an independent assessment by two review authors of the titles and abstracts using the Rayyan web application.[13] Discrepancies during the evaluation were resolved by a third author. All papers that passed the first phase were fully read and evaluated by two authors independently. Disagreements between the two authors on the selection of studies were resolved by a third author.

The outcome variable of interest was PPH, which was defined as blood loss greater than or equal to 500 ml, whereas severe PPH was considered as blood loss greater than or equal to 1,000 ml or when the blood loss caused hemodynamic instability and/or signs or symptoms of hypovolemia.[3] Furthermore, FM was defined as a fetal birth weight greater than or equal to 4,000 g or greater than the 90th percentile for the gestational age reported in each study.[7]

Data extraction was performed independently by two authors using Excel (Microsoft Corp., Redmond, WA, USA), and data accuracy was evaluated by a third author. For the extraction, a pilot test of 5 articles was performed. After the inclusion of additional items, the authors collected the following information: first author, year of publication, period of data collection, country, journal, title, setting, objective, selection criteria, age of the women, sample size, operational definition of PPH and FM, number of PPH and FM cases, estimated risk ratio (RR) or odds ratio (OR) with its respective confidence interval (CI), statistical test used, and conclusions.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the studies.[14] This assessment was performed independently by two authors with a final consensus by a third author.

The characteristics of the studies included were described using data extraction performed in Excel (Microsoft Corp.). For the studies included, the *meta esize* command of the Stata 17 statistical program (StataCorp LLC., College Station, TX, USA) was used to calculate the effect sizes of the binary summary data (OR). Then the overall effect size was estimated along with the 95% CI using the *meta summarize* command.[15] When a study did not report the OR, it was calculated using the *csi* command. To evaluate the heterogeneity of the studies, the I^2 statistic was used, with values of 25, 50, and 75% being considered as low, moderate, and high heterogeneity, respectively.[16] The studies' findings were illustrated in the form of a forest plot. Publication bias was not assessed because the meta-analyses were performed with fewer than ten studies, as recommended in the Cochrane handbook.[17]

The leave-one-out method was used as a sensitivity analysis, excluding one study at a time to verify the stability of the results and the sources of heterogeneity.

Ethics committee approval was not sought because the data from the studies are public domain, which precludes identification of the participants in each study.

Results

A total of 1,044 articles were evaluated by title and abstract, 8 of which were eligible for full-text evaluation. Of these articles, 5 met the selection criteria and were included in the present systematic review (►**Fig. 1**). The 3 excluded articles were due to being a thesis published in a repository and, thus, it had not been evaluated in a peer review process, which is a quality standard recognized by the scientific community,[18] while the other two[19,20] were excluded due to not having operationally defined the PPH variable (►**Chart 2**).

The studies included were published between 2003 and 2020. One was considered multi-country because it was conducted in Argentina and Uruguay,[21] one was performed in West Indies,[22] one in Antigua and Barbuda,[23] one in the French Guyana,[24] and one in Suriname.[25] Regarding the design of the studies, one was a cohort study,[21] and the rest had a case-control design. Regarding the context of

Chart 1 Search Strategies

Database	MEDLINE Date: November 4, 2021		Results
Search Strategy	#1	Postpartum Hemorrhage[Mesh] OR Shock, Hemorrhagic[Mesh] OR Uterine Inertia[Mesh] OR Uterine Hemorrhage[Mesh] OR Abruptio Placentae [Mesh] OR Blood Loss, Surgical[Mesh] OR Blood Transfusion[Mesh] OR Placenta Accreta[Mesh] OR Placenta Previa[Mesh] OR uterine inversion [Mesh] OR Uterine Artery Embolization[Mesh] OR Uterine Contraction[Mesh] OR Obstetric Labor Complications[Mesh] OR Postpartum Hemorrhag*[tiab] OR Postpartum Haemorrhag*[tiab] OR post partum hemorrhage[tiab] OR post-partum hemorrhage[tiab] OR PPH[tiab] OR Abruptio Placentae[tiab] OR abruption[tiab] OR blood loss*[tiab] OR blood transfusion[tiab] OR placenta accreta[tiab] OR placenta previa[tiab] OR shock[tiab] OR placenta praevia[tiab] OR placental previa[tiab] OR placental praevia[tiab] OR atony[tiab] OR atonic[tiab] OR atonic uterus [tiab] OR uterine atony[tiab] OR uterine inertia[tiab] OR uterine bleeding[tiab] OR uterine hemorrhage[tiab] OR uterine hemorrhage[tiab] OR uterus inversion[tiab] OR uterine artery embolization[tiab] OR uterine contraction[tiab] OR labor complication*[tiab] OR labor complication*[tiab] OR delivery complication*[tiab]	467,480
	#2	Fetal Macrosomia[Mesh] OR Fetal Disease[Mesh] OR Fetal Macrosomia[tiab] OR Macrosom*[tiab] OR fetal overgrowth[tiab] OR large-for-gestational-age[tiab] OR Fetal complication*[tiab]	77,119
	#3	#1 AND #2	11,950
	#4	Americas[MeSH Terms:noexp] OR America*[tiab] OR Latin America[Mesh] OR Latin America*[tiab] OR Latinamerica*[tiab] OR Latinoamerica*[tiab] OR Latin*[tiab] OR Hispanic Americans[Mesh] OR Hispanic America*[tiab] OR Hispanoamerica*[tiab] OR Iberoamerica*[tiab] OR Ibero Americ*[tiab] OR Panamerican*[tiab] OR Central America[Mesh] OR Central America*[tiab] OR Centroamerica*[tiab] OR Mesoamerica*[tiab] OR Meso America*[tiab] OR Middle America*[tiab] OR South America[Mesh] OR South America*[tiab] OR Southamerica*[tiab] OR Sudamerica*[tiab] OR "America del sur"[tiab] OR Caribbean Region[Mesh] OR Caribbean[tiab] OR Caribe*[tiab] OR West Indies[Mesh] OR West Indi*[tiab] OR Antill*[tiab] OR Indians, South American[Mesh] OR Indians, Central American[Mesh] OR Amerindian*[tiab] OR Indians[tiab] OR American Indian*[tiab] OR Native America*[tiab] OR Patagoni*[tiab] OR Andes[tiab] OR Andean*[tiab] OR Amazon*[tiab] OR Argentin*[ad] OR Argentin*[tiab] OR Argentina[pl] OR Bolivia*[ad] OR Bolivia*[tiab] OR Bolivia[pl] OR Brazil*[ad] OR Brasil*[ad] OR Brazil*[tiab] OR Brasil*[tiab] OR Brazil[pl] OR Colombia*[ad] OR Colombia*[tiab] OR Colombia[pl] OR Chile*[ad] OR Chile*[tiab] OR Chile[pl] OR Ecuador*[ad] OR Ecuator*[ad] OR Ecuador*[tiab] OR Ecuador[pl] OR Guiana*[ad] OR Guiana*[tiab] OR French Guiana[pl] OR Guyan*[ad] OR Guyan*[tiab] OR Guyana [pl] OR Paraguay*[ad] OR Paraguay*[tiab] OR Paraguay[pl] OR Peru*[ad] OR Peru*[tiab] OR Peru[pl] OR Surinam*[ad] OR Surinam*[tiab] OR Suriname[pl] OR Uruguay*[ad] OR Uruguay*[tiab] OR Uruguay[pl] OR Venez*[ad] OR Venez*[tiab] OR Venezuela[pl] OR Belize*[ad] OR Belize*[tiab] OR Belize[pl] OR Costa Ric*[ad] OR Costarric*[ad] OR Costaric*[ad] OR Costa Ric*[tiab] OR Costarric*[tiab] OR Costaric*[tiab] OR Costa Rica[pl] OR Salvador*[ad] OR Salvador*[tiab] OR El Salvador[pl] OR Guatemal*[ad] OR Guatemal*[tiab] OR Guatemala[pl] OR Hondur*[ad] OR Hondur*[tiab] OR Honduras[pl] OR Nicaragu*[ad] OR Nicaragu*[tiab] OR Nicaragua[pl] OR Panam*[ad] OR Panam*[tiab] OR Panama[pl] OR Mexico[Mesh] OR Mexic*[ad] OR Mexic*[tiab] OR Mejic*[tiab] OR Mexico[pl] OR Aruba*[ad] OR Aruba*[tiab] OR Aruba[pl] OR Caribbean Netherland*[ad] OR Caribbean Netherland*[tiab] OR Caribbean Netherlands[pl] OR Curacao*[ad] OR Curacao*[tiab] OR Curacao[pl] OR "Sint Maarten"[ad] OR "Sint Maarten"[tiab] OR "Sint Maarten"[pl] OR Guadeloup*[ad] OR Guadeloup*[tiab] OR Guadeloupe[pl] OR Martiniqu*[ad] OR Martiniqu*[tiab] OR Martinique[pl] OR "Panama Canal Zone"[ad] OR "Panama Canal Zone"[tiab] OR "Panama Canal Zone"[pl] OR "Antigua and Barbuda"[ad] OR "Antigua and Barbuda"[tiab] OR "Antigua and Barbuda"[pl] OR Baham*[ad] OR Baham*[tiab] OR Bahamas[pl] OR Barbad*[ad] OR Barbad*[tiab] OR Barbados[pl] OR "British Virgin Island"[ad] OR "British Virgin Island"[tiab] OR "British Virgin Islands"[pl] OR Cayman Island*[ad] OR Cayman Island*[tiab] OR Cayman Islands[pl] OR Grenad*[ad] OR Grenad*[tiab] OR Grenada[pl] OR "Saint Kitts and Nevis"[ad] OR "Saint Kitts and Nevis"[tiab] OR "Saint Kitts and Nevis"[pl] OR Saint Lucia*[ad] OR Saint Lucia*[tiab] OR Saint Lucia[pl] OR "Saint Vincent and the Grenadines"[ad] OR "Saint Vincent and the Grenadines"[tiab] OR Saint Vincent and the Grenadines[pl] OR "Trinidad and Tobago"[ad] OR "Trinidad and Tobago"[tiab] OR "Trinidad and Tobago"[pl] OR "Turks and Caicos Island"[ad] OR "Turks and Caicos Island"[tiab] OR "Turks and Caicos Islands"[pl] OR "United States Virgin Islands"[ad] OR "United States Virgin Islands"[tiab] OR "United States Virgin Islands"[pl] OR Anguill*[ad] OR Anguill*[tiab] OR Anguilla[pl] OR Leeward Island*[ad] OR Leeward Island*[tiab] OR Leeward Islands[pl] OR Montserrat*[ad] OR Montserrat*[tiab] OR Montserrat[pl] OR Windward Island*[ad] OR Windward Island*[tiab] OR Windward Islands[pl] OR Cuba*[ad] OR Cuba*[tiab] OR Cuba[pl] OR Dominic*[ad] OR Dominic*[tiab] OR Dominican Republic[pl] OR Haiti*[ad] OR Haiti*[tiab] OR Haiti[pl] OR Jamaic*[ad] OR Jamaic*[tiab] OR Jamaica [pl] OR Puerto Ric*[tiab] OR Puertorric*[tiab] OR Puertoric*[tiab]	1,662,291
	#5	#3 AND #4	556

(*Continued*)

Chart 1 (*Continued*)

Database	Embase Date: November 4, 2021		Results
Search Strategy	#1	'postpartum hemorrhage'/exp OR 'postpartum hemorrhage' OR 'hemorrhagic shock'/exp OR 'hemorrhagic shock' OR 'uterus bleeding'/exp OR 'uterus bleeding' OR 'solutio placentae'/exp OR 'solutio placentae' OR 'bleeding'/exp OR 'bleeding' OR 'operative blood loss'/exp OR 'operative blood loss' OR 'blood transfusion'/exp OR 'blood transfusion' OR 'placenta accreta'/exp OR 'placenta accreta' OR 'placenta previa'/exp OR 'placenta previa' OR 'uterus inversion'/exp OR 'uterus inversion' OR 'uterine artery embolization'/exp OR 'uterine artery embolization' OR 'uterus contraction'/exp OR 'uterus contraction' OR 'abruptio placentae':ti,ab OR 'abruption':ti,ab OR 'surgical blood loss':ti,ab OR 'blood loss':ti,ab OR 'blood transfusion':ti,ab OR 'placenta accreta':ti,ab OR 'shock':ti,ab OR 'haemorrhagic shock':ti,ab OR 'hemorrhagic shock':ti,ab OR 'placental accreta':ti,ab OR 'placenta previa':ti,ab OR 'placenta praevia':ti,ab OR 'placental previa':ti,ab OR 'placental praevia':ti,ab OR 'pph':ti,ab OR 'postpartum hemorrhage':ti,ab OR 'postpartum hemorrhage':ti,ab OR 'post partum hemorrhage':ti,ab OR 'post partum hemorrhage':ti,ab OR 'post-partum hemorrhage':ti,ab OR 'post-partum hemorrhage':ti,ab OR 'atony':ti,ab OR 'atonic':ti,ab OR 'atonic uterus':ti,ab OR 'uterine atony':ti,ab OR 'uterine inertia':ti,ab OR 'uterine bleeding':ti,ab OR 'uterine hemorrhage':ti,ab OR 'uterine hemorrhage':ti,ab OR 'labor complication':ti,ab OR 'delivery complication':ti,ab OR 'labor complication':ti,ab OR 'uterus inversion':ti,ab OR 'uterine artery embolization':ti,ab OR 'uterine contraction':ti,ab	1,590,724
	#2	'macrosomia'/exp OR 'macrosom*:ti,ab' OR 'fetus disease'/exp OR 'fetal macrosomia:ti,ab' OR 'fetal overgrowth:ti,ab' OR 'large for gestational age:ti,ab' OR 'fetal complication:ti,ab'	132,774
	#3	#1 AND #2	18,763
	#4	americas:ti,ab OR 'south and central america'/exp OR ((latin NEAR/1 america*):ti,ab) OR latinamerica*:ti,ab OR latinoamerica*:ti,ab OR hispanoamerica:ti,ab OR iberoamerica*:ti,ab OR ((ibero NEAR/1 americ*):ti,ab) OR panamerica*:ti,ab OR ((south NEAR/1 america*):ti,ab) OR southamerica*:ti,ab OR sudamerica*:ti,ab OR (america:ti,ab AND del:ti,ab AND sur:ti,ab) OR ((central NEAR/1 america*):ti,ab) OR centroamerica*:ti,ab OR mesoamerica*:ti,ab OR ((meso NEAR/1 america*):ti,ab) OR ((middle NEAR/1 america*):ti,ab) OR 'caribbean'/exp OR 'caribbean islands'/exp OR caribbean*:ti,ab OR caribe*:ti,ab OR ((west NEAR/1 indi*):ti,ab) OR antill*:ti,ab OR 'american indian'/exp OR amerindian*ti,ab OR indians:ti,ab OR ((native NEAR/1 america*):ti,ab) OR patagoni*:ti,ab OR andes:ti,ab OR andean*:ti,ab OR amazon*:ti,ab OR 'argentina'/exp OR argentin*:ti,ab OR 'bolivia'/exp OR bolivia*:ti,ab OR 'brazil'/exp OR brazil*:ti,ab OR brasil*:ti,ab OR 'colombia'/exp OR colombia*:ti,ab OR 'chile'/exp OR chile*:ti,ab OR 'ecuador'/exp OR ecuador*:ti,ab OR 'french guiana'/exp OR guiana*:ti,ab OR 'guyana'/exp OR guyan*:ti,ab OR 'paraguay'/exp OR paraguay*:ti,ab OR 'peru'/exp OR peru*:ti,ab OR 'suriname'/exp OR surinam*:ti,ab OR 'uruguay'/exp OR uruguay*:ti,ab OR 'venezuela'/exp OR venez*:ti,ab OR 'belize'/exp OR beliz*:ti,ab OR 'costa rica'/exp OR 'costa rica':ti,ab OR costarric*:ti,ab OR costaric*:ti,ab OR 'el salvador'/exp OR salvador*:ti,ab OR 'guatemala'/exp OR guatemal*:ti,ab OR 'honduras'/exp OR hondur*:ti,ab OR 'nicaragua'/exp OR nicaragu*:ti,ab OR 'panama'/exp OR panam*:ti,ab OR 'mexico'/exp OR mexic*:ti,ab OR mejic*:ti,ab OR 'cuba'/exp OR cuba*:ti,ab OR 'dominican republic'/exp OR dominica*:ti,ab OR 'haiti'/exp OR haiti*:ti,ab OR 'jamaica'/exp OR jamaic*:ti,ab OR 'puerto rico'/exp OR ((puerto NEAR/1 ric*):ti,ab) OR puertoric*:ti,ab OR puertorric*:ti,ab	575,956
	#5	#3 AND #4	264
Database	**CINAHL Complete** **Date: November 4, 2021**		**Results**
Search Strategy	S1	(MH "Postpartum Hemorrhage")	3,869
	S2	(MH "Shock, Hemorrhagic")	2,094
	S3	(MH "Uterine Inertia")	253
	S4	(MH "Uterine Hemorrhage")	2,151
	S5	(MH "Abruptio Placentae")	809
	S6	(MH "Blood Loss, Surgical")	5,892
	S7	(MH "Blood Transfusion")	13,703

Chart 1 (*Continued*)

S8	(MH "Placenta Accreta")	1,190
S9	(MH "Placenta Previa")	1,091
S10	(MH "uterine inversion")	96
S11	(MH "Uterine Artery Embolization")	666
S12	(MH "Uterine Contraction")	1,055
S13	(MH "Obstetric Labor Complications")	2,338
S14	TI (Postpartum N1 Hemorrhag*) OR AB (Postpartum N1 Hemorrhag*)	2,221
S15	TI (Postpartum N1 Haemorrhag*) OR AB (Postpartum N1 Haemorrhag*)	941
S16	TI (post-partum hemorrhage*) OR AB (post-partum hemorrhage*)	222
S17	TI (post-partum N1 hemorrhage*) OR AB (post-partum N1 hemorrhage*)	192
S18	TI PPH OR AB PPH	1,155
S19	TI (Abruptio N1 Placentae) OR AB (Abruptio N1 Placentae)	202
S20	TI abruption OR AB abruption	1,165
S21	TI (blood N1 loss*) OR AB (blood N1 loss*)	13,587
S22	TI (blood N1 transfusion) OR AB (blood N1 transfusion)	12,005
S23	TI (placenta N1 accreta) OR AB (placenta N1 accreta)	1,089
S24	TI (placenta N1 previa) OR AB (placenta N1 previa)	1,042
S25	TI shock OR AB shock	30,290
S26	TI (placenta N1 praevia) OR AB (placenta N1 praevia)	200
S27	TI (placental N1 previa) OR AB (placental N1 previa)	60
S28	TI (placental N1 praevia) OR AB (placental N1 praevia)	20
S29	TI atony OR AB atony	349
S30	TI atonic OR AB atonic	212
S31	TI (atonic N1 uterus) OR AB (atonic N1 uterus)	17
S32	TI (uterine N1 atony) OR AB (uterine N1 atony)	293
S33	TI (uterine N1 inertia) OR AB (uterine N1 inertia)	15
S34	TI (uterine N1 bleeding) OR AB (uterine N1 bleeding)	1,291
S35	TI (uterine N1 hemorrhage) OR AB (uterine N1 hemorrhage)	136
S36	TI (uterine N1 hemorrhage) OR AB (uterine N1 hemorrhage)	136
S37	TI (uterus N1 inversion) OR AB (uterus N1 inversion)	4
S38	TI "uterine artery embolization" OR AB "uterine artery embolization"	861
S39	TI (uterine N1 contraction) OR AB (uterine N1 contraction)	778

(*Continued*)

Chart 1 (*Continued*)

	S40	TI labor complication* OR AB labor complication*	725
	S41	TI labor complication* OR AB labor complication*	725
	S42	TI delivery complication* OR AB delivery complication*	1,899
	S43	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42	77,892
	S44	(MH "Fetal Macrosomia")	1,288
	S45	(MH "Fetal Disease")	2,991
	S46	TI (Fetal N1 Macrosomia) OR AB (Fetal N1 Macrosomia)	358
	S47	TI Macrosom* OR AB Macrosom*	1,648
	S48	TI (fetal N1 overgrowth) OR AB (fetal N1 overgrowth)	91
	S49	TI large-for-gestational-age OR AB large-for-gestational-age	1,297
	S50	TI Fetal complication* OR AB Fetal complication*	1,349
	S51	S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	4,369
	S52	S43 AND 51	517
	S53	TI (Latin America* OR Latinamerica* OR Latinoamerica* OR Latin* OR Hispanic Americans OR Iberoamerica* OR Ibero Americ* OR Panamerican* OR Central America* OR Centroamerica* OR Mesoamerica* OR Meso America* OR Middle America* OR South America* OR Southamerica* OR Sudamerica* OR America del sur OR Caribbean OR Caribe* OR West Indi* OR Antill* OR Amerindian* OR Indians OR American Indian* OR Native America* OR Patagoni* OR Andes OR Andean* OR Amazon* OR Argentin* OR Bolivia* OR Brazil* OR Brasil* Colombia* OR Colombia* OR Colombia OR Chile* OR Ecuador* OR Guiana* OR Guyan* OR Guyan* OR Paraguay* OR Paraguay* OR Peru* OR Surinam* OR Surinam* OR Uruguay* OR Venez* OR Belize* OR Costa Ric* OR Costarric* OR Costaric* OR Costa Ric* OR Costarric* OR Salvador* OR Salvador* OR El Salvador OR Guatemal* OR Guatemal* OR Guatemala OR Hondur* OR Nicaragu* Panam* OR Mexic* OR Cuba* OR Dominic* OR Dominic* OR Haiti* OR Jamaic* OR Puerto Ric* OR Puertorric* OR Puertoric*)	66,056
	S54	AB (Latin America* OR Latinamerica* OR Latinoamerica* OR Latin* OR Hispanic Americans OR Iberoamerica* OR Ibero Americ* OR Panamerican* OR Central America* OR Centroamerica* OR Mesoamerica* OR Meso America* OR Middle America* OR South America* OR Southamerica* OR Sudamerica* OR America del sur OR Caribbean OR Caribe* OR West Indi* OR Antill* OR Amerindian* OR Indians OR American Indian* OR Native America* OR Patagoni* OR Andes OR Andean* OR Amazon* OR Argentin* OR Bolivia* OR Brazil* OR Brasil* Colombia* OR Colombia* OR Colombia OR Chile* OR Ecuador* OR Guiana* OR Guyan* OR Guyan* OR Paraguay* OR Paraguay* OR Peru* OR Surinam* OR Surinam* OR Uruguay* OR Venez* OR Belize* OR Costa Ric* OR Costarric* OR Costaric* OR Costa Ric* OR Costarric* OR Salvador* OR Salvador* OR El Salvador OR Guatemal* OR Guatemal* OR Guatemala OR Hondur* OR Nicaragu* Panam* OR Mexic* OR Cuba* OR Dominic* OR Dominic* OR Haiti* OR Jamaic* OR Puerto Ric* OR Puertorric* OR Puertoric*)	99,564
	S55	S53 OR S54	125,766
	S56	S52 AND S54	10
Database	**Scopus** **Date: November 4, 2021**		**Results**
Search Strategy	#1	TITLE-ABS-KEY ("Postpartum Hemorrhage")) OR (TITLE-ABS-KEY ("Shock, Hemorrhagic")) OR (TITLE-ABS-KEY ("Uterine Inertia")) OR (TITLE-ABS-KEY ("Uterine Hemorrhage")) OR (TITLE-ABS-KEY ("Uterine Hemorrhage")) OR (TITLE-ABS-KEY ("Abruptio Placentae")) OR (TITLE-ABS-KEY ("Blood	839,680

Chart 1 (*Continued*)

		Loss, Surgical")) OR (TITLE-ABS-KEY ("Blood Transfusion")) OR (TITLE-ABS-KEY ("Placenta Accreta")) OR (TITLE-ABS-KEY ("Placenta Previa")) OR (TITLE-ABS-KEY ("uterine inversion")) OR (TITLE-ABS-KEY ("Uterine Artery Embolization")) OR (TITLE-ABS-KEY ("Uterine Contraction")) OR (TITLE-ABS-KEY ("Obstetric Labor Complication*")) OR (TITLE-ABS-KEY ("Postpartum Haemorrhag*")) OR (TITLE-ABS-KEY ("post-partum haemorrhage")) OR (TITLE-ABS-KEY ("post-partum hemorrhage")) OR (TITLE-ABS-KEY (pph)) OR (TITLE-ABS-KEY (abruption)) OR (TITLE-ABS-KEY (shock)) OR (TITLE-ABS-KEY ("placenta praevia")) OR (TITLE-ABS-KEY ("placental previa")) OR (TITLE-ABS-KEY ("placental praevia")) OR (TITLE-ABS-KEY (atony)) OR (TITLE-ABS-KEY (atonic)) OR (TITLE-ABS-KEY ("atonic uterus")) OR (TITLE-ABS-KEY ("uterine atony")) OR (TITLE-ABS-KEY ("uterine inertia")) OR (TITLE-ABS-KEY ("uterine bleeding")) OR (TITLE-ABS-KEY ("uterine haemorrhage"))) OR (TITLE-ABS-KEY ("uterus inversion")) OR (TITLE-ABS-KEY ("labor complication*")) OR (TITLE-ABS-KEY ("labour complication*")) OR (TITLE-ABS-KEY ("delivery complication*")	
	#2	TITLE-ABS-KEY ("Fetal Macrosomia")) OR (TITLE-ABS-KEY ("Fetal Disease*")) OR (TITLE-ABS-KEY (macrosom*)) OR (TITLE-ABS-KEY ("fetal overgrowth")) OR (TITLE-ABS-KEY ("large-for-gestational-age")) OR (TITLE-ABS-KEY ("Fetal complication*")	38,064
	#3	#1 AND #2	
	#4	TITLE-ABS-KEY ("latin america" OR "Latinoamerica" OR latin* OR "central america" OR "Centroamerica" OR "south America" OR sudamerica OR caribbean OR caribe* OR "west indies" OR antill* OR patagoni* OR andes OR andean OR amazon OR "Puerto rico" OR puertoric* OR puertorric* OR jamaica OR jamaic* OR haiti OR haiti* OR "dominican republic" OR dominica* OR cuba OR cuba* OR mexico OR mexic* OR mejic* OR panama OR panam* OR nicaragua OR nicaragu* OR honduras OR hondur* OR guatemala OR guatemal* OR "el Salvador" OR salvador* OR "costa rica" OR costarric* OR costaric* OR belize OR beliz* OR venezuela OR venez* OR uruguay OR uruguay* OR suriname OR surinam* OR peru OR peru* OR paraguay OR paraguay* OR guyana OR guyan* OR "french guiana" OR guiana* OR guayan* OR ecuador OR ecuador* OR chile OR chile* OR colombia OR colombia* OR brazil OR brazil* OR brasil* OR bolivia OR bolivia* OR argentina OR argentin*	1,414,676
	#5	#3 AND #4	38
Database	**The Cochrane Library** **Date: November 4, 2021**		**Results**
Search Strategy	#1	MeSH descriptor: [Postpartum Hemorrhage] explode all trees	697
	#2	MeSH descriptor: [Shock, Hemorrhagic] explode all trees	111
	#3	MeSH descriptor: [Uterine Inertia] explode all trees	47
	#4	MeSH descriptor: [Uterine Hemorrhage] explode all trees	1,871
	#5	MeSH descriptor: [Abruptio Placentae] explode all trees	31
	#6	MeSH descriptor: [Blood Loss, Surgical] explode all trees	2,749
	#7	MeSH descriptor: [Blood Transfusion] explode all trees	3,681
	#8	MeSH descriptor: [Placenta Accreta] explode all trees	31
	#9	MeSH descriptor: [Placenta Previa] explode all trees	63
	#10	MeSH descriptor: [Uterine Inversion] explode all trees	0
	#11	MeSH descriptor: [Uterine Artery Embolization] explode all trees	55
	#12	MeSH descriptor: [Uterine Contraction] explode all trees	381
	#13	MeSH descriptor: [Obstetric Labor Complications] explode all trees	4,162
	#14	(Postpartum Hemorrhag*):ti,ab,kw	2,002
	#15	(Postpartum Haemorrhag*):ti,ab,kw	761

(*Continued*)

Chart 1 (*Continued*)

#16	(post-partum hemorrhage):ti,ab,kw	415
#17	(post-partum hemorrhage):ti,ab,kw	413
#18	(PPH):ti,ab,kw	768
#19	(Abruptio Placentae):ti,ab,kw	81
#20	(abruption):ti,ab,kw	424
#21	(blood loss*):ti,ab,kw	33,271
#22	(blood transfusion):ti,ab,kw	13,489
#23	(placenta accreta):ti,ab,kw	112
#24	(placenta previa):ti,ab,kw	379
#25	(shock):ti,ab,kw	11,523
#26	(placenta praevia):ti,ab,kw	52
#27	(placental previa):ti,ab,kw	110
#28	(placental praevia):ti,ab,kw	13
#29	(atony):ti,ab,kw	259
#30	(atonic):ti,ab,kw	171
#31	(atonic uterus):ti,ab,kw	32
#32	(uterine atony):ti,ab,kw	217
#33	(uterine inertia):ti,ab,kw	60
#34	(uterine bleeding):ti,ab,kw	3,029
#35	(uterine hemorrhage):ti,ab,kw	1,801
#36	(uterine hemorrhage):ti,ab,kw	1,801
#37	(uterus inversion):ti,ab,kw	14
#38	(uterine artery embolization):ti,ab,kw	294
#39	(uterine contraction):ti,ab,kw	1,053
#40	(labor complication*):ti,ab,kw	3,563
#41	(labor complication*):ti,ab,kw	3,560
#42	(delivery complication*):ti,ab,kw	8,252
#43	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	69,302
#44	MeSH descriptor: [Fetal Macrosomia] explode all trees	135
#45	MeSH descriptor: [Fetal Diseases] explode all trees	1,099

Chart 1 (*Continued*)

	#46	(Fetal Macrosomia):ti,ab,kw	347
	#47	(Macrosom*):ti,ab,kw	655
	#48	(Fetal overgrowth):ti,ab,kw	24
	#49	(large-for-gestational-age):ti,ab,kw	351
	#50	(Fetal complication*):ti,ab,kw	3,212
	#51	(Fetal disease*):ti,ab,kw	2,413
	#52	#44 OR #45 OR #46 #47 OR #48 OR #49 OR #50 OR #51	5,662
	#53	#43 AND #52	2,761
	#54	MeSH descriptor: [Americas] explode all trees 27162	27,162
	#55	MeSH descriptor: [Latin America] explode all trees	127
	#56	MeSH descriptor: [Hispanic Americans] explode all trees	1,475
	#57	MeSH descriptor: [Central America] explode all trees	288
	#58	MeSH descriptor: [South America] explode all trees	2,662
	#59	MeSH descriptor: [Caribbean Region] explode all trees	407
	#60	MeSH descriptor: [West Indies] explode all trees	389
	#61	MeSH descriptor: [Indians, South American] explode all trees	12
	#62	MeSH descriptor: [Indians, Central American] explode all trees	1
	#63	MeSH descriptor: [Mexico] explode all trees	661
	#64	(Amerindian* OR "Indians" OR "American Indian*" OR "Native America*" OR patagoni* OR "andes" OR Andean* OR amazon* OR argentin* OR Bolivia* OR Brazil* OR Brasil* OR Colombia* OR Chile* OR Ecuador* OR Ecuator* OR Guiana* OR "Guyana" OR "French Guiana" OR Guyan* OR Paraguay* OR Peru* OR Surinam* OR "Suriname" OR Uruguay* OR "Venezuela" OR Belize* OR "Costa Ric*" OR Costarric* OR Costaric* OR Salvador* OR Guatamal* OR Hondur* OR Nicaragu* OR Panam* OR Mexic* OR Mejic* OR Aruba* OR "Caribbean Netherland*" OR Curacao* OR "Sint Maarten" OR Guadeloup* OR Martiniqu* OR "Panama Canal Zone" OR "Antigua and Barbuda" OR Baham* OR Barbad* OR "British Virgin Island" OR "Cayman Island*" OR Grenad* OR "Saint Kitts and Nevis" OR "Saint Lucia*" OR "Saint Vincent and the Grenadines" OR "Trinidad and Tobago" OR "Turks and Caicos Island" OR "United States Virgin Islands" OR Anguill* OR "Leeward Island*" OR Montserrat* OR "Windward Island*" OR Cuba* OR Dominic* OR "Dominican Republic" OR Haiti* OR Jamaic* OR "Puerto Ric*" OR Puertorric* OR Puertoric):ti,ab,kw	19,858
	#65	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	43,671
	#66	#53 AND #65	227
Database	**Scielo** **Date: November 4, 21**		**Results**
Search Strategy	#1	((ti:((Postpartum Hemorrhage) OR (Shock, Hemorrhagic) OR (Uterine Inertia) OR (Uterine Hemorrhage) OR (Abruptio Placentae) OR (Blood Loss, Surgical) OR (Blood Transfusion) OR (Placenta Accreta) OR (Placenta Previa) OR (uterine inversion) OR (Uterine Artery Embolization) OR (Uterine Contraction) OR (Obstetric Labor Complications) OR (Postpartum Hemorrhag*) OR (Postpartum Haemorrhag*) OR (post-partum hemorrhage) OR (post-partum hemorrhage) OR (PPH) OR (Abruptio Placentae) OR (abruption) OR (blood loss*) OR (blood transfusion) OR (placenta accreta) OR (placenta previa) OR (shock) OR (placenta praevia) OR (placental previa) OR (placental praevia) OR (atony) OR (atonic) OR (atonic uterus) OR	307

(*Continued*)

Chart 1 (*Continued*)

		(uterine atony) OR (uterine inertia) OR (uterine bleeding) OR (uterine hemorrhage) OR (uterine hemorrhage) OR (uterus inversion) OR (uterine artery embolization) OR (uterine contraction) OR (labor complication*) OR (labor complication*) OR (delivery complication*) OR (Hemorragia Posparto) OR (Hemorragia Pós-Parto) OR (Choque Hemorrágico) OR (Placenta Previa) OR (Placenta Prévia) OR (Contracción Uterina) OR (Contração Uterina))) OR (ab:((Postpartum Hemorrhage) OR (Shock, Hemorrhagic) OR (Uterine Inertia) OR (Uterine Hemorrhage) OR (Abruptio Placentae) OR (Blood Loss, Surgical) OR (Blood Transfusion) OR (Placenta Accreta) OR (Placenta Previa) OR (uterine inversion) OR (Uterine Artery Embolization) OR (Uterine Contraction) OR (Obstetric Labor Complications) OR (Postpartum Hemorrhag*) OR (Postpartum Haemorrhag*) OR (post partum hemorrhage) OR (post-partum hemorrhage) OR (PPH) OR (Abruptio Placentae) OR (abruption) OR (blood loss*) OR (blood transfusion) OR (placenta accreta) OR (placenta previa) OR (shock) OR (placenta praevia) OR (placental previa) OR (placental praevia) OR (atony) OR (atonic) OR (atonic uterus) OR (uterine atony) OR (uterine inertia) OR (uterine bleeding) OR (uterine hemorrhage) OR (uterine hemorrhage) OR (uterus inversion) OR (uterine artery embolization) OR (uterine contraction) OR (labor complication*) OR (labor complication*) OR (delivery complication*) OR (Hemorragia Posparto) OR (Hemorragia Pós-Parto) OR (Choque Hemorrágico) OR (Placenta Previa) OR (Placenta Prévia) OR (Contracción Uterina) OR (Contração Uterina)))) AND ((ti:((Fetal Macrosomia) OR (Fetal Disease*) OR (Fetal Macrosomia) OR (Macrosom*) OR (fetal overgrowth) OR (large-for-gestational-age) OR (Fetal complication*) OR (Macrosomía Fetal) OR (Macrossomia Fetal))) OR (ab:((Fetal Macrosomia) OR (Fetal Disease*) OR (Fetal Macrosomia) OR (Macrosom*) OR (fetal overgrowth) OR (large-for-gestational-age) OR (Fetal complication*) OR (Macrosomía Fetal) OR (Macrossomia Fetal))) OR (ab:((Fetal Macrosomia) OR (Fetal Disease*) OR (Fetal Macrosomia) OR (Macrosom*) OR (fetal overgrowth) OR (large-for-gestational-age) OR (Fetal complication*) OR (Macrosomía Fetal) OR (Macrossomia Fetal))) OR (ab:((Fetal Macrosomia) OR (Fetal Disease*) OR (Fetal Macrosomia) OR (Macrosom*) OR (fetal overgrowth) OR (large-for-gestational-age) OR (Fetal complication*) OR (Macrosomía Fetal) OR (Macrossomia Fetal))))	
Database	**LILACS** **Date:** November 4, 2021		**Results**
Search Strategy	#1	(mh:(Postpartum Hemorrhage) OR Hemorragia Posparto OR Hemorragia Pós-Parto OR mh:(Shock, Hemorrhagic) OR Choque Hemorrágico OR Uterine Inertia OR mh:(Uterine Hemorrhage) OR Hemorragia Uterina OR mh:(Abruptio Placentae) OR Desprendimiento Prematuro de la Placenta OR Descolamento Prematuro da Placenta OR mh:(Blood Loss, Surgical) OR mh:(Blood Transfusion) OR mh:(Placenta Accreta) OR mh:(Placenta Previa) OR mh:(uterine inversion) OR mh:(Uterine Artery Embolization) OR mh:(Obstetric Labor Complications) OR Postpartum Hemorrhag$ OR Postpartum Haemorrhag$ OR post-partum hemorrhage OR post-partum hemorrhage OR PPH OR abruption OR blood loss$ OR placental previa OR placental praevia OR placenta praevia OR atony OR atonic OR atonic uterus OR uterine atony OR atoni$ OR uterine inertia OR uterine bleeding OR sangrado uterino OR sangramento uterino OR uterine hemorrhage OR uterine hemorrhage OR labor complication$ OR labor complication$ OR delivery complication$) AND (mh:(Fetal Macrosomia) OR Macrosomía Fetal OR Macrossomia Fetal OR mh:(Fetal Disease) OR Enfermedades fetales OR Doenças Fetais OR Fetal Macrosom$ OR Macrosom$ OR fetal overgrowth OR large-for-gestational-age OR Fetal complication$)	39

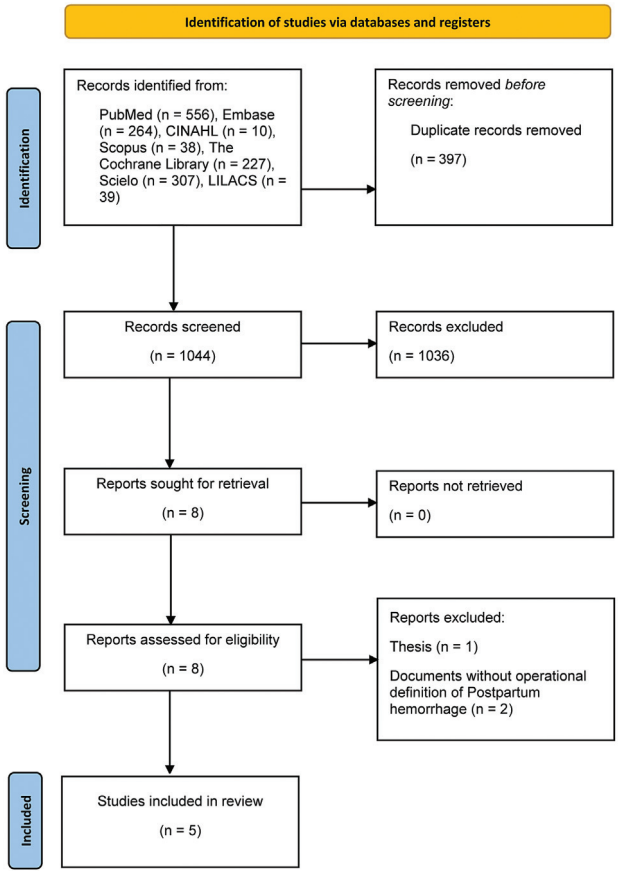

Fig. 1 PRISMA 2020 flow diagram of study selection.

participant recruitment, three studies were conducted in a single hospital,[22–24] and two were conducted in more than one setting.[21,25] Regarding the characteristics of the population included in the selected studies, the reporting of participants' age was heterogeneous; the age range included does not allow specification of the upper limit but does allow specification of the lower limit, so none of the studies included patients younger than 12-years-old. Also, due to the data collection process, all studies were based on medical record review. The studies' characteristics are summarized in ►**Chart 3**.

Regarding the operational definition of PPH, most studies presented a similar definition for this entity. All the included studies define it as a blood loss greater than or equal to 500 ml after delivery. Of the five studies, only three included the operational definition of severe PPH. Sosa et al.,[21] defined it as blood loss greater than or equal to 1,000 ml; Firmin et al.,[24] as the loss of at least 4 g/dl of hemoglobin, or the need for transfusion of at least four packs of red cell concentrates (RCC), the need for surgery, and/or maternal death; and Kodan et al.,[25] as blood loss of at least 1,000 ml, bleeding associated with arterial hypotension, or the need to transfuse at least three RCC packs. Concerning the operational definition of FM, all studies define it as a birth weight greater than or equal to 4,000g. The pooled OR of FM cases reporting PPH in the LAC region, calculated from a meta-analysis of 5 eligible studies, was 2.10 (95% CI: 1.79–2.47), with low heterogeneity described between studies (I^2: 0%) (►**Fig. 2a**). The meta-analysis of severe PPH (≥1,000 ml of postpartum blood loss) was performed with three studies by measuring the presence of this outcome.[21,24,25] The pooled OR of severe PPH was 1.61 (95% CI: 0.40–6.48), with high heterogeneity among studies (I^2: 91.89%) (►**Fig. 2b**). A subgroup analysis according to the severity of PPH only for the studies that measured severe PPH is presented in ►**Fig. 3**, with the pooled OR for nonsevere cases being 2.68 (95% CI: 1.43–5.04), pooled OR of 1.61 (95% CI: 0.40–6.48) for the severe PPH, and a total pooled OR of 2.46 (95% CI: 1.84–3.27) (►**Fig. 3**).

In relation to the quality of the studies included, according to the modified NOS, two[21,24] were of high quality (score of 7–9 points) and three were of fair quality[22,23,25] (score of 4–6 points) (►**Chart 4**). Additionally, we estimated the association between PPH and FM, and severe PPH and FM. In relation to the studies with fair quality, a pooled OR of 2.14 (95% CI: 1.61–2.84; I^2: 0%) was observed for PPH, while the high-quality studies had a pooled OR of 3.62 (95% CI: 0.92–14.21; I_2: 83.13%) and 0.96 (95% CI: 0.06–15.36; I_2: 86.00%) for common and severe PPH, respectively, presenting high heterogeneity in both cases (►**Fig. 4 a** e **b**).

Chart 2 List of excluded studies

Study		Reason
1	Machado, O., 2017. [Factors associated with uterine atonia in the postwork of the Hospital Uldarico Rocca Fernández in Villa el Salvador, in the period January - December 2014]. Repository of the San Martín de Porres University. https://repositorio.usmp.edu.pe/handle/20.500.12727/2684?locale-attribute=de	The study is a thesis published in a repository.
2	Salazar de Dugarte G, González de Chirivella X, Faneite Antique P. Incidencia y factores de riesgo de macrosomía fetal. Rev Obstet Ginecol Venezuela. 2004; 64(1):15–21.	Does not operationally define the variable postpartum hemorrhage.
3	Galarza MP de L. Indicadores clínico epidemiológicos y materno-fetales de atonía uterina en puérperas post cesárea primaria en una clínica privada de agosto 2017–agosto 2018. Rev Fac Med Humana. 2019; 19(2):7–7.	Does not operationally define the variable postpartum hemorrhage.

Chart 3 Characteristics of the studies included

Author (year)	Country(ies)	Study design	Data collection period	Setting	Age (years), in mean (SD) or range	Number of women with PPH	Number of women with severe PPH	Sample size (n)	Quality assessment (NOS)
Sosa et al., 2009	Argentina, Uruguay	Cohort	Data collected during 3 periods, but only 2 were used. First period: October to December 2003 Third period: October to December 2005	Hospital	NR	1,221	309	11,323	8
Richardson et al., 2017	West Indies	Case-control	January 2007 to December 2009	Hospital	29.84 (6.1)	50	NE	316 cases; 316 controls	6
Martin et al., 2003	Antigua and Barbuda	Case-control	July 1991 to January 1997	Hospital	27.9	52	NE	157 cases; 157 controls	6
Firmin et al., 2019	French Guiana	Case-control	September 2014 to September 2015	Maternity Department of Hospital	NR	154	39	154 cases; 308 controls	8
Kodan et al., 2020	Suriname	Case-control	January to December 2017	Hospital	12–35 and > 35	585	216	8747	6

Abbreviations: PPH, postpartum hemorrhage; NOS, Newcastle-Otawa scale; NR, not reported; NE, not evaluated; SD, standard deviation.

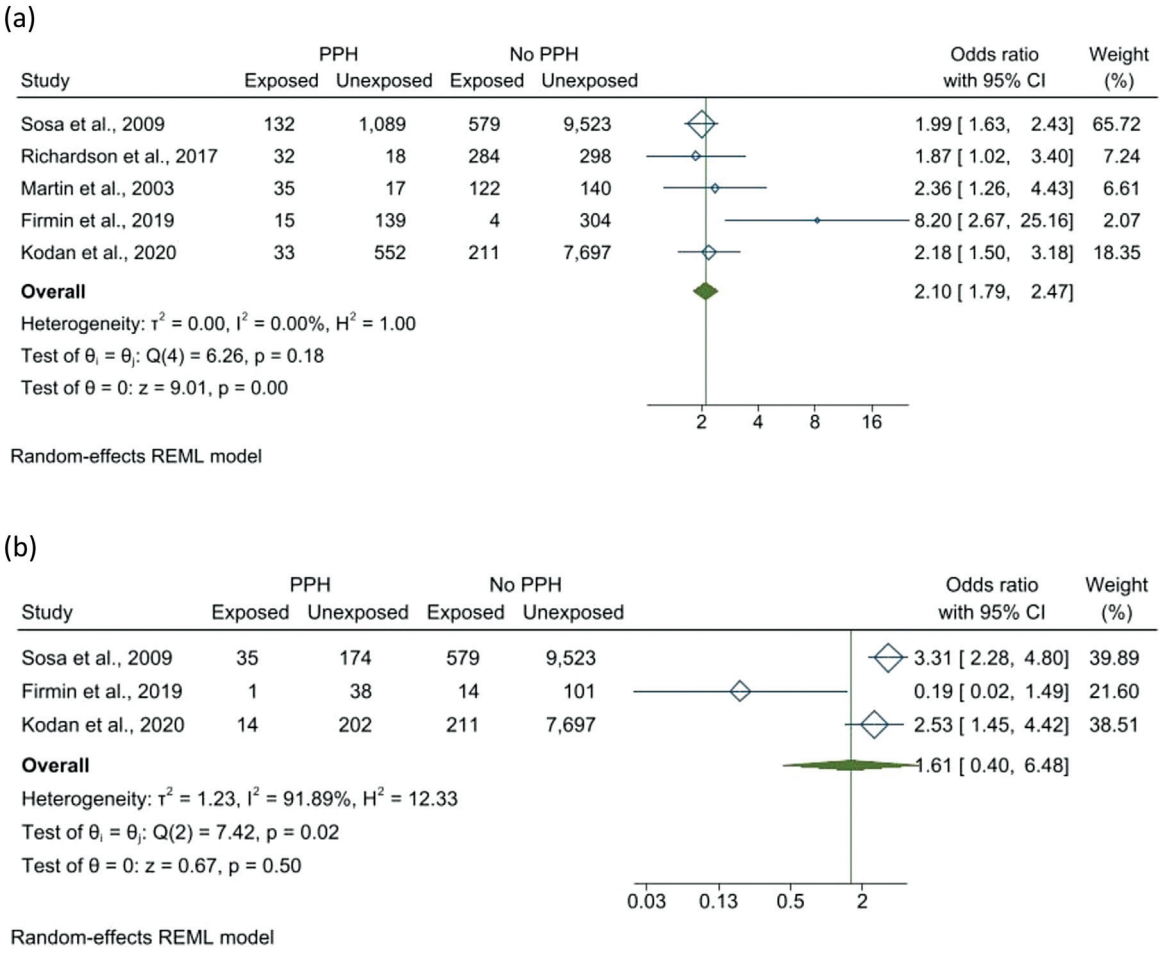

Fig. 2 Forest plot showing the pooled odds ratio of association between postpartum hemorrhage (a), severe postpartum hemorrhage (b) and fetal macrosomia. **Abbreviations:** CI, confidence interval; PPH, postpartum hemorrhage.

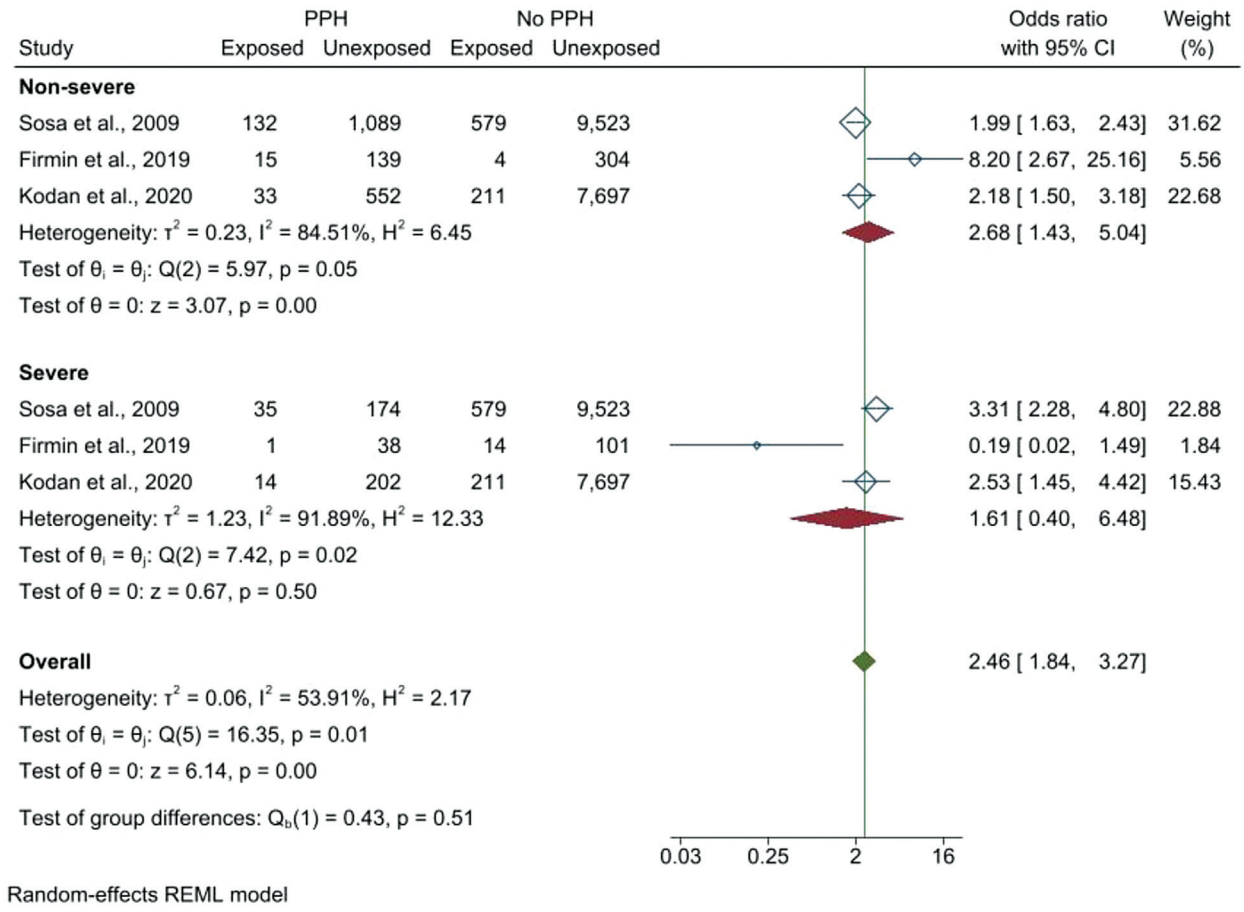

Fig. 3 Forest plots showing the pooled odds ratio for fetal macrosomia according to the severity of postpartum hemorrhage in studies measuring severe postpartum hemorrhage. **Abbreviations:** CI, confidence interval; PPH, postpartum hemorrhage.

The sensitivity analysis consisted of the leave-one-out method showing pooled OR values of 2.32 (95% CI: 1.76–3.06) with the exclusion of the study by Sosa et al.[21] and 2.12 (95% CI: 1.79–2.51) excluding the study of Richardson et al.[22] These values were within the estimated CI of the combined OR with all the studies to estimate the association between PPH and FM (►**Fig. 5**). For severe PPH, the sensitivity analysis showed combined OR values of 3.05 (95% CI: 2.23–4.15) with the exclusion of the study by Firmin et al.,[24] and 0.96 (95% CI: 0.06–15.36) with the exclusion of the study by Kodan et al.,[25] being a value that was not within the estimated CI of the combined OR with all the studies (►**Fig. 6**).

Discussion

The present study sought to determine the association between FM and PPH in LAC women. A total of 5 articles met the eligibility criteria established for this systematic review. The meta-analysis performed showed that FM is a risk factor for PPH in pregnant women in LAC, with low heterogeneity among the studies in this analysis. Regarding the associations between FM and severe PPH, only 3 studies were found, and the meta-analysis showed no association between these clinical conditions, although there was high heterogeneity.

The pooled analysis showed that FM cases in LAC were more likely to develop PPH compared with deliveries in which FM was not present. This result was similar to a previous systematic review conducted in Asian, European, and African populations (OR: 2.05; 95% CI: 1.90–2.22). Thus, the strength and direction of the association between FM and PPH found in LAC are consistent with those of other regions of the world. Regarding the mechanism that would explain this relationship, it is postulated that uterine overdistension is the main mechanism of the relationship between the two variables.[26] It is also described that a larger placental size could increase the surface area for postpartum bleeding and, thus, the risk of PPH.[27] In LAC, there has been an increase in cases of FM in recent decades, possibly explained by the increase in the prevalence of obesity among women.[9] The increase in the prevalence of FM in LAC requires timely diagnosis and appropriate medical management, as well as protocols for the care of women who may present complications, such as PPH, related to the presence of FM. Also, during the third stage of labor, the utility of using oxytocin or other uterotonics to prevent PPH (prophylactic use) is described.[28] Only three included studies reported data about using oxytocin or other uterotonics to prevent it.[21,24,25] However, these data are not sufficiently presented to

Chart 4 Quality assessment of the included studies

N°	Year	Author	Journal	Title	Criteria								Total
					Selection				Comparability	Outcome			
					1	2	3	4	1	1	2	3	
1	2009	Sosa et al.	Obstetrics & Gynecology	Risk Factors for Postpartum Hemorrhage in Vaginal Deliveries in a Latin-American Population	*	*	*	–	**	*	*	*	8
2	2017	Richardson et al.	West Indian Medical Journal	Outcome of macrosomic infants at the university hospital of the West Indies	*	*	*	*	–	*	*		6
3	2003	Martin et al.	West Indian Medical Journal	A Case Control Study of the Prevalence of Perinatal Complications Associated with Fetal Macrosomia in Antigua and Barbuda	*	*	*	*	–	*	*		6
4	2019	Firmin et al.	Journal of Gynecology Obstetrics and Human Reproduction	Postpartum hemorrhage: incidence, risk factors, and causes in Western French Guiana	*	*	*	*	**	*	*		8
5	2020	Kodan et al.	PLoS ONE	Postpartum hemorrhage in Suriname: A national descriptive study of hospital births and an audit of case management	*	*	–	–	**	*	*		6

Abbreviations: NOS, Newcastle-Ottawa scale. **Note:** The modified Newcastle-Ottawa scale (NOS) was used to assess the quality of the studies included.

obtain the proportion of use of prophylactic uterotonics according to the presence of PPH or FM. As such, while it was not possible to describe or evaluate the influence of prophylaxis measures in these cases, it is reasonable to think these measures may influence bleeding. Hence, future studies could evaluate the influence of prophylactic uterotonics for PPH in FM cases.

The studies included in this review were conducted in South and Central American countries. Although no data are available regarding the association of PPH and FM in other LAC countries, similar results are expected to be found among the different countries of this region since they are mostly low- and middle-income countries. Globally, LAC is one of the regions with the highest maternal mortality rates, and in this regard, PPH is an important public health problem. Although there was a reduction in deaths in both Latin America (124 to 69 per 100,000 live births) and the Caribbean (276 to 175 per 100,000 live births) from 1990 to 2015, the expected target of a 75% reduction in maternal mortality described in the Millennium Development Goals was not achieved.[29] While the main causes of maternal death are preventable, including PPH, inequalities in access to health services and quality of care received by women in this region of the world explain why PPH continues to be the leading cause of maternal death in LAC countries.[8] There is a need for proper identification of cases of FM during clinical management, and to ensure that the necessary resources are available for possible complicated deliveries, including cases of PPH. The improvement and implementation of programs to detect and prevent early factors that may condition the presence of PPH and other maternal complications are also needed.[30]

Regarding severe PPH, only three studies could be included to evaluate this outcome and its association with FM, because the remaining studies did not report the number of cases of PPH greater than or equal to 1,000 ml. No association was found between FM and the presence of severe PPH. The low number of studies that evaluated this outcome, as well as the high heterogeneity among these studies, could explain the lack of association between FM and severe PPH in the meta-analysis and the sensitivity analysis, reaffirming what was described. Since FM was found to be associated with PPH, it would be expected that severe PPH would also be related to this clinical condition. A few studies in the literature have evaluated and described an association between FM and severe PPH.[4,31] Thus, future studies of adequate methodological rigor are needed to evaluate the association between FM and severe PPH in LAC. Defining this association would be useful to emphasize the need for timely identification of FM cases during the care of pregnant women to reduce the risk of maternal complications and mortality in this region.

Some limitations should be considered in the interpretation of the results of this systematic review. The first limitation is due to the high number of covariates used in the included studies as confounding variables, which makes it impossible to perform a meta-regression to evaluate the association between PPH and FM adjusting for variables that are relevant in the point estimate. The second limitation

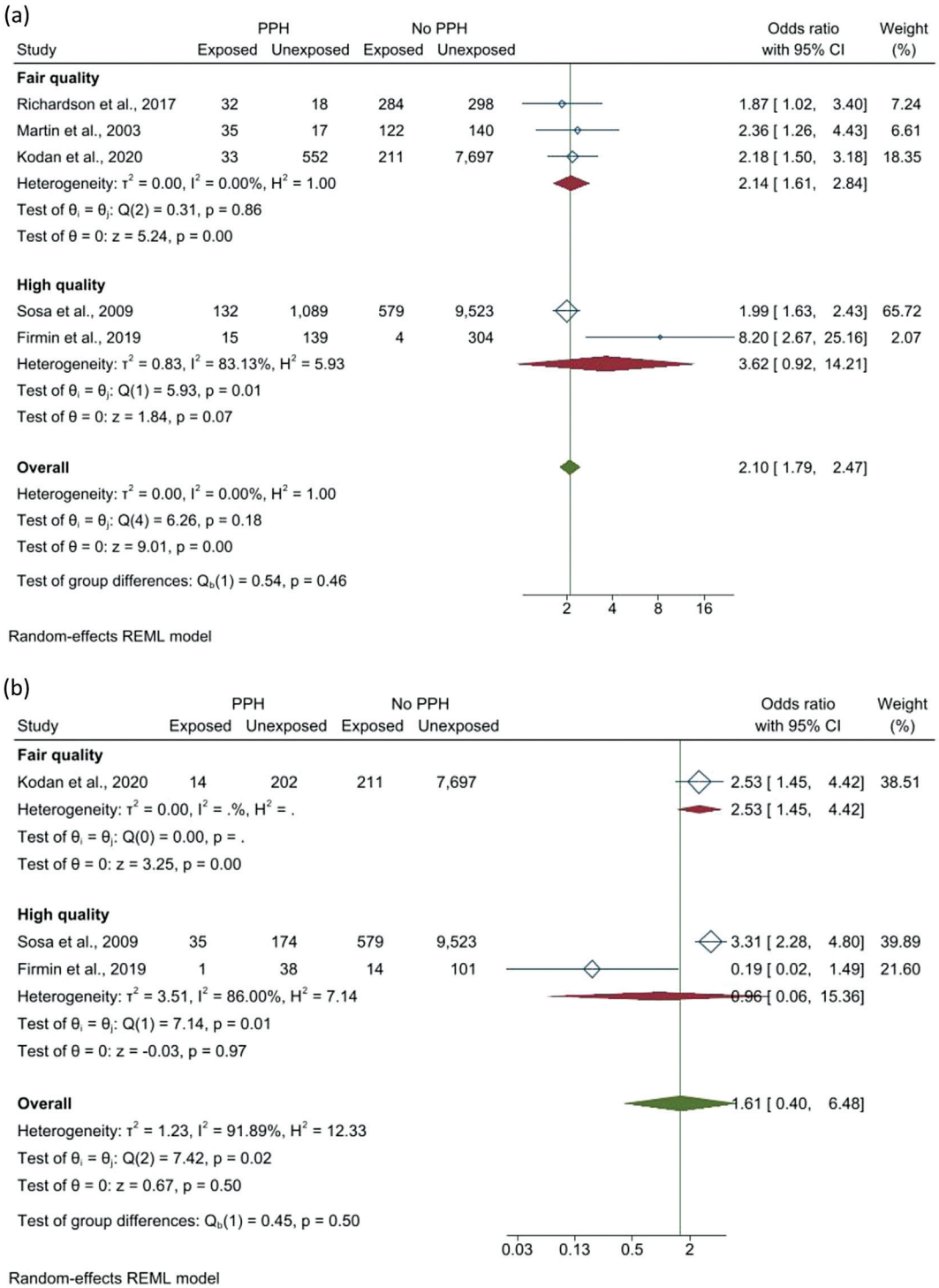

Fig. 4 Subgroup analysis according to the quality of the included studies (a) association between postpartum hemorrhage and fetal macrosomia; (b) association between severe postpartum hemorrhage and fetal macrosomia. **Abbreviations:** CI, confidence interval; PPH, postpartum hemorrhage.

is the presence of high methodological heterogeneity found in the second analysis (association of FM and severe PPH), which does not allow acceptable certainty regarding the estimate obtained for this association, although the literature reports an association between these two clinical conditions. This lack of certainty prevents a conclusive analysis, requiring new evaluations including studies with less heterogeneity. The third limitation lies in the scarcity of information, since only studies in populations from less than half of the LAC countries were found. Although it is expected to find similar results in these other countries, the generalization of these results should be considered with caution.

Despite the aforementioned limitations, the present study's preparation rigorously followed the updated PRISMA 2020 guidelines for systematic reviews.[11] Furthermore, sensitivity analysis and subgroup analysis were conducted to

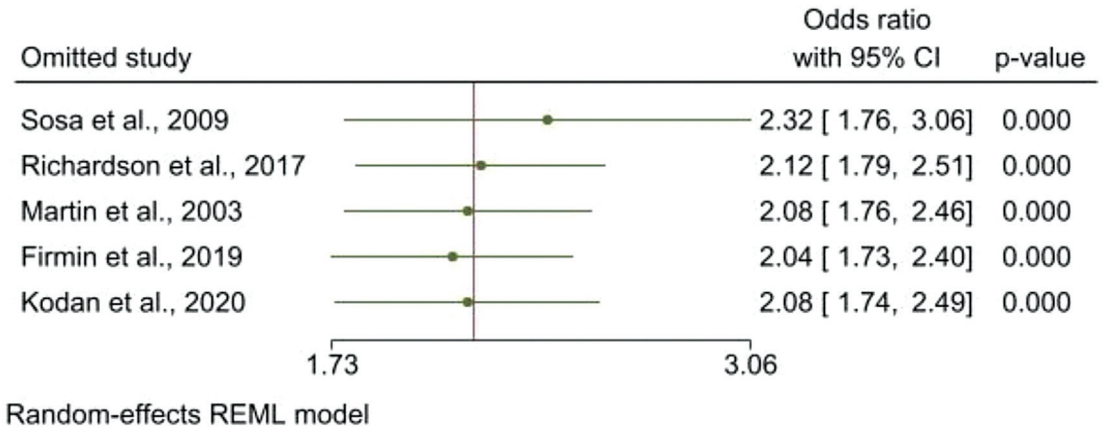

Fig. 5 Leave-one-out sensitivity analysis of the pooled OR of association between postpartum hemorrhage and fetal macrosomia. **Abbreviations:** CI, confidence interval.

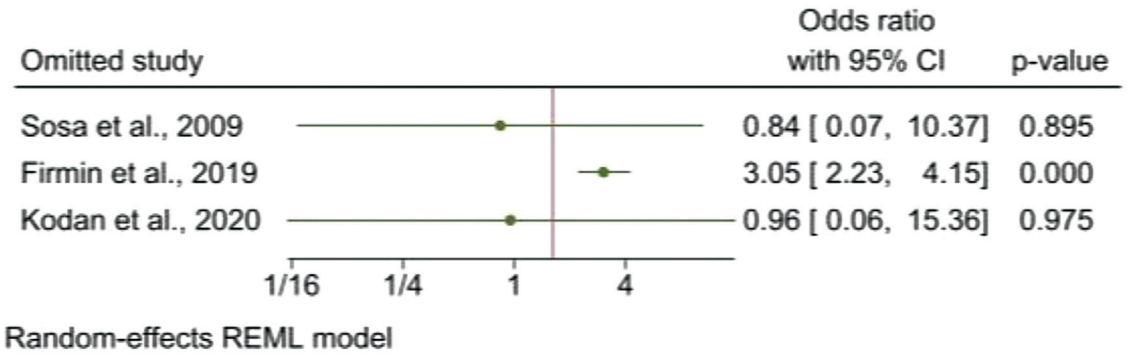

Fig. 6 Leave-one-out sensitivity analysis of the pooled OR of association between severe postpartum hemorrhage and fetal macrosomia. **Abbreviations:** CI, confidence interval.

strengthen the conclusions and credibility of the findings. Additionally, each article included was evaluated according to the criteria of the NOS. Therefore, we consider the assessment of the association of interest in the LAC population to be adequate.

Conclusion

In conclusion, the results of this systematic review indicate that FM is related to PPH in the LAC population. The evidence available to date included the evaluation of this association in only some LAC countries, with results in line with the current scientific literature.

Regarding FM and its association with severe PPH, further research following a rigorous study design and measurement of severe PPH are required to evaluate this association. Adequate identification of FM as well as the implementation or improvement of maternal health services, including more human resources prepared for the care of obstetric emergencies, as well as appropriate resources and infrastructure for the care or transfer of patients presenting PPH are necessary for the management of this health problem in LAC. Likewise, raising awareness and training health personnel to identify patients with PPH is of vital importance to prevent complications associated with this condition, as well as for better decision making and improved quality of care.

Conflict of Interests

The authors have no conflict of interests to declare.

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Effect of Lubricant Use on Cervicovaginal Cytology – What's the Evidence?

Efeito do uso de lubrificante na citologia cervicovaginal – Qual a evidência?

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Abstract

Objective To determine if the use of lubricating gel on the speculum during the cervicovaginal cytology examination interferes with the results obtained, as well as whether it reduces reported discomfort in patients.

Data sources A systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations, with a search in the Pubmed/Medline, Scielo, Cochrane Library, Embase databases of articles published between January 2011 and May 2022. The keywords used were *cytology*, *speculum*, *lubricant, result, and pain*.

Selection of studies The initial search resulted in 306 articles, of which were excluded three because they were duplicates, 257 after reading the title and abstract and 41 after reading the full text. Thus, five articles were selected for the study: four randomized clinical trials and one metanalysis.

Data collection The selection of articles was performed by two investigators. The 5 selected articles were read in full and submitted to a comparative analysis.

Data synthesis Screening through cervicovaginal cytology allows for early diagnosis and reduction of associated mortality, but the procedure can be associated with pain. A small amount of aqueous lubricating gel in the speculum can be used to reduce the discomfort associated with performing cervicovaginal cytology.

Conclusion The use of lubricating gel in the speculum does not seem to be associated with a change in the cytology result and reduces the discomfort associated with its insertion into the vagina.

Keywords
- Cytology
- Speculum
- Lubricant
- Result
- Pain

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Resumo

Objetivo Determinar se o uso de gel lubrificante no espéculo durante o exame de citologia cervicovaginal interfere com os resultados obtidos e se diminui o desconforto relatado por pacientes.

Fontes de dados Foi realizada uma revisão sistemática segundo as recomendações do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), com pesquisa nas bases de dados Pubmed/Medline, Scielo, Cochrane Library, Embase, de artigos publicados entre janeiro de 2011 e julho de 2022. Utilizaram-se as palavras-chave *citologia*, *espéculo*, *lubrificante, resultado e dor*.

Seleção dos estudos A pesquisa inicial resultou em 306 artigos, dos quais foram excluídos três por se encontrarem duplicados, 257 após a leitura do título e do resumo e 41 após a leitura integral. Assim, foram selecionados cinco artigos para o estudo: quatro ensaios clínicos aleatorizados e uma metanálise.

Coleta de dados A seleção dos artigos foi realizada por dois investigadores. Os cinco artigos selecionados foram lidos na íntegra e submetidos a uma análise comparativa.

Síntese dos dados O rastreio através da citologia cervicovaginal permite um diagnóstico precoce e redução da mortalidade associada, mas a sua realização pode estar associada a dor. Uma pequena quantidade de gel lubrificante aquoso pode ser utilizada no espéculo para diminuir o desconforto associado à realização da citologia cervicovaginal.

Conclusão A utilização de gel lubrificante não está associada a alteração do resultado da citologia e diminui o desconforto associado à sua introdução na vagina.

Palavras-chave

- Citologia
- Espéculo
- Lubrificante
- Resultado
- Dor

Introduction

Cervicovaginal cytology (CVC) is an effective screening test for early diagnosis of cervical cancer, allowing a marked reduction in associated mortality.[1–4] According to the literature, most of the women who died from cervical cancer did not undergo cervical cytology during the previous 5 years.[3] The discomfort caused by the introduction of the speculum can decrease the rate of adherence to screening. Theoretically, the use of lubricant while introducing the speculum can minimize this discomfort and, thus, increase adherence rates for this test.[1,3,4] The Family Doctor has a key role in the prevention of disease in Primary Health Care. However, this approach is controversial, and many studies have assessed the possible effects of lubricants on cytology results.[4,5] In this sense, it was considered relevant to review the existing scientific evidence on the use of lubricating gel in the speculum during the performance of cervicovaginal cytology, as well as its influence on the results obtained and patients' reported discomfort during the test.

Methods

A nonquantitative systematic search (evidence-based review) was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[6] Clinical guidelines, systematic reviews, meta-analyses and original studies were searched in the PUBMED databases, Cochrane Library, EMBASE, published between January 2011 and May 2022. The keywords *cytology*, *speculum*, *lubricant, result, and pain* were used. Full text studies in either Portuguese, English, or Spanish and carried out in humans were included. The following inclusion criteria were considered during study selection: 1) Population: women who underwent cervical cancer screening using the conventional technique or in liquid base; 2) Intervention: use of lubricating gel when introducing the speculum for cytology collection; 3) Comparison: use of lubricant in gel versus not using it when introducing the speculum; 4) Outcome: interference of the use of lubricant in the cytology's results and in the relief of patients' reported pain and discomfort. The following exclusion criteria were considered: duplicates, opinion articles, classic theme reviews, and articles that disagreed with this review's objective. The selection of articles for review was made by two authors who, in case of doubt, would discuss the inclusion/exclusion of the article with the third one. The agreement rate between authors in the selection of articles was 100%. All authors fully read and assessed the quality and level of evidence (LE) of the selected articles. The quality of the studies, and subsequent attribution of the level of evidence and the strength of recommendation (FR) were evaluated using the American Family Physician's Strength of Recommendation Taxonomy (SORT) scale.[7]

Results

After searching all databases, a total of 306 articles were obtained, of which only 5 met the inclusion criteria: four randomized clinical trials (RCTs) and one metanalysis (MA).

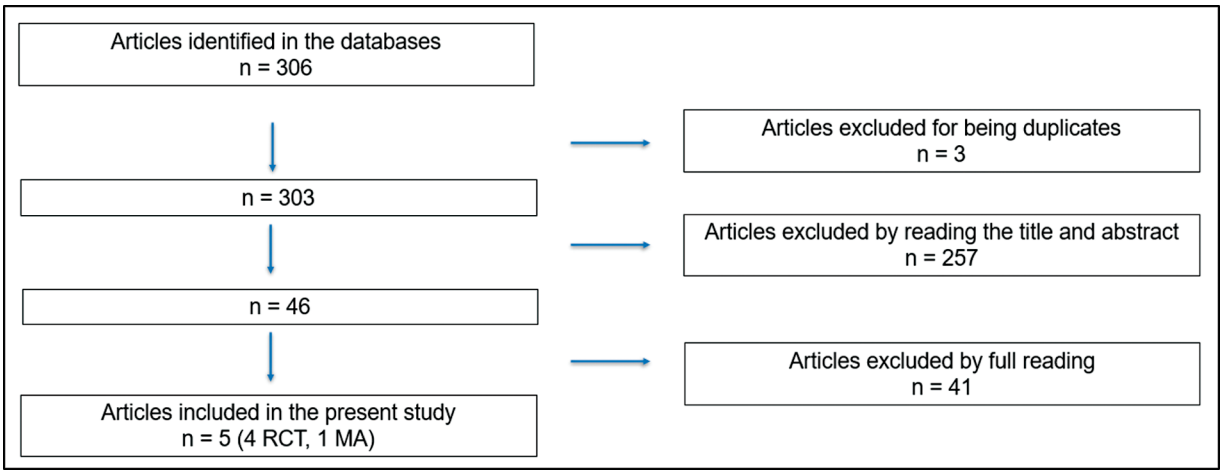

Fig. 1 Article selection flowchart.

Table 1 Summarized description of selected articles

Ref	E	Target population and study design	Results/Conclusions	Limitations	EL
1	RCT	Aqueous lubricant vs. control n = 1,580. Age: 20–72 years Conventional cytology	A small quantity of aqueous lubricant diminishes reported pain by women in childbearing age and postmenopausal without altering the results of the cytology.	No evidence on other lubricant types.	1
2	RCT	Aqueous lubricant vs. water n = 400 Age: 23–67 years Conventional and liquid-based cytology	A small quantity of aqueous lubricant in the speculum does not affect cytology results and significantly diminishes reported pain during speculum insertion in postmenopausal women but not in childbearing age.	No evidence on other lubricant types.	1
3	RCT	Aqueous lubricant vs. water n = 120 Age: 18–50 years Liquid-based cytology	The use of lubricant gel was correlated with less pain in speculum insertion, without altering cytology results.	Small sample size; no postmenopausal women included; no evidence on other lubricant types.	1
4	RCT	Liquid petrolatum topical vs. control n = 83. Age: 15–44 years Liquid-based cytology	A small quantity of liquid petrolatum topical used as a lubricant did not alter cytology results, nor did it significantly improve reported discomfort.	Small sample size; exam performed by a wide range of physicians; few patients tested positive for epithelial lesion; no evidence on other lubricant types.	1
5	MA	7 studies Rates the impact of lubricant use in CVC's result and in reported pain during speculum insertion Conventional cytology	The use of aqueous lubricant does not interfere with ratio of unsatisfactory results of conventional CVC, neither does it significantly alleviate discomfort felt during procedure.	Clinical and statistic heterogeneity of included studies.	2

Abbreviations: CCV, cervico-vaginal cytology; E, type of study; LE, level of evidence; MA, metanalysis; Ref, bibliographic reference; RCT, randomized clinical trial.

The article selection phases are specified in ►**Figure 1**. ►**Table 1** summarizes the characteristics of the studies selected for review and their results.

The double-blind randomized clinical trial by Simavli et al.,[1] carried out in Turkey between July 2011 and December 2012, aimed to investigate the effect of the use of aqueous lubricant on the outcome of conventional cytology, as well as on the reduction of pain or discomfort associated with vaginal introduction of the speculum. A population of 1,580 patients was evaluated, aged between 20 and 72 years, randomly divided into experimental (aqueous lubricating gel) and control (dry speculum) groups. A numerical pain scale (0–10) was used to assess pain in two phases of the procedure (introduction and opening of the speculum). They concluded that the use of a small amount of aqueous lubricant decreases the pain experienced by women, both of childbearing age and postmenopausal, without altering the quality of cytology results (unsatisfactory, premalignant lesion, or sign of inflammation) ($p < 0.001$).

Also, in Turkey, Uygur et al.,[2] carried out a double-blind randomized clinical trial, between May and September 2011, in which they studied the effect of lubrication on reported

pain and on the result of conventional or liquid-based cervical cytology (unsatisfactory result, presence of abnormal cells). The study population included 400 women aged between 23 and 67 years and was randomly divided into two groups of 200 elements each: experimental (aqueous lubricating gel) and control (hot water). Each of these groups was randomly divided into two subgroups: in the first one, conventional cytology was performed; in the second one, liquid based lubricant was used during cytology. They concluded that the use of a small amount of lubricant in the speculum does not affect the interpretation of cervicovaginal cytology (conventional and liquid medium) and significantly reduces the pain caused by the introduction of the speculum in postmenopausal women ($p < 0.05$), but not significantly in women of reproductive age.

The single-blind randomized clinical trial by Hill et al.,[3] conducted in Florida between February and July 2011, studied the effectiveness of using lubricating gel in reducing pain associated with the introduction of a vaginal speculum compared to using water. It included 120 women of childbearing age, between 18 and 50 years old, with criteria for performing cytology in liquid medium. The participants were randomly divided into two groups: experimental (lubricating gel) and control (water). Pain was classified using the visual analogue scale (VAS: 0–10). It was found that the pain felt by the experimental group (with gel) was significantly lower ($p < 0.01$). This study did not aim to evaluate the cytology results, but they were satisfactory in both groups. Hill et al. concluded that the use of a small amount of aqueous lubricating gel is associated with less pain during the introduction of the vaginal speculum, so evidence-based medicine should encourage clinicians to use aqueous lubricating gel during this procedure.

In Brazil, Nunes et al.[4] performed a double-blind randomized clinical trial between August 2012 and June 2013, with the objective of evaluating the effect of the use of lubricating gel in the speculum during cervicovaginal cytology examination. It included 83 women aged between 15 and 44 years, randomly divided into two groups: group 1 (cervicovaginal cytology was first performed with a dry speculum and later with a small amount of liquid petroleum jelly) and group 2 (both cervicovaginal cytology exams were performed with a dry speculum). There were 42 women in the first group and 43 in the second one. The exam's result and the degree of discomfort were compared between the first and second cytology, as well as between both groups. The CVC's result was evaluated by the quality of the sample (satisfactory/unsatisfactory), presence of artifacts, normal or inconclusive results, inflammation, and presence of human papilloma virus. Discomfort/pain was classified using a numerical scale from 0 to 10. There was a significantly lower discomfort when performing the second CVC in group 1 compared to group 2 ($p = 0.03$). No significant difference was observed between the results of the first and second CVC samples in both groups. Therefore, the use of a small amount of liquid petroleum jelly as a lubricant in the introduction of the speculum did not alter the quality of the result and significantly improved the discomfort felt by participants.

Pergialiotis et al.[6] carried out a metanalysis with the objective of evaluating the impact of the use of lubricant on the CVC exam's result and reported pain when introducing the speculum. It included seven studies: five randomized clinical trials and 2 near randomized clinical trials. The authors concluded that speculum lubrication does not interfere with the rate of unsatisfactory results of conventional cytology. Since only two studies had unsatisfactory results due to lubricant use during CVC, it was not possible to draw firm conclusions. On the other hand, there was no significant relief from the discomfort felt during the examination with the use of aqueous lubricant. The studies included in this metanalysis show clinical and statistical heterogeneity.

Discussion

In summary, the first two RCTs included both women of childbearing age and postmenopausal and concluded that the use of aqueous lubricating gel does not change the CVC's results and decreases reported pain, although in Uygur et al.'s RCTs, this conclusion only applies to postmenopausal women.[2] As for Hill et al. and Nunes et al.'s RCTs, they included only women of childbearing age and concluded that the use of lubricating gel decreases the pain felt, without altering the CVC result.[3,4] Finally, the metanalysis by Pergialiotis et al. concluded that the use of aqueous lubricant on the speculum does not interfere with the result of conventional CCV nor does it significantly alleviate the discomfort felt.

Evaluating potential limitations, it should be noted that the results cannot be generalized to any type of lubricant other than the one used in each study. Furthermore, the technique used for result collection was different between the studies. Some studies had a small sample size and did not include postmenopausal women. The included metanalysis presented heterogeneous results. The methodology of these studies did not follow a double-blind approach.

Conclusion

The results observed here are mainly in agreement that the use of a small amount of lubricating gel in the speculum is not associated with a change in CVC exam results and, instead, can reduce the discomfort associated with its introduction into the vagina, with a grade A recommendation force.

Homogeneous studies with larger samples are recommended, to compare the effects of different types of lubricants on the CVC results and to stratify the reported pain and discomfort in pre- and postmenopausal women, in order to reinforce these results. Primary care physicians have a key role in disease prevention. Improving the comfort of women during CVC examination certainly improves adherence to cervical cancer screening, which translates to a decrease in morbidity and mortality caused by this pathology.

Conflict of Interests

The authors have no conflict of interests to declare.

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Sexual Function of Patients with Deep Endometriosis after Surgical Treatment: A Systematic Review

Função sexual em pacientes com endometriose profunda após o tratamento cirúrgico: Revisão sistemática

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Abstract

Objective To review the current state of knowledge on the impact of the surgical treatment on the sexual function and dyspareunia of deep endometriosis patients.

Data Source A systematic review was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We conducted systematic searches in the PubMed, EMBASE, LILACS, and Web of Science databases from inception until December 2022. The eligibility criteria were studies including: preoperative and postoperative comparative analyses; patients with a diagnosis of deep endometriosis; and questionnaires to measure sexual quality of life.

Study Selection Two reviewers screened and reviewed 1,100 full-text articles to analyze sexual function after the surgical treatment for deep endometriosis. The risk of bias was assessed using the Newcastle-Ottawa scale for observational studies and the Cochrane Collaboration's tool for randomized controlled trials. The present study was registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration CRD42021289742).

Data Collection General variables about the studies, the surgical technique, complementary treatments, and questionnaires were inserted in an Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, United States) spreadsheet.

Synthesis of Data We included 20 studies in which the videolaparoscopy technique was used for the excision of deep infiltrating endometriosis. A meta-analysis could not be performed due to the substantial heterogeneity among the studies. Classes III and IV of the revised American Fertility Society classification were predominant and multiple

Keywords
- systematic review
- endometriosis
- sexual health
- surgery
- dyspareunia

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surgical techniques for the treatment of endometriosis were performed. Standardized and validated questionnaires were applied to evaluate sexual function.
Conclusion Laparoscopic surgery is a complex procedure that involves multiple organs, and it has been proved to be effective in improving sexual function and dyspareunia in women with deep infiltrating endometriosis.

Resumo

Objetivo Revisar a literatura publicada sobre o impacto do tratamento cirúrgico na função sexual e na dispareunia de pacientes com endometriose profunda.
Fonte de Dados Uma revisão sistemática foi realizada de acordo com as diretrizes Meta-Analysis of Observational Studies in Epidemiology (MOOSE). Realizamos pesquisas sistemáticas nas bases de dados PubMed, EMBASE, LILACS e Web of Science desde o início até dezembro de 2022. Os critérios de elegibilidade foram estudos que incluíam: análises comparativas pré- e pós-operatórias; pacientes com diagnóstico de endometriose profunda; e a aplicação de questionários para avaliar a função sexual.
Seleção dos Estudos Dois revisores selecionaram e revisaram 1.100 artigos para analisar a da função sexual após o tratamento cirúrgico da endometriose profunda. O risco de viés foi calculado usando-se a escala de Newcastle-Ottawa para estudos observacionais e a ferramenta para ensaios clínicos randomizados da Cochrane Collaboration. O estudo foi cadastrado no International Prospective Register of Systematic Reviews (PROSPERO; cadastro CRD42021289742).
Coleta de dados Variáveis gerais sobre os estudos, a técnica cirúrgica, os tratamentos complementares e os questionários foram inseridas em uma planilha do Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, Estados Unidos).
Síntese dos dados Foram incluídos 20 estudos em que se usou a técnica de videolaparoscopia para a excisão da endometriose profunda. Uma meta-análise não pôde ser realizada devido à heterogeneidade substancial entre os estudos incluídos. As classes III e IV da escala revisada da American Fertility Society foram predominantes, e múltiplas técnicas cirúrgicas foram usadas para o tratamento da endometriose. Questionários padronizados e validados foram aplicados para avaliar a função sexual.
Conclusão A cirurgia laparoscópica é um procedimento complexo que envolve múltiplos órgãos, e provou ser eficaz na melhora da função sexual e da dispareunia em mulheres com endometriose profunda.

Palavras-chave
- revisão sistemática
- endometriose
- saúde sexual
- cirurgia
- dispareunia

Introduction

Endometriosis is defined as the presence of endometrial stroma and glands outside the uterine cavity. It is present in 3% to 15% of fertile women,[1] and it affects women's quality of life, causing chronic pelvic pain, dyspareunia, infertility, as well as certain deleterious sexual effects in 67% of the cases.[2] In contrast, deep infiltrating endometriosis (DIE) consists of the penetration of the endometrial tissue more than 5 mm below the peritoneal surface.[3]

The literature reports that endometriotic disease is the main cause of dyspareunia, and it affects 60% to 70% of women undergoing surgery. The common presence of DIE on cardinal and uterosacral ligaments, on the pouch of Douglas and on the posterior vaginal fornix represents a nine-old increase in the risk of developing dyspareunia.[2,4]

Dyspareunia does not cause only pain: it is also associated with psychological and psychosocial injury. Feelings of fear during intercourse, as well as guilt, are predominant among DIE patients, and they directly and indirectly affect domains of sexual function such as desire, frequency, pleasure and orgasm.[5]

The treatment for endometriosis is mainly focused on pain control and quality of life improvement, including, sexual life. Hormonal therapies are effective for pain control during disease progression, but they can also lead to gonadal suppression and reduced sexual response.[6] However, surgical procedures and radical resection of all visible endometriosis nodules may improve quality of life in up to 85% to 95% of severe to moderate cases.[7]

According to international guidelines, endometriosis is a chronic disease that requires a life-long management plan to control pain symptoms and to avoid multiple surgical procedures.[8] Hormonal therapies to achieve a hypoestrogenic status are effective to control pain and disease progression, but they are also associated with gonadal suppression and

reduced sexual response.[6] The aim of the surgical treatment is the excision of all endometriosis lesions to improve pain and infertility. However, in cases of extensive DIE, surgery is associated with peri- and postoperative complications, as well as a decrease in sexual function.[9]

Thus, the present systematic review aims to assess how surgery affects sexual function and dyspareunia in patients undergoing surgical treatment to treat DIE.

Materials and Methods

The present systematic review was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The study protocol was registered at the at the International Prospective Register of Systematic Reviews (PROSPERO; registration CRD 42021289742) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

We performed a search in the following databases: PubMed, EMBASE, Cochrane Library, LILACS, and Web of Science from inception to December 2022. The main keywords used were *deep endometriosis*, *sexual function*, *resection*, and *shaving*. The full search strategy used can be found in ►**Chart 1**.

Two independent reviewers (GC and DF) were invited to analyze all articles found. Initially, an analysis of the titles and abstracts was performed to screen for potential eligible studies. Later, the reviewers evaluated the fully screened articles to select eligible studies. Disagreements were resolved by joint review and consensus among reviewers.

To comply with the objectives of the present systematic review, the eligibility criteria were as follows: comparative studies on female sexual function before and after surgery for deep endometriosis; studies with women previously diagnosed with deep endometriosis by physical examination or complementary imaging exams submitted to surgery; and studies with the application of standardized questionnaires to assess sexual function and dyspareunia. No clinical treatment associated with surgery was established, neither a limited time of follow-up after surgery, nor were there language restrictions during the initial search. The exclusion criteria were: conference abstracts, case reports, case series, reviews, and duplicate studies. In the full-text analysis, articles published in languages other than English, Portuguese, Italian, Spanish, and French were also excluded.

The two reviewers (GC and DF) inserted the data from all the included studies in a Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, United States) spreadsheet. We extracted general variables form the studies, such as authorship, year of publication, country, type of study, follow-up, surgery performed, age of the patients, and the number of patients included. We also recorded the name of the questionnaire used for the evaluation of sexual function and dyspareunia. The heterogeneity among the studies and questionnaires found in the literature did not enable the performance of a meta-analysis.

The outcome of interest was the assessment of sexual function before and after surgery using a validated questionnaire. The presence of dyspareunia before and after the surgery was also evaluated.

Chart 1 Searchstrategy for the selection of studies

Database	Search Strategy	Number Of Studies
PubMed	(*deep endometriosis* OR *deep infiltrating endometriosis* OR *endometrioma*) AND (*resection* OR *excision* OR *nodulectomy* OR *cystectomy* OR *shaving* OR *rectosigmoidectomy*) AND *(dyspareunia OR (sexual AND (function OR quality OR behavior) OR (pain OR dysfunction) AND (sexual OR sexual intercourse)*	313
EMBASE	(*deep endometriosis/exp* OR *deep endometriosis* OR *deep infiltrating endometriosis/exp* OR *deep infiltrating endometriosis* OR *endometrioma/exp* OR *endometrioma*) AND (*resection/exp* OR *resection* OR *excision/exp* OR *excision* OR *nodulectomy/exp* OR *nodulectomy* OR *cystectomy/exp* OR *cystectomy* OR *shaving/exp* OR *shaving* OR *rectosigmoidectomy/exp* OR *rectosigmoidectomy*) AND *dyspareunia OR (sexual AND (function OR quality OR sexual behavior) OR (pain OR dysfunction) AND (sexual OR sexual intercourse) AND (article/it OR article in press/it OR review/it) AND [female]*	597
Cochrane Library	(*deep endometriosis* OR *deep infiltrating endometriosis* OR *endometrioma*) AND (*resection* OR *excision* OR *nodulectomy* OR *cystectomy* OR *shaving* OR *rectosigmoidectomy*) *AND (dyspareunia OR (sexual AND (function OR quality OR sexual behavior) OR (pain OR dysfunction) AND (sexual OR sexual intercourse)*	20
LILACS	(*deep endometriosis* OR *deep infiltrating endometriosis* OR *endometrioma*) AND (*resection* OR *excision* OR *nodulectomy* OR *cystectomy* OR *shaving* OR *rectosigmoidectomy*) AND (*dyspareunia* OR *(sexual AND (function OR quality OR sexual behavior) OR (pain OR dysfunction) AND (sexual OR sexual intercourse)*	9
Web of Science	(*deep endometriosis* OR *deep infiltrating endometriosis* OR *endometrioma*) AND (*resection* OR *excision* OR *nodulectomy* OR *cystectomy* OR *shaving* OR *rectosigmoidectomy*) AND (*dyspareunia* OR *(sexual AND (function OR quality OR sexual behavior)) OR (pain OR dysfunction) AND (sexual OR sexual intercourse)*	161

To evaluate the risk of bias in non-randomized studies (such as case-control and cohort studies), we used the Newcastle-Ottawa Scale (NOS), while the risk of bias in randomized controlled trials (RCT) was evaluated using the Cochrane Collaboration's tool (RoB-1).[11,12]

The NOS is based on a star scoring system in which the observational study is assessed in terms of three broad parameters: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or the outcome of interest for case-control or cohort studies respectively.[11] On the other hand, the RoB-1 covers six domains of the possible biases of RCTs: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain is classified as low, high, or unclear risk of bias.[12]

Results

We found 1,100 studies; after removing the duplicates, 831 studies were screened for titles and abstracts by 2 reviewers who selected 108 studies for full-text analyses. Finally, a total of 20 studies fulfilled the eligibility criteria and were included in the present systematic review. A flowchart of the search and selection of studies is summarized in ►**Fig. 1**.

Observational studies and one RCT were included in the review. Half of the cohort studies (50%) had a score ≥ 7 stars on the NOS scale, while 38% had 6 stars, and 2, ≤ 5 stars. The RCT had a score of 6 stars on the NOS scale; it was on a comparison of laparoscopic surgeries with and without uterosacral ligament resection, and it presented an unclear risk of bias for random sequence generation and allocation sequence concealment, and a high risk for blinding of the outcome assessment. In total, the studies included evaluated 2,145 patients with follow-ups ranging from 3 to 69 months. The characteristics of the included studies are presented in ►**Chart 2**.

A comparison of the pre- and postoperative outcomes regarding sexual function and dyspareunia is shown in ►**Chart 3**.

The predominant surgical technique used to treat DIE patients was laparoscopic surgery. A total of 14 articles used only the laparoscopy technique for DIE excision, while 3 studies associated it with the CO_2 laser technique.[13–15] Two studies performed vaginal surgery associated with the laparoscopic procedure, when necessary,[16,17] and one combined laparoscopy with transurethral surgery.[18]

In one study,[18] transurethral and laparoscopic surgeries to resect bladder endometriosis presented a significancy improvement in sexual function in all 6 domains of the Female Sexual Function Index (FSFI), with a postoperative score of 28.2 +/− 1.7. Setälä et al.[16] and Fritzer et al.[17] performed vaginal surgery associated with videolaparoscopy procedures to resect vaginal endometriosis lesions, resulting in a significant increase on sexual comfort and pleasure according to the modified McCoy Female Sexuality Questionnaire (MFSQ).[16] However, the study by Fritzer et al.[17] did not show significant results in the final FSFI score in any of the three population groups compared (DIE, vaginal resection, and peritoneal endometriosis).[17] Sexual function after the CO_2 laser technique was evaluated by two different

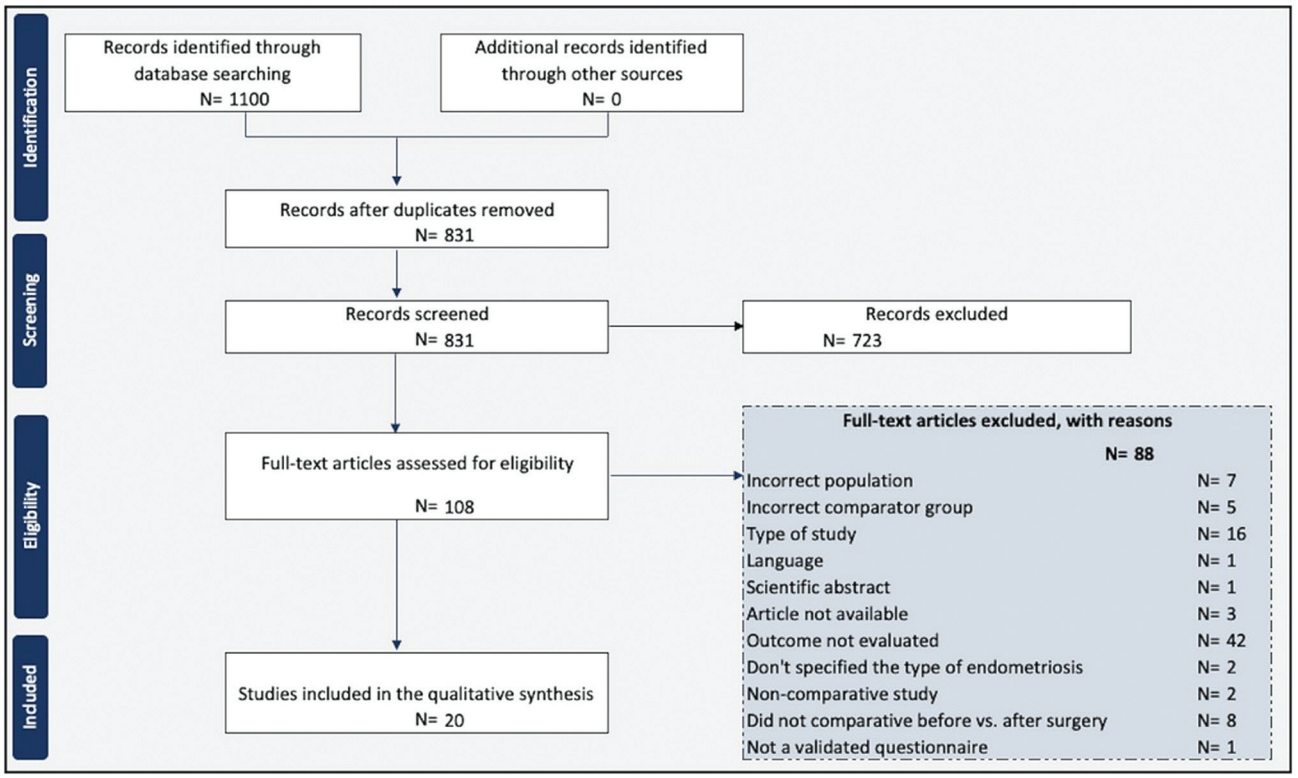

Fig. 1 Flowchart o the search and selection of studies.

Chart 2 Characteristics of the studies selected

Author, year	Country	Type of study	N	Type of surgery	Age in years	Sexual function questionnaire	Dyspareunia questionnaire
Garry et al.,[27] 2000	United Kingdom	Prospective	57	Laparoscopic excision surgery	–	SAQ	NRS
Abbot et al.,[24] 2003	Australia	Prospective	254	Laparoscopic excision surgery	Median: 31 (range 20–48)	SAQ	VAS
Vercellini et al.,[32] 2003	Italy	Randomized controlled trial	180	Laparoscopic excision surgery	Mean 30 ± 5	SSRS	VAS
Ferrero et al.,[26] 2007	Italy	Prospective	98	Laparoscopic excision surgery	Mean 34.6 ± 3.4	DSFI; GSSI	–
Ferrero et al.,[25] 2007	Italy	Prospective	73	Laparoscopic excision surgery	Mean 34.7 ± 4.3	DSFI; GSSI	VAS
Meuleman et al.,[15] 2009	Belgium	Retrospective	56	Laparoscopic excision surgery with CO_2 laser	Median:32 (range: 24–42)	SAQ	VAS
Meuleman et al.,[13] 2012	Belgium	Retrospective	45	Laparoscopic excision surgery with CO_2 laser	Median 30 (range: 18–42)	SAQ	VAS
Mabrouk et al.,[33] 2012	Italy	Prospective	125	Laparoscopic excision surgery	Mean 35.4 ± 5.5	SHOW-Q	VAS
Setälä et al.,[16] 2012	Finland	Prospective	22	Laparoscopic excision surgery or combined laparoscopic vaginal surgery	Median: 29 (range: 19–40)	MFSQ	VAS
Kossi et al.,[21] 2013	Finland	Prospective	26	Laparoscopic excision surgery	Median: 33.5 (range: 22–46)	MFSQ	–
Van den Broeck et al.,[14] 2013	Belgium	Prospective	203 (total); 76 WB; 127 WOB	Laparoscopic excision surgery with CO_2 laser	–	SSFS	–
Di Donato et al.,[31] 2015	Italy	Prospective	250 DIE; 250 HG	Laparoscopic excision surgery	DIE: mean 34 ± 5 HG: mean 32 ± 6	SHOW-Q	–
Fritzer et al.,[17] 2016	Germany	Prospective	96	Laparoscopic excision surgery or combined laparoscopic vaginal surgery	Median: 30.8 (range: 18–45)	FSDS; FSFI	NRS
Pontis et al.,[18] 2016	Italy	Prospective	16			FSFI	–

(*Continued*)

Chart 2 (*Continued*)

Author, year	Country	Type of study	N	Type of surgery	Age in years	Sexual function questionnaire	Dyspareunia questionnaire
				Combined transurethral and laparoscopicd surgeries	Mean: 29.12 ± 4.33		
Riiskjaer et al.,[20] 2016	Denmark	Prospective	128	Laparoscopic excision surgery	Mean: 33.8 ± 5.3	SVQ	1: never; 2: a little; 3: often; 4: very often
Uccella et al.,[29] 2018	Italy	Prospective	34	Laparoscopic excision surgery	Median 39 (range: 27–51)	FSFI	–
Lermann et al.,[19] 2019	Germany	Retrospective	134 WOB; 113 WB; 100 CG	Laparoscopic excision surgery	WOB: mean 34.3 ± 6; WB: mean – 37.7 ± 6.	KFSP	–
Ianieri et al.,[28] 2022	Italy	Retrospective	100	Laparoscopic Excision Surgery	Mediana:38 (32,5–43)	FSFI	VAS
Martínez-Zamora et al.,[34] 2021	Spain	Prospective	193 (total); 129 DIE; 64 CG	Laparoscopic excision surgery	DIE: mean 33.5 ± 6.04; CG: mean 34.7 ± 4.5	SQoL-F; FSDS; B-PFSF	–
Zhang et al.,[30] 2022	China	Retrospective	55	Laparoscopic excision surgery	Mean: 30 ± 3	FSFI	–

Abbreviations: B-PFSF, Brief Profile of Female Sexual Function; CG, control group; CO_2, carbon dioxide; DIE, deep infiltrating endometriosis; DSFI, Derogatis Sexual Functioning Inventory; FSDS, Female Sexual Distress Scale, revised; FSFI, Female Sexual Function Index; GSSI, Global Sexual Satisfaction Index; HG, healthy group; KFSP, Kurzfragebogen Sexualität und Partner-schaft; MFSQ, McCoy Female Sexuality Questionnaire modified by Wiklund et al; NRS, Numeric Rating Scale; SAQ, Sexual Activity Questionnaire; SSFS, Short Sexual Functioning Scale; SHOW-Q, Sexual Health Outcomes in Women Questionnaire; SQoL-F, Sexual Quality of Life – Female Questionnaire; SQV, Sexual Function-Vaginal Changes Questionnaire; SSRS, Sabbatsberg Sexual Rating Scale; VAS, Visual Analogue Scale; WB, with bowel resection; WOB, without bowel resection.

Chart 3 Preoperative and postoperative comparison of sexual function and dyspareunia according to the questionnaires applied

		Sexual Function			Dyspareunia		
Autor, year	**Follow-up (months)**	**Preoperatively**	**Postoperatively**	**Significance**	**Preoperatively**	**Postoperatively**	**Significance**
Questionnaire: SAQ							
Garry et al.,[27] 2000	4	Pleasure: 11 (6 ± 13)	Pleasure: 13 (9 ± 16)	Pleasure: 0.002	7 (5.5 ± 9)	0 (0 ± 4)	0.0001
		Discomfort: 3 (1.5 ± 5)	Discomfort: 1 (0 ± 3)	Discomfort: < 0.05			
		Habit:1 (0 ± 1)	Habit:1 (1 ± 2)	Habit: < 0.002			
Abbott, et al.,[24] 2003	60	Pleasure:10 (5 ± 12)	Pleasure:12 (9 ± 16)	Pleasure: 0.001	Median: 6.0 (0.0–9.0)	0.0 (0.0–4.0)	< 0.001
		Discomfort: 3 (1 ± 5)	Discomfort: 2 (1.5 ± 3)	Discomfort: < 0.012			
		Habit:1 (0 ± 1)	Habit:1(1 ± 1)	Habit:0.001			
Meuleman et al.,[15] 2009	29	–	–	Pleasure: < 0.0001	5 (0–10)	1 (0–10)	< 0.0001
				Discomfort: < 0.0001			
				Habit< 0.0001			
Meuleman et al.,[13] 2012	27	–	–	Pleasure: 0.009	28 (0–95)	1 (0–63)	< 0.0001
				Discomfort: 0.026			
				Habit: 0.0003			
Questionnaire: FSFI							
Pontis et al.,[18] 2016	12	26 ± 2.5	28 ± 1.7	< 0.001	–	–	–
Uccella et al.,[29] 2018	6	19.1 (1.2–28.9)	22.7 (12.2–31)	0.004	–	–	–
Ianieri et al.,[28] 2022	3	P: 19.4 ± 9.8	P: 21.6 ± 10.8	0.34	P: 5.2 ± 3.6	P: 0.9 ± 2.2	< 0.001
		NP 23.8 ± 3.7	NP: 23.7 ± 8.1		NP: 3.7 ± 3.5	NP: 0.1 ± 0.5	
Zhang et al.,[30] 2022	26	26.1 ± 3	26.8 ± 3	0.25	–	–	–
Questionnaire: FSFI and FSDS							
Fritzer et al.,[17] 2016	10 FSFI	–	–	DIE: 0.21	DIE: 6.18	DIE: 2.49	< 0.001
				Vaginal: 0.98			
				Peritoneal: 0.11	Vaginal: 6.64	Vaginal: 2.18	< 0.001
	FSDS	–	–	DIE: 0.04			
				Vaginal: 0.25	Peritoneal: 5.05	Peritoneal: 2.85	< 0.001
				Peritoneal: 0.34			
Questionnaire: SHOW-Q							
Mabrouk et al.,[33] 2012	6	Satisfaction: 51	Satisfaction: 65	< 0.0005	7 ± 3	1 ± 3	< 0.0001
		Orgasm: 57	Orgasm: 59	0.7			
		Desire: 55	Desire: 64	< 0.0004			

(*Continued*)

Chart 3 (*Continued*)

		Sexual Function			Dyspareunia		
Autor, year	**Follow-up (months)**	**Preoperatively**	**Postoperatively**	**Significance**	**Preoperatively**	**Postoperatively**	**Significance**
Di Donato et al.,[31] 2015	12	Satisfaction: 50	Satisfaction: 75	< 0.001	–	–	–
		Orgasm:63	Orgasm:62	Not significant			
		Desire: 58	Desire: 72	< 0.001			
Questionnaire: DSFI and GSSI							
Ferrero et al.,[26] 2007	3 DSFI	Frequency with USL: 1.3 ± 0.7; without USLE: 1.6 ± 0.7	Frequency with USL: 2.3 ± 0.7; without USL: 2.2 ± 0.8	Frequency ith USL: < 0.001; without USL: 0.004	–	–	–
	3 DSFI	Orgasm with USL: 2.3 ± 1.0; without USL: 2.9 ± 1.0	Orgasm with USL: 4.4 ± 1.1; without USL: 3.1 ± 1.5	Orgasm with USL: 0.001; without USL: 0.003			
	3 GSSI	With USL: 3.4 ± 1.7; without USL: 4.1 $+/-$ 1.7	With USL: 5.5 ± 1.9; without USL: 5.3 $+/-$ 1.8	With USL: 0.001; without USL: 0.003			
Ferrero et al.,[25] 2007	6 DSFI	Frequency with USL: 1.1 ± 0.6; without USL: 1.3 ± 0.9	Frequency with USL: 1.8 ± 0.8; without USL: 2.2 ± 1.1	Frequency with USL: < 0.001; without USL: < 0.001	With USL: 7.6 ± 1.1; without USL: 7.1 ± 1.0	With USL: 2.8 ± 1.9; without USL: 2.4 ± 1.8	< 0.001
	6 DSFI	Orgasm with USL: 2.3 ± 1.2; without USL: 3.1 ± 1.0	Orgasm with USL: 1.3 ± 0.9; without USL: 4.2 ± 1.3	Orgasm with USL: < 0.001; without ULSE: < 0.003			
	6 GSSI	With USL: 3.2; without USL: 3	With USL: 5; without USL: 5.8	< 0.001 < 0.001			
	12 DSFI	Frequency with USL: 1.1 ± 0.6; without USL: 1.3 ± 0.9	Frequency with USL: 1.9 ± 0.7; without USL: 2.2 ± 1.1	Frequency with USL: < 0.001; without USL: < 0.027	With USL: 7.6 ± 1.1; without USL: 7.1 ± 1.0	With USL: 2.8 ± 2.2; without USL: 2.2 ± 1.8	< 0.001
	12 DSFI	Orgasm with USL: 2.3 ± 1.2; without USL: 3.1 ± 1.0	Orgasm with USL: 1.9 ± 0.7; without USL: 4.0 ± 1.0	Orgasm with USL: < 0.001; without USL: < 0.118			
	12 GSSI	With USL: 3.2; without USL: 3	With USL: 5.2; without USL: 5.6	< 0.001 < 0.001			
Questionnaire: MFSQ							
Setälä et al.,[16] 2012	12	Sexual satisfaction: 21.1	Sexual satisfaction: 2.1	< 0.05	4.3	1.7	< 0.05
		Sexual problem: 6.3	Sexual problem: 1.4	< 0.05			
		Partner satisfaction: 12.1	Partner satisfaction: 0.8	Not significant			

Chart 3 (*Continued*)

		Sexual Function			Dyspareunia		
Autor, year	**Follow-up (months)**	**Preoperatively**	**Postoperatively**	**Significance**	**Preoperatively**	**Postoperatively**	**Significance**
Kossi et al.,[21] 2013	12	Sexual satisfaction: 20.1	Sexual satisfaction: 2.8	< 0.01	–	–	–
		Sexual problem: 7	Sexual problem: 1.1	< 0.10			
		Partner satisfaction: 12.1	Partner satisfaction: 0.7	< 0.10			
Questionnaire: KFSP							
Lermann et al.,[19] 2019	69	WB: 24	WB: 25	0.416	–	–	–
		WOB: 27.5	WOB: 19.5	0.001			
Questionnaires: SQOL, FSDS and B-PFSF							
Martínez-Zamora et al.,[34] 2021	36	SQOL-F: 70	SQOL-F: 77	< 0.001	–	–	–
		FSDS: 17	FSDS: 10	< 0.001			
		B-PFSF: 18	B-PFSF: 25	< 0.001			
Questionnaire: SQV							
Riiskjaer et al.,[20] 2016	12	Satisfaction: 3 (1–7)	Satisfaction: 4 (1–7)	0.0001	3 (1–4)	2 (1–4)	< 0.0001
		Frequency: 2 (1–5)	Frequency: 3(1–5)	0.0004			
		Desire: 2 (1–4)	Desire: 2 (1–4)	0.0003			
Questionnaire: SFSS							
Van den Broeck et al.,[14] 2013	6	Orgasm – WB:10.5%; WOB:16.3%	Orgasm – WB: 0%; WOB: 10%	< 0.01	WB: 44.8%; WOB: 31.3%	WB: 10.4%; WOB: 12.7%	> 0.05
		Excitation – WB:21.6%; WOB:11.5%	Excitation – WB:7.4%; WOB:13%%	> 0.05			
		Desire – WB:31.7%; WOB: 28.4%	Desire – WB:9.4%; WOB:19.4%	> 0.05			
	18	Orgasm – WB:16.3%; WOB:10,5%	Orgasm – WB: 6.3%; WOB: 2.9%	> 0.05	WB: 44.8%; WOB: 31.3%	WB: 6.3%; WOB: 20%	> 0.05
		Excitation – WB: 21.6%; WOB: 11.5%	Excitation – WB: 6.3%; WOB: 2.9%	> 0.05			
		Desire – WB: 28.4%; WOB: 31.7%	Desire – WB: 12.1%; WOB: 5.7%	> 0.05			

(*Continued*)

Chart 3 (*Continued*)

		Sexual Function			Dyspareunia		
Autor, year	Follow-up (months)	Preoperatively	Postoperatively	Significance	Preoperatively	Postoperatively	Significance
Questionnaire: SSRS							
Vercellini et al.,[32] 2003	18	USL:45.4 ± 19.9 CG: 44.7 ± 20.8	USL:53.8 ± 18.8 CG: 55.4 ± 15.6	0.763	USL: 58 (45–72) CG: 54 (26–67)	USL: 22 (0–35) CG: 18 (0–30)	0.0001 0.0001

Abbreviations: B-PFSF, Brief Profile of Female Sexual Function; CG, control group; DIE, deep infiltrating endometriosis; DSFI, Derogatis Sexual Functioning Inventory; FSDS, Female Sexual Distress Scale, revised; FSFI, Female Sexual Function Index; GSSI, Global Sexual Satisfaction Index; KFSP, Kurzfragebogen Sexualität und Partner-schaft; MFSQ, McCoy Female Sexuality Questionnaire modified by Wiklund et al; NP, no parametrial group; P, parametrial group; SAQ, Sexual Activity Questionnaire; SFSS, Short Sexual Functioning Scale; SHOW-Q, Sexual Health Outcomes in Women Questionnaire; SQoL-F, Sexual Quality of Life – Female Questionnaire; SQV, Sexual Function-Vaginal Changes Questionnaire; SSRS, Sabbatsberg Sexual Rating Scale; USL, uterosacral ligament; WB, with bowel resection; WOB, without bowel resection.

questionnaires.[13–15] The Sexual Activity Questionnaire (SAQ) showed significant postoperative improvement on the following pillars of sexual function: pleasure, habit[13,15] and discomfort.[15] The Short Sexual Function Scale (SSFS) only presented significant improvement in the pillar of orgasm after surgery.[14]

Other articles also evaluated sexual function and DIE of the bowel. A comparative study[19] analyzed sexual function for the following sixty-nine months after DIE surgery with and without bowel resection. Postoperatively, the patients without bowel resection improved significantly in all categories on the Kurzfragebogen Sexualität und Partner-schaft (KFSP) questionnaire. Not only no significant postoperative improvement was observed in the patients in the bowel endometriosis group, but this group had significantly poorer scores in comparison with the control group.[19] Riiskjaer et al.[20] performed laparoscopy for DIE of the bowel and observed positive results on the Sexual Function-Vaginal Changes Questionnaire (SQV) after one year of follow-up: there was a significant increase in vaginal changes, general sexual satisfaction, desire for sexual intercourse, and frequency of sexual intercourse. Laparoscopic resection for bowel endometriosis also resulted in an increase in sexual satisfaction on the overall MFSQ score one year after surgery in one study.[21] Sexual problems and satisfaction with partner scores did not change significantly in another study.[22]

The surgical data related to the female sexual function response in the studies analyzed were collected and presented in ►**Chart 4**.

The extension of the endometriosis was ascertained intraoperatively using the revised American Fertility Society (rAFS)[22] and the Enzian scale[23] in 13 studies.[13–17,19,24–30] In the evaluated articles, 45.32% of the patients were classified as rAFS class IV (severe), followed by 27.67% as class III (moderate),13.65% as class II (mild), and 13.40% as class I (minimal). The most common pelvic sites of DIE involvement were: the uterosacral ligaments (51.24%), the bowel (31.56%), the vagina (14.45%), the rectovaginal septum (8.89%) and the retrocervical nodule (6.46%).[14,19–21,25,26,28–31]

Three comparative studies[25,26,32] evaluated sexual function after resection of the uterosacral ligament. In two of them,[25,26] the authors used the Derogatis Sexual Functioning Inventory (DSFI) and Global Sexual Satisfaction Index (GSSI) to analyze sexual function 6 and 12 months postoperatively, and found a significant increase in sexual function up to 6 months. Frequency and orgasm on the DSFI were not significant at the 12-month follow-up.[25,26] Similar results were presented by Vercellini et al.[32] after 18 months of follow-up, with no significant improvement in sexual function on the Sabbatsberg Sexual Rating Scale (SSRS).

An improvement in sexual function was also observed on FSFI scores after resection of bladder endometriosis,[18] as well as a significant improvement in sexual satisfaction and intercourse pain on the MFSQ after twelve months of surgery in a group of women with DIE submitted to vaginal nodule resection.[16]

Chart 4 Surgical data as reported by the studies selected

Author, year	Histological analysis	Endometriosis classification	Intraoperative classification	Nerve-sparing technique	Procedures	Other endometriosis location (%)	Retro cervical (%)	USL (%)	Rectovaginal septum (%)	Vagina (%)	Bowel (%)
Garry et al.,[27] 2000	No	rAFS	III: 63.2%	No	Complication: 1,9% – bruises	Ovaries: 40.3%; total pouch of Douglas obliteration: 30.4%; partial pouch of Douglas obliteration: 33.3%	33.3%	No Specific side: 77.2%	59.6%	38.52%	56.1%
Abbot et al.,[24] 2003	Yes	rAFS	I:14%; II: 28%; III: 17%; IV: 41%	No	Complication: 0.3% – iatrogenic bowel injury; 0.6% – transfusion; 0.3% –vaginal deiscense	Total pouch of Douglas obliteration: 32%; partial pouch of Douglas obliteration: 18%; bilateral endometrioma: 12%; right: 18%; left: 12%	–	Unilateral 88%; bilateral: 57%	–	6%	–
Vercellini et al.,[32] 2003	No	rAFS	I: 39%; II: 22%; III: 20%; IV: 19%	No	–	–	–	No specific side: 100%	–	–	–
Ferrero et al.,[26] 2007	Yes	–	–	No	–	–	–	No specific side: 65.3%	–	–	–
Ferrero et al.,[26] 2007	Yes	rAFS	IV-III: 86.9%; II-I: 12.32%	No	–	–	–	No specific side: 64.7%	–	–	–
Meuleman et al.,[15] 2009	Yes	rAFS	II: 2.22%; III: 4.44%; IV: 95%	Yes	Oophorectomy: 9%; appendectomy: 14%; salpingectomy: 30%; cystectomy: 39%; ureterolysis: 86%; adhesiolysis: 100%; complication: 3.5% – vascular anastomosis; 5.3% – compartmental syndrome	–	11%	–	–	–	Anterior bowel resection: 36%; sigmoid resection: 39%
Meuleman et al.,[13] 2012	Yes	rAFS	III: 2%; IV: 98%	Yes	Oophorectomy 2%; bladder suture: 7%; appendectomy: 9%; salpingectomy: 38%; cystectomy: 42%; ureterolysis: 91%; complication: 2.2% – transitory urinary retention	–	16%	–	–	–	Sigmoid resection: 90%
Mabrouk et al.,[33] 2012	Yes	–	–	Yes	Complications: 0.8% – vascular injury; 1.6% –transfusion; 4% – transitory urinary retention; 1.6% – retovaginal fistula; 0.8% – ureterovaginal fistula	55%	–	72%	–	25%	Sigmoid resection: 17%; shaving: 30%
Setälä et al.,[16] 2012	No	rAFS	–	No	Appendicectomy: 14%; urinary bladder resection: 14%; salpingectomy: 14%; adhesiolysis: 100%; complications: 14% – transitory urinary retention; 4.5% – anemia; 4% – vaginal deiscense	Pouch of Douglas obstruction 7%; peritoneal lesions: 68%	95%	14%	86%	100%	50%

(*Continued*)

Chart 4 (*Continued*)

Author, year	Histological analysis	Endometriosis classification	Intraoperative classification	Nerve-sparing technique	Procedures	Other endometriosis location (%)	Retro cervical (%)	USL (%)	Rectovaginal septum (%)	Vagina (%)	Bowel (%)
Kossi et al.,[21] 2013	Yes	–	–	No	Resection of urinary bladder: 7%; appendectomymy: 11%; salpingectomy: 26%; ureterolysis 80%; adhesiolysis: 100%; complications:11.5% – transitory urinary retention; 3.8% – bowel bleeding	Peritoneal lesions: 53%	–	No specific side: 88%	–	61%	100%
Van den Broeck et al.,[14] 2013	Yes	rAFS	III: 33%; IV: 66%	Yes	–	–	–	–	–	–	100%
Di Donato et al.,[31] 2015	Yes	–	–	No	–	–	–	–	–	–	–
Fritzer et al.,[17] 2016	Yes	rAFS	I: 28%; II: 21%; III: 26%; IV: 25%	No	–	Peritoneal lesions: 41%; DIE: 59%	–	–	–	37%	–
Pontis et al.,[18] 2016	Yes	–	–	No	–	Bladder: 100%	–	–	–	–	–
Riiskjaer et al.,[20] 2016	No	–	–	No	–	–	–	–	–	–	100%
Uccella et al.,[29] 2018	No	Enzian	A1 B2 C3 (20.6%); A2 B2 C3 (26.5%); A3 B1 C1 (2.9%); A3 B2 C1 (5.9%); A3 B3 C1 (2.9%); A3 B3 C2 (5.9%); A3 B1 C0 FB (5.9%); A0 B3 C2 FA (5.9%); A3 B1 C1 FA (17.6%); A3 B1 C2 FA (2.9%); A3 B1 C1 FO (2.9%)	Yes	Bilateral adnexectomy/castration: 8.8%; ureterolysis: 100%; complications: 17.6% – transitory urinary retention	–	–	–	–	50%	47.1%
Lermann et al.,[19] 2019	No	Enzian	–	No	–	WOB: 75.3%; WB: 72.4%	–	Unilateral – WOB: 48.3%; WB:8%; bilateral – WOB: 27%; WB: 24.1%	WOB: 89.9%; WB:87.4%	WOB: 41.6%; WB: 75.9%	WB: 74.33%
Ianieri et al.,[28] 2022	Yes	rAFS	II: 2.9%; III: 43.5%; IV: 53.6%	Yes	Complications: 1% – hemoperitoneum; 2% – iatrogenic bowel injury	–	48%	–	–	15%	64%
Martínez-Zamora et al.,[34] 2021	Yes	–	–	No	–	Endometriomas – bilateral: 11.62%; left: 24.8%; right: 13.95%; ureter (no specific side): 24%; bladder: 28.68%; peritoneal lesions: 76%	47.28%	No specific side: 68.99%	11.62%	8.52%	39.53%
Zhang et al.,[30] 2022	Yes	rAFS	I + II: 20%; III + IV: 35%	No	–	–	–	No specific side: 25.45%	43.63%	–	18%

Abbreviations: DIE, deep infiltrating endometriosis; rAFS, revised American Fertility Society classification; USL, uterosacral ligament; WO, with bowel resection; WOB, without bowel resection.

The nerve-sparing surgical technique for DIE excision was described as necessary in six articles,[13–15,28,29,33] in which different results were found: two studies[15,29] showed a significant improvement on the SAQ and the FSFI's global sexual function score; two other studies[13,33] reported partial improvement in some domains on the FSFI and on the Sexual Health Outcomes in Women Questionnaire (SHOW-Q); and the two remaining studies[14,28] reported no difference in sexual response after the nerve-sparing surgery. Only one article[28] aimed to evaluate the functional results after nerve-sparing posterolateral parametrial surgery, and the authors observed an increased risk of postoperative dyspareunia and sexual dysfunction. The FSFI sexual function score improved in the group without parametrial surgery, but not significantly.[28]

The diagnosis of endometriosis was confirmed by histological examination of specimens removed during surgery in 15 studies.[13–15,17,18,20,21,24–26,28,30,31,33,34] Complementary surgical procedures for the treatment of endometriosis, including ureterolysis, adhesiolysis, salpingectomy and appendicectomy, were performed in ten articles.[13–16,21,24,27–29,33] Intraoperative or postoperative complications were reported in nine studies,[13,15,16,21,24,27–29,33] and the most common findings were transfusions caused by bleeding, transitory urinary retention, and bowel iatrogenic injury. Despite the complication rates reported, only one study[28] did not show a significant increase in sexual function after surgery.

The clinical treatment was an important point observed on this review. Some articles did not establish inclusion or exclusion criteria regarding the use of hormonal drug treatment associated with the procedure, but six studies[13,17,25,26,32–34] defined these criteria as In five studies,[17,25,26,32,34] hormonal treatment with gonadotropin-releasing hormone (GnRH) analogues and combined or isolated contraceptives were discontinued six months before the procedure, and two studies[25,32] did not reintroduce any type of hormonal treatment postoperatively. All studies presented an increase on sexual function, except, the one by Vercellini et al.,[32] which did not show positive results on the SSRS after surgery.

One study[13] included a GnRH analogue preoperatively, and other studies included combined contraceptives preoperatively[31,33] and postoperatively.[33] Despite the differences regarding the hormonal treatment, the sexual function score on the SAQ and SHOW-Q improved postoperatively in two of these studies.[31,33]

Dyspareunia, also called by some authors deep dyspareunia (DD) or pain during sexual intercourse, was assessed in 12 articles,[13–17,20,24,26–28,32,33] mainly through the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS). Only Riiskjaer et al.[20] observed dyspareunia as an isolated finding, and evaluated it with its specific scale.

Three studies[17,27,34] identified a significant decrease in dyspareunia according to the NRS scale in all groups in the pre and postoperative comparison. The VAS was applied by the other articles to evaluate dyspareunia after surgery, and all articles reported a significant improvement in pain during intercourse after surgery, including progressive improvement in dyspareunia over time. Only one study[14] did not report a decrease in dyspareunia after 18 months of follow-up.

Discussion

Due to its diverse origin, endometriosis presents great heterogeneity in terms of anatomical presentation and clinical manifestations, especially if associated with the complexity of multifactorial sexual aspects.

Qualitative and quantitative studies have shown that symptomatic endometriosis negatively affects female sexual function, causing discomfort, and they have analyzed these results through global scores. The isolated analysis of the domains of sexual function is unclear, and it is often not the main objective of studies, which limits a comprehensive assessment of sexual functioning. Therefore, the evidence in the literature lacks quality in terms of research design, diagnostic instruments, power of the study, or adjustment for confounding factors.

The present review helped expand the knowledge on the types of surgery performed to treat deep endometriosis, and we systematically analyzed the techniques used according to the location and staging of the disease, histopathological confirmation, nerve preservation, and the types of procedures performed for lesion resection.

The improvement in sexual function and dyspareunia after the surgical treatment in DIE patients was duly expressed by the authors of the studies reviewed. The laparoscopic surgery technique showed precision to treat DIE, in addition to the surgeons' experience. This statement is corroborated when there are positive results after surgeries, in addition to the correlation with other types of drug treatments.

All groups of patients classified according to the rAFS showed improvement in the quality of sexual life, especially those in classes IV and III; however it was not possible to identify the statistical relevance of the improvement in sexual function correlated with each group separately.[35,36]

Autonomic, sympathetic, and parasympathetic nerves control the vessels in the genital region, and they are responsible for sexual satisfaction and lubrication. The nerve-sparing surgery for DIE is recommended to reduce patient morbidity.[37] However, 73.68% of the studies in this review did not perform the nerve-sparing surgery, neither did they find a direct correlation with female sexual function, as the literature.[29,38]

The presence of DIE in the vagina and uterosacral ligaments is associated with impaired sexual function and dyspareunia.[39] The present review showed an improvement in female sexual function and postoperative dyspareunia despite the location of the endometriosis lesions, disease severity, and surgical treatment performed. We believe that the excision of inflammatory and angiogenic factors caused by DIE during surgery is the main factor for pain relief during sexual intercourse. Getting rid of feelings of fear and anguish caused by pain are also related to the improvement on other factors of sexual function.

In addition, the analysis related to deep dyspareunia still needs to be better developed, since the use of the NRS or probing alone is very simplistic compared with the psychological tests to distinguish deep dyspareunia from vulvodynia or vaginismus, which can also be triggered by chronic pelvic pain.

The lack of standardization among the questionnaires used to assess sexual function was a limiting factor in the present review, and it is due to the absence of an instrument capable of encompassing the complexity of DIE and its association with female sexual function. However, we were able to oppose some limiting factors found in the literature, such as follow-up time and questionnaire results.[40] We evaluated some studies with a follow-up longer than one year and with sexual function results demonstrated through the analysis of the domains involved in sexual response, such as arousal, satisfaction, pleasure and others.

Conclusion

Highly-complex surgical approaches for the treatment of endometriosis have always been associated with the risk of complications arising from the excision of deep endometriotic lesions located mainly in the posterior vaginal fornix, rectal muscular layer, and inferior hypogastric plexus, which could worsen the patient's sexual quality of life and pain symptoms. Despite this, the present review demonstrated that radical surgeries for the treatment of DIE improved dyspareunia and sexual function, and they should be provided to women as a treatment alternative. Healthcare professionals should address the topic of sexual health in consultations with women with endometriosis because improvements following surgery can be expected. The present study not only demonstrates a significant reduction in dyspareunia symptoms, but it also shows that the resection of both minimal and extensive endometriotic disease causes major positive changes in sexual function.

Conflict of Interests

The authors have no conflict of interests to declare.

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Instructions to Authors

About the journal

Basic information

The *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO - Revista Brasileira de Ginecologia e Obstetrícia – ISSN 1806-9339) is a monthly scientific publication of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo). It is aimed at obstetricians, gynecologists and professionals in related areas with the purpose to publish research results on relevant topics in the field of Gynecology, Obstetrics and related areas. The journal is open to national and international contributions and accepts submissions in English only.

As a **Vision**, the *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO) intends to become an internationally recognized reference as a journal for research in Gynecology and Obstetrics (GO), becoming one of the world's leading journals in the specialty. The RBGO will be an essential vehicle to disseminate Brazilian and international scientific production and it can become a support reference in the training of undergraduate and postgraduate students and residents and in the scientific improvement of preceptors and researchers in GO.

The RBGO's **Mission** is to contribute to the development of Brazilian research in GO and become a facilitating instrument for the dissemination of research results that can contribute to the improvement of women's care and their quality of life.

The **Values** cultivated by the RBGO in its editions will always be innovation and commitment to quality and respect for **Ethics** in research.

Subareas of knowledge of interest GO:

1. Basic and translational science in ObGyn;
2. Bioethics
3. Contraception;
4. Epidemiology and Statistics in ObGyn;
5. Fetal Medicine;
6. General Gynecology;
7. Gynecological Endocrinology;
8. Gestational Trophoblastic Neoplasia
9. Gynecological Endoscopy;
10. Gynecological Oncology;
11. Gynecological Surgery and Urogynecology;
12. High Risk Pregnancy;
13. Human Reproduction and Assisted Fertilization;
14. Image in ObGyn;
15. Lower Genital Tract Diseases;
16. Mastology;
17. Menopause;
18. Multidisciplinarity and ObGyn;
19. Obstetrics;
20. Pediatric and Adolescent Gynecology;
21. Physiology in ObGyn;
22. Primary care in ObGyn;
23. Quality of Life and ObGyn;
24. Sexually Transmitted Infection;
25. Sexuality;
26. Teaching and Training in ObGyn;
27. Technology;
28. Transgender.

Indexing sources:

- PubMed/Medline;
- Isi – Web of Science (*Emerging Sources Citation Index*);
- Scopus;
- SciELO – *Scientific Electronic Library on-line*;
- Lilacs –Latin American and Caribbean Health Sciences Literature

Intellectual property

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RBGO does not receive any type of support from funding sources. It is fully maintained by the Brazilian Federation of Gynecology and Obstetrics Associations and receives sponsorships.

Responsibilities of the Editorial Board

Responsibilities of the Editor-in-Chief

- Ensure that the journal is published within the established deadlines.
- Ensure the quality of selected texts and their appropriateness to the interests of readers.
- Establish the policy for manuscript submission, peer review, reviews and resubmission.
- Ensure that articles are reviewed and accepted only on the basis of scientific merit and not on the basis of any influence, whether commercial or personal.
- Maintain transparency throughout the manuscript review and editing process.
- Investigate all complaints and/or doubts related to submissions to the journal, whether accepted or not, and give authors the opportunity to respond whenever necessary.
- Provide support for the selection process of members of the journal's editorial board to define the types of publication and selection criteria for manuscripts accepted by the journal.
- Develop policies and procedures to attract scientific quality manuscripts.
- Examine the digital proofs of the journal, ensuring their quality.
- Adopt procedures protecting ethical issues, conflicts of interest and compliance with the policies adopted by the Brazilian Federation of Gynecology and Obstetrics Associations to which it is affiliated.
- Treat all individuals with respect, impartiality and without discrimination based on gender identity, race, sexual orientation, religion or political beliefs and geographic region.

- Maintain impartiality and clarity in the publication of sponsored supplements and/or with any other type of sponsorship/funding.
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- Read and evaluate the scientific quality of manuscripts received from the Editor-in-Chief.
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- Reviewers have the responsibility to review the manuscript objectively and fairly.
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- Maintain the confidentiality of any information provided by the editor.
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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.
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- 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;
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- 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;
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- 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:

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- 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;
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- 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).
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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

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Randomized clinical trial:

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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

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