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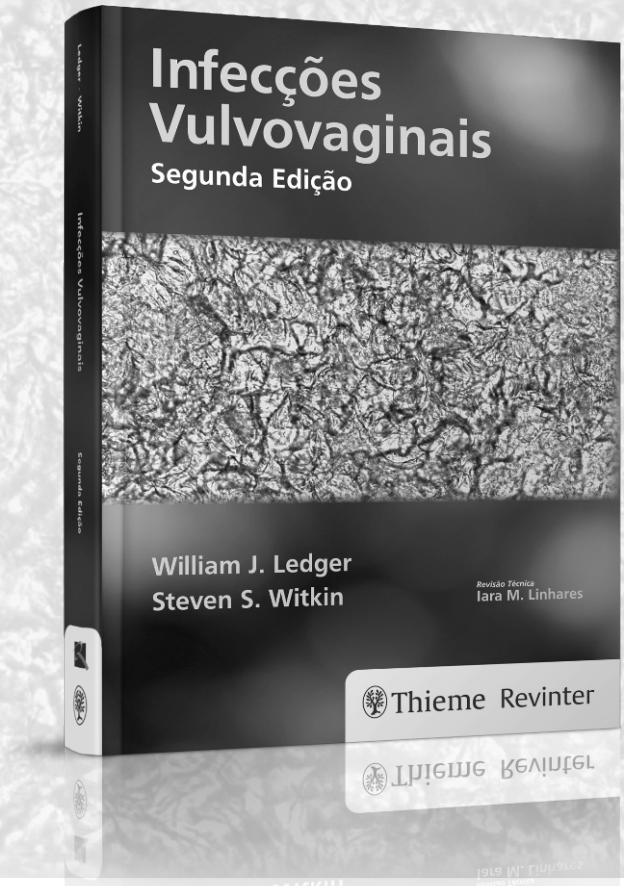

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I***nfecções Vulvovaginais, Segunda Edição***, apresenta as mais recentes descobertas sobre o tema. Destaca também problemas que permanecem não resolvidos e as áreas mais promissoras para investigação. Nesta obra, os ginecologistas encontrarão orientações práticas para a resolução de cenários clínicos da vida real. Inicialmente, são abordadas a microbiologia da vagina e a imunologia vaginal. A seguir, discute o diagnóstico das doenças vulvovaginais através da anamnese, exame físico e testagem laboratorial. Em continuidade, apresenta capítulos sobre as principais infecções vulvovaginais, incluindo vulvovaginite por Candida, vaginose bacteriana, vaginite por *T. vaginalis*, vaginites citolítica, aeróbica e inflamatória descamativa, herpes genital, infecções pelo papilomavírus humano e muito mais.

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Editorial

Progressive Resistance Training as Complementary Therapy for Polycystic Ovarian Syndrome

Treinamento de Resistência Progressiva como Terapia Complementar Para Síndrome de Ovário Policístico

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Polycystic ovarian syndrome (PCOS) significantly impacts women, since the broad spectrum of clinical manifestations associated with it are significant and include reproductive dysfunction, menstrual irregularities, and an increased risk of infertility. However, the consequences of PCOS go beyond the reproductive axis, with psychological and social impairments, including stress, depression, anxiety, and sexual dissatisfaction.[1] There is also a high prevalence of dyslipidemia, hyperinsulinemia, obesity, hypertension, and glucose intolerance, which are risk factors that predispose women to cardiovascular disease (CVD) and diabetes mellitus type 2 (DM2).[2] Therefore, PCOS assumes aspects of a chronic disease, as these factors extend throughout life. If not prevented and treated, they can lead to increased morbidity and mortality.[3] The etiology of PCOS has not been fully elucidated, but it is known to be linked to excess androgens.[4,5] Insulin resistance (IR) is a common feature of PCOS,[6] and although it is not considered a diagnostic criterion, it is a key factor in the syndrome's etiology and evolution.[7]

In 2008, the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) published a consensus suggesting lifestyle changes as the first line of treatment for women with PCOS.[8] This consensus was reinforced in 2009 by The Androgen Excess and Polycystic Ovary Syndrome Society,[9] which investigated evidence of lifestyle management (dietary, exercise, or behavioral interventions) for obesity in women with PCOS. Since then, the benefits of lifestyle changes resulting from PCOS therapy have been well documented.[10,11] The rationale for this non-pharmacological therapy is based on regular exercise and a healthy diet, as well as combined interventions that aim to achieve and maintain a healthy weight to minimize hormonal and reproductive complications, reduce the long-term risks of chronic diseases such as CVD and DM2, and consequently improve quality of life. In this way, weight loss has been considered the main goal of PCOS therapy in obese women.

Moderate- to high-intensity aerobic physical exercise[12] has been predominantly recommended as a treatment for PCOS.[13] Preliminary data from our group with an interval aerobic training protocol (exercises alternating in intensity from moderate to heavy effort with low-effort recovery periods) showed a decreased central obesity index measured by anthropometric measures and improved testosterone levels. However, other training programs, such as aerobic exercises, alone or in combination with resistance training, with or without dietary restriction, have also effectively reduced total and abdominal body fat or body fat percentile,[12,14–16] leading to improved menstrual frequency and/or ovulation,[12,17] reduced serum testosterone concentrations and fasting plasma glucose levels,[12] and improved insulin sensitivity.[18,19]

More recently, a review presented evidence that progressive resistance training (PRT), or strength training, may also be beneficial for women with PCOS, promoting changes in body composition and associated factors, especially IR.[20] However, this type of physical exercise has not been well explored in terms of its therapeutic purposes. Faced with the phenotypic characteristics of PCOS, we set out to perform a periodic protocol of resistance exercises in lean, overweight, and obese women with the intention of evaluating the results of this therapy. The PRT improved hyperandrogenism and the menstrual cycle, as well as the functional capacity with increased muscle strength, and resulted in changes in body

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composition with increased lean muscle mass and decreased central obesity, without a reduced total weight.[21] There were also improvements in quality of life and sexual function as complementary benefits.[22,23]

Evidence in the literature suggests that a PRT protocol associated with the practice of calisthenics (exercises that use the body's own weight as the primary tool) promoted significant changes in body composition, even with the increase of total weight and lean muscle strength in overweight and obese individuals. It also promoted improvements in several health-related domains, such as anxiety, depression, and quality of life.[24] There was also a significant improvement in body composition without reductions in the total weight of lean women, regardless of the type of training when high-intensity interval aerobic physical exercise and PRT were compared.[25] These studies are pioneers in the evaluation of PRT alone, in women with PCOS, and attest that strength training can be an excellent and effective exercise option.

The improvement in body composition, with little or no effective change in total body weight, may be related to the concomitance of the increase in lean muscle mass and reduced body fat promoted by this type of exercise.[26] The loss of fat mass is probably mediated by an increase in the basal metabolic rate that results from an increase in lean muscle mass, which is considered a metabolically active tissue that causes the body to increase its caloric expenditure.[27,28] This anabolic action adds to the improved insulin sensitivity,[27,29,30] since the skeletal muscles are predominantly involved in insulin-mediated glucose uptake,[31,32] while muscle contractile activity may stimulate the translocation of glucose transporter type 4 (GLUT4) molecules in the absence of insulin.[33,34] This is a key consideration for women with PCOS, since IR is implicated in the etiology of the disease.[6,7]

The obesity that affects most women with PCOS[35] is associated with reduced muscle strength, difficulties in postural control, and changes in the biomechanical behavior of the lower limbs,[36] and may be a limiting factor for some physical activities. In particular, those physical activities with a great cyclic impact, such as walking, running, and those that require great joint amplitude are affected by obesity, since the excess weight alone puts a significant amount of stress on the joints. In addition, rapid exhaustion due to reduced physical fitness and functional capacity, even with low physical effort, contributes to the non-compliance with this type of exercise. In addition to the aforementioned benefits, as a therapy for obese women, PRT improves daily functional capacity, increases resistance to joint impact, promotes muscle strengthening, reduces the risk of injury, and favors subsequent aerobic exercises[37] within the recommended levels.[12]

Intervention programs with aerobic training or strength training performed exclusively induce favorable adaptations in women with PCOS. Although aerobic exercises are more highly recommended, a consistent training protocol including aerobic and strength exercises, either in the same session or on alternate days, can be both efficient and capable of improving the variables of the components of physical fitness related to health, such as muscle strength, and of preventing loss of lean mass. This protocol can also improve disease-related characteristics, such as central obesity, hyperandrogenism, and insulin sensitivity.

Physical performance depends not only on the factors inherent to the suggested training program, but also on the degree of motivation for certain activities. With the proven effectiveness of the different physical training modalities, the possibility that it will provide personal satisfaction is increased, which can promote better adherence to the training program. Evidently, the positive effects of exercise may vary significantly among lifestyles as well as exercise program levels, such as intensity, frequency, and duration.[38] These should be prescribed individually by a physical educator with a focus on the expectations and motivations of women with PCOS and, above all, the safety of the proposed exercises. It is believed that therapeutic orientations based on non-pharmacological therapy may favor behavioral changes and the adoption of healthy lifestyle habits for women with PCOS.

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Potential Drug Interactions and Drug Risk during Pregnancy and Breastfeeding: An Observational Study in a Women's Health Intensive Care Unit

Interações medicamentosas potenciais e risco de medicamentos durante a gravidez e amamentação: um estudo observacional em unidade de terapia intensiva

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Abstract

Introduction In the pregnancy-puerperal cycle, women may develop complications that require admission to the Intensive Care Unit (ICU). Thus, special attention to pharmacotherapy is necessary, particularly to potential drug interactions (PDIs) and to the effect of the drugs on the fetus and newborn.

Objective The aim of this study was to determine the profile of PDIs and the potential risk of drugs used during pregnancy and breastfeeding among patients admitted to the ICU.

Methods We conducted an observational, cross-sectional and prospective study, including pregnant and breastfeeding women admitted to the ICU at the Women's Hospital of a university in the city of Campinas, Brazil, for one year. Online databases were used to identify and classify the PDIs and the potential risk of the drugs used during pregnancy and breastfeeding.

Results We evaluated 305 prescriptions of 58 women, 31 pregnant and 27 breastfeeding, and 284 (91%) prescriptions presented PDIs. A total of 175 different combinations of PDIs were identified in the prescriptions, and adverse effects caused by the simultaneous use of drugs were not actually observed in the clinical practice. A

Keywords
- intensive care unit
- potencial drug interactions
- pregnancy
- breastfeeding
- patient safety

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total of 26 (1.4%) PDIs were classified as contraindicated. We identified 15 (13.8%) drugs prescribed with risk D, and 2 (1.8%) with risk X for pregnant women, as well as 4 (4.9%) drugs prescribed with high risk for breastfeeding women.
Conclusions This study demonstrates that there is a high incidence of PDIs in prescriptions. Most drugs used by pregnant and breastfeeding women at the ICU did not present serious risks to their fetus and newborns, but sometimes drugs with risk D or X are necessary in the course of the treatment.

Resumo

Introdução No ciclo gravídico-puerperal, as mulheres podem desenvolver complicações que necessitam de internação na Unidade de Terapia Intensiva (UTI). Assim, é necessária uma atenção especial à farmacoterapia, particularmente às interações medicamentosas potenciais (IMPs) e ao risco dos medicamentos para o feto e o recém-nascido.
Objetivo Determinar o perfil das IMPs e o risco potencial dos medicamentos utilizados durante a gravidez e a amamentação entre as mulheres internadas em UTI.
Métodos Foi realizado um corte transversal e prospectivo, observacional, incluindo mulheres grávidas e lactantes internadas na UTI do Hospital da Mulher de uma universidade de Campinas durante um ano. Bases de dados online foram usadas para identificar e classificar as IMPs e o potencial risco de uso de medicamentos durante a gravidez e a amamentação.
Resultados Foram avaliadas 305 prescrições de 58 mulheres, 31 grávidas e 27 lactantes, e 284 (91%) prescrições apresentaram IMPs, sendo que 175 combinações diferentes de IMPs foram identificadas nas prescrições, e não foram observados efeitos nocivos pelo uso concomitante dos medicamentos na prática clínica. Um total de 26 (1,4%) IMPs foram classificadas como contraindicadas. Foram identificados 15 (13,8%) medicamentos prescritos com risco D, e 2 (1,8%) com risco X para mulheres grávidas, e foram identificados 4 (4,9%) medicamentos prescritos como de alto risco para as mulheres que estavam amamentando.
Conclusões Este estudo demonstra que há uma alta incidência de IMPs nas prescrições. A maioria dos medicamentos utilizados por mulheres grávidas e lactantes em UTI não apresentou sérios riscos para o feto e o recém-nascido, mas às vezes são necessários medicamentos categorizados como risco D ou X.

Palavras-chave
- unidades de terapia intensiva
- interações medicamentosas potenciais
- gravidez
- amamentação
- segurança do paciente

Introduction

In women's health care, special attention is required during the pregnancy-puerperium cycle, when a woman can develop several obstetric and non-obstetric complications that can require admission to an Intensive Care Unit (ICU).[1–5]

During hospitalization, pregnant and breastfeeding women use a complex pharmacotherapy with many drugs prescribed, leading to potential drug interactions (PDIs). Potential drug interactions are defined as pharmacological or clinical responses to the administration of two or more drugs, which is different from the response when these agents are used individually.[6] Due to the highly complex environment of the ICUs and to the great number of medications that most critical patients need, their prescriptions are more susceptible to have potential drug–drug interactions.[7] A study conducted by Plaza et al[8] showed that 23% of clinically significant adverse events observed in a studied ICU in Chile were related to drug interactions.

The use of drugs during pregnancy calls for special attention because it may result in damage to the mother and the fetus. In order to avoid undesirable side effects, especially in the first trimester, the appropriate selection of drugs according to the gestational age is required. Reducing medication errors and improving patient safety are the important areas of discussion here.[9,10]

Risk evaluation of the drugs used during breastfeeding in postpartum patients admitted to the ICU requires knowledge of the factors that determine if a medication is safe to be used during this period, such as lipid solubility, the ability to bind protein, the level of ionization, the half-life, and the bioavailability of these drugs. These concepts are relevant because some drugs are excreted in the breast milk and therefore may cause problems to the newborn.[9–14]

The aim of this study was to determine the profile of PDIs and the risk categorization of the drugs used during pregnancy and breastfeeding found in the prescriptions of the women admitted to an ICU specialized in women's health.

Methods

Study Design and Participants

We conducted a prospective cross-sectional study in the ICU at the Women's Hospital of a university in the city of Campinas, Brazil, a referral center in women's health. This ICU has 6 adult beds, and serves acutely ill women with obstetric, gynecological, and oncological morbidities who require intensive life support. This ICU has a multidisciplinary team composed of members from different healthcare professions, such as physicians, nurses, pharmacists, physiotherapists, psychologists and nutritionists. Pregnant or breastfeeding women over 18 years old admitted to the ICU from Monday to Friday were included. Women in the postpartum period, non-breastfeeding, and patients who were admitted to the ICU and discharged on weekends were excluded from the study.

Data Collection Procedures

Electronic prescriptions of the patients throughout the course of one year (from October 2012 to September 2013) were evaluated through the computerized system that stores data, enabling the search by the date of the prescriptions and the inpatient unit (one prescription was evaluated per day of hospitalization, per patient). Patient data comprised of identification (number of hospital record); age (in years); number of prescriptions; name of each drug prescribed; number of units prescribed; and average number of drugs per prescription. The PDIs and the risk categorization of the drugs during pregnancy and breastfeeding found in the prescriptions were quantified and classified.

For the identification and classification of the PDIs, an interactive system called DrugReax System was used. This system is part of the international database called Thomson Micromedex. To use this system, each generic name of the drugs prescribed must be entered in the system.[15] The system returns with a drug-drug combination showing the interactions. The severity of each interaction is classified as secondary, moderate, important and contraindicated ("secondary" interactions generally do not require a major intervention in the treatment, and "contraindicated" indicates that the drugs are contraindicated for concomitant use). Its most likely mechanism is a review of the documentation regarding this drug interaction, onset and the available literature.[15] The therapeutic classes and affected organs involved in the PDIs were classified according to the first level of the Anatomical Therapeutic Chemical (ATC) Classification System.[16]

To analyze the risk of the drugs to the pregnancy, the classification of the Food and Drug Administration (FDA) was adopted. It consists of five categories: A, B, C, D and X; A is the safest, and X is absolutely contraindicated.[17] The risk of the drugs ingested by a newborn through breastfeeding was consulted in the database called E-lactancia.org.[18] The risk in this database is categorized as "very low risk," "low risk," "high risk" and "very high risk"; "very low risk" is the safest category, and "very high risk" is absolutely contraindicated. Furthermore, this database shows alternatives to the patients' drug therapy, enabling rapid decision when choosing a safe medication.[18]

Data Processing and Analysis

The PDIs and the risk of specific drugs during pregnancy and breastfeeding were estimated and classified in spreadsheets using the Microsoft Excel (Microsoft, Redmond, WA, US) software, so all data was tabulated and analyzed. The descriptive analysis to evaluate the frequencies (n) and percentages (%) for the categorical variables and the descriptive statistics for the numeric variables were performed. The total of PDIs, the risks of the drugs and their severity, and the average of the prescribed drugs during the hospital stay, all for each patient, were calculated and evaluated to establish the prevalence of the PDIs and the risk of using specific drugs during pregnancy and breastfeeding. The present study was approved by the Research Ethics Committee of the institution (CAAE: 1187.0.146.000–11). The present study followed the checklist research of the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[19]

Results

Demographic Characteristics and Profile Prescriptions

During the period from October 2012 to September 2013, 58 patients were admitted to the ICU; 31 pregnant and 27 breastfeeding women. The average age was 30.2 ± 6.0 (average $\pm$ standard deviation [SD]; between 19 and 46 years old); the number of days in the ICU was 5.3 ± 9.1, with a range one of 1 to 58 days of stay; and 1 patient died in the postpartum period of uncontrolled systemic lupus erythematosus.

The most common reasons for admissions were: hypertensive disorders (69.0%), post-operative postpartum (23.2%), and sepsis (7.8%). A total of 34 patients had no comorbid conditions; 17 patients showed 1 comorbid condition, and 7 patients had more than 1 comorbid conditions. ►**Table 1** demonstrates the demographic characteristics of the study population.

We evaluated 305 prescriptions (200 for pregnant women and 105 for breastfeeding women), with a mean of 5.7 ± 9.1 prescriptions per patient. A total of 138 different drug types were prescribed, with an average of 13.9 ± 3.2 drugs per prescriptions. The most prescribed drugs for the pregnant women were: dipyrone, enoxaparin and hydralazine (6.5%, 5.9% and 3.7% respectively). For the breastfeeding women, the most prescribed drugs were: dipyrone, enoxaparin and simethicone (7.2%, 5.9% and 4.4%, respectively).

Potential Drug Interactions

Among the 138 different drugs prescribed, 97 drugs (70.3%) were involved in at least one PDI, and 284 (91%) prescriptions had PDIs, totalizing 1,849 PDIs in all prescriptions (6.0 ± 5.7 per prescription), with a range of 1 to 17 PDIs. Among the PDIs found in this study, 850 were moderate (632 [47.1%] for the pregnant women, and 218 [42.8%] for the breastfeeding women); 589 were important (497 [29.6%] for the pregnant women, and 192 [37.8%] for the breastfeeding women); 384

Table 1 Demographic characteristics of the study population

Characteristics	No. (%)
Patients	58
Pregnant women	31 (53.5)
Breastfeeding women	27 (46.5)
Age (years) (mean ± standard deviation)	30.2 ± 6.6
Ethnicity of the mother	
White	44 (75.9)
Non-white	14 (24.1)
Trimester of pregnancy	
2nd trimester	18 (58.1)
3rd trimester	13 (41.9)
Mode of delivery	
Cesarean	25 (92.5)
Vaginal	2 (7.5)
Comorbid conditions*	
Diabetes	7 (25.9)
Thrombosis	4 (14.8)
Hypothyroidism	3 (11.1)
Cardiopathy	3 (11.1)
Chronic obstructive pulmonary disease	2 (7.4)
Other conditions	8 (29.6)

Note: *Presence of underlying diseases in the patients.

were classified as secondary (298 [22.2%] for the pregnant women, and 86 [17.0%] for the breastfeeding women); and 26 were contraindicated (14 [1.0%] for the pregnant women, and 12 [2.4%] for the breastfeeding women).

A total of 175 different combinations of PDIs were identified in the prescriptions, with 6 combinations considered contraindicated (4 for the pregnant women, and 2 for the breastfeeding women), 55 considered important (40 for the pregnant women, and 28 for the breastfeeding women), 90 considered moderate (71 for the pregnant women, and 42 for the breastfeeding women), and 24 considered secondary (22 for the pregnant women, and 10 for the breastfeeding women). These PDIs were not actually observed in practice. ►**Table 2** shows the most frequent PDIs.

The main therapeutic classes and affected organs involved in the PDIs were those used for the nervous system (21; 26.6%), cardiovascular system (16; 20.3%), blood and the blood forming organs (13; 16.5%), anti-infectives for systemic use (11; 13.9%) and alimentary system (8; 10.1%).

Risk Categorization of Drugs during Pregnancy and Breastfeeding

Through the prescriptions, it was also possible to classify and identify the risk categorization of the drugs prescribed during pregnancy and breastfeeding, and the most frequently prescribed drugs that women were exposed to (►**Table 3**).

A total of 127 types of drugs were prescribed by the doctors for the pregnant group, and 109 drugs were classified according to the FDA risk classification. A total of 18 drugs used in Brazil are not classified by the FDA, including dipyrone. The most frequently prescribed drugs were those classified as category C.

Drugs with a negative risk–benefit (FDA category D or X) ratio were prescribed to 19 women (27.6%): category D drugs were prescribed to 16 patients (66.0%), and those classified as category X were prescribed to 3 patients (6.0%). Drugs prescribed during the second trimester and classified as risk D and X were found in 14 prescriptions (12 belonging to pregnant women, and 2 belonging to breastfeeding women);

Table 2 Characteristics and frequency (% in the study) of the prevalence of PDIs in the prescriptions

Pregnant Women			
Drugs involved	**Severity**	**Warning**	**Total (%)***
dipyrone x enoxaparin sodium	Important	Bleeding	152 (11.3)
dipyrone x propranolol	Moderate	Decreased antihypertensive effect	45 (3.4)
amlodipine x dipyrone	Secondary	Gastrointestinal hemorrhage	43 (3.2)
hydralazine x propranolol	Moderate	Increased risk of propranolol adverse effects	39 (2.9)
furosemide x hydralazine	Moderate	Enhanced diuretic response to furosemide	38 (2.8)
Breastfeeding Women			
Drugs involved	**Severity**	**Warning**	**Total (%)***
dipyrone x enoxaparin sodium	Important	Bleeding	83 (16.3)
captopril x dipyrone	Moderate	Decreased antihypertensive efficacy	29 (5.7)
amlodipine x dipyrone	Secondary	Gastrointestinal hemorrhage	24 (4.7)
fentanyl x midazolam	Important	Increased risk of CNS depression	19 (3.7)
dipyrone x propranolol	Moderate	Decreased antihypertensive effect	15 (2.9)

Abbreviations: CNS, central nervous system; PDIs, potential drug interactions.
Notes: Severity classification and other information available in Micromedex (Truven Health Analytics, Ann Arbor, MI, US).
*Number of times in which the PDIs appeared in prescriptions.

Table 3 Risk categorization of drugs used during pregnancy and breastfeeding, and some drugs implicated

Pregnant Women			
Risk categorization	**Patients**	**Drugs (%)**	**Type of drugs**
A	25	3 (2.8)	magnesium sulfate, levothyroxine, folic acid.
B	31	29 (26.6)	enoxaparin sodium, methyldopa, dimenhydrinate, metoclopramide, ranitidine.
C	31	60 (55.0)	omeprazole, hydralazine, dextrose, methadone, potassium chloride.
D	16	15 (13.8)	phenytoin, lorazepam, midazolam, clonazepam, diazepam
X	3	2 (1.8)	misoprostol, pravastatin.
Breastfeeding Women			
Risk Categorization	**Patients**	**Drugs (%)**	**Type of drugs**
Very low risk	27	58 (71.6)	enoxaparin sodium, simethicone, metoclopramide, bromopride, magnesium sulfate.
Low risk	27	18 (22.2)	dipyrone, tramadol, furosemide, ranitidine, dimenhydrinate.
High risk	4	4 (4.9)	chloramphenicol, nitroprusside, diazepam, dexchlorpheniramine, prometazine.

during the third trimester, those drugs were found in 2 prescriptions of pregnant women, and in 1 prescription of a breastfeeding woman.

For the breastfeeding women, 94 different drugs were prescribed, and 81 were classified by the E-lactancia.org database. Some drugs, such as mineral oil, oxytocin, and pindolol, were not found in this database, and were not classified. Many of the most frequently prescribed drugs were classified as very low risk.

High risk drugs were found in 4 prescriptions of breastfeeding women (14.8%) and low risk drugs were found in 24 prescriptions (22.9%).

Discussion

Our study confirms that the prescriptions for pregnant and breastfeeding women hospitalized in an ICU, which mainly included anti-infective drugs for systemic use, and nervous system and cardiovascular system drugs, have a high incidence of PDIs. However. most of the drugs used by these women in the ICU did not present serious risks to their fetus and newborns.

The average age of the pregnant and breastfeeding patients who needed ICU admission was $\sim$ 30 years, and a similar age was found in other studies in which the patients required admission to the obstetric ICU.[20,21] In the present study, the most common cause of ICU admission was pregnancy-induced hypertensive disorders, which is in agreement with the study by Demirkiran et al,[22] who analyzed 125 patients admitted to the ICU. Overall, few women become sufficiently ill to require hospitalization in an ICU, but the normal adaptive physiology of the pregnancy and the presence of a fetus or breastfeeding a newborn make these women different from other critically ill patients. Furthermore, the short ICU stay ($\sim$ 5 days) suggests that most of these patients did not have major complications.[23,24]

A total of 91% of the prescriptions presented at least one PDI, and all 4 classifications are present in the studied PDIs, (from contraindicated to secondary), and the most frequent interactions are moderate. The most recurrent moderate PDI observed was the interaction between dipyrone and captopril or propranolol. This PDIs have theoretical clinical relevancy, as caution in the use of both drugs is recommended: to monitor the antihypertensive efficacy and assess renal function periodically, but do not offer significant risks to the patients. Important PDIs were the second most prevalent, and the most frequent was the interaction between dipyrone and enoxaparin. The clinical management states the suspension of dipyrone or, if maintained, a continuous monitoring of bleeding episodes is necessary.[7,15] Despite this clinical management, the choice of anticoagulant in this setting is based upon careful consideration of the maternal and fetal risks discussed with the patient. Considering this combination, which is classified as important, the symptoms should be monitored to avoid the possible adverse events described in the literature.[7]

Numerous drug classes are specially relevant for the high risk of interactions, and, in many cases, the management of the interaction would depend on the patients' clinical status, the routes and timing of drug administration, drug doses, or the response/lack of response to the current pharmacotherapy.[25] Nervous system drugs were the most related with PDIs when grouped by ATC classification, and this high number can be justified considering that sedation and analgesia are essential components in the treatment of patients in intensive care.[26] Drugs that act on the cardiovascular system were the second most related to PDIs when grouped by ATC classification. A study in a teaching hospital's ICU in Brazil demonstrated that the prescription of antihypertensive drugs is also considered the main cause of drug interactions among prescription drugs.[27]

Even though this research showed the high number of important, moderate and secondary PDIs found in the

prescriptions (►**Table 2**), this does not necessarily correspond to the clinical relevancy, and the PDIs were not actually observed in practice at this Brazilian ICU. Thereby, even though some studies have reported drug interactions with some drug classes prescribed to pregnant and breastfeeding women, our findings prove that ours is a relevant study for this population in critical state, and it is important to support health professionals in making therapy decisions.[28–30]

Regarding the risk categorization for the pregnant women, most medications used were from category C, followed by category B, and similar results were found by a study conducted in a teaching hospital in Croatia in which the majority of pregnant women were exposed to category C (56%) and B (41%) drugs.[31] A small number of different drugs were responsible for the majority of prescriptions for category D drugs, as well as for category X drugs during the analysis of the electronic prescriptions. Category D also comprehended a small number of different drugs, notably benzodiazepines (lorazepam, midazolam, clonazepam). It is clear that some category D drugs are being appropriately used considering the maternal benefit, such as antiepileptic drugs (phenytoin).[31,32] In this research, the drugs classified as category X include misoprostol. Despite the use of misoprostol not being authorized by the FDA, this drug, classified as risk X, is used for cervical ripening and labor induction, and its use is oriented by various guidelines.[32,33] Its use in the puerperium is also safe and indicated in cases of postpartum hemorrhage and secondary to uterine atony.[32] Other drugs classified by the FDA as risk X can be cited, such as pravastatin, which was prescribed for a pregnant patient during hospitalization as a substitute for omega 3.[21,34]

The breastfeeding women included in the study were women declared able to breastfeed by the multidisciplinary team, even as they required intensive care. In the study period, 22 non-breastfeeding women admitted to the ICU were excluded. During the study, we observed that most of the drugs used by the breastfeeding women posed no serious risks to the newborn, since the "very low risk" category was the most prevalent, followed by the "low risk" category. Most drugs considered as "high risk" are being appropriately prescribed, taking into consideration the maternal benefit, but other drugs, such as diazepam, could be substituted by safer alternatives, which demonstrates that the clinical pharmacists of the ICU could provide direct patient care.[18,34] There are no researches with a classification of drug safety during breastfeeding according to the E-lactancia database.[18]

Among the various publications that report on the use of drugs during breastfeeding, the reference basic studies used are provided by the American Academy of Pediatrics (AAP).[11,35,36] According to the AAP, certain classes of drugs can be problematic, either because of accumulation in the breast milk, or due to their effects on the nursing infant or mother. The most common drugs include pain medications, antidepressants, and drugs to treat substance/alcohol abuse or smoking.[35] In the E-lactancia database, the classes of drugs that can be problematic to the newborn are the same drugs according to the AAP, the only thing that differs is the risk categorization.

The main strength of this study is its setting: the ICU of a Brazilian teaching hospital for women's healthcare, which treats pregnant and breastfeeding women. Moreover, this study had other advantages: the presence of electronic prescriptions in the teaching hospital, and the access to databases for evaluating the drugs presented in the prescriptions. A limitation of this study was that a pilot study to sample the calculation was not performed. However, taking into consideration the period of a year of study, and after the data analysis, this sample could be considered significant, because of the number of patients, the number of beds in the ICU, and the number of prescriptions analyzed.

Conclusion

This study demonstrated that there is a high incidence of PDIs in the pharmacotherapy prescribed to pregnant and breastfeeding women. This study also showed that most of the drugs used during pregnancy and breastfeeding at the ICU did not present serious risks to the fetus and the newborns.

Declaration of Conflicts of Interest
The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Syphilis in Pregnancy and Congenital Syphilis: Reality in a Portuguese Central University Hospital

Sífilis na gravidez e sífilis congênita: realidade de um hospital universitário central português

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Abstract

Purpose To evaluate maternal-fetal surveillance and follow-up of infants at risk for congenital syphilis (CS).

Methods Retrospective cohort study in a Portuguese Tertiary Referral Hospital. The main inclusion criterion was a positive syphilis serology. The study included all pregnant women that delivered in our hospital between January 2004 and December 2013. The neonates were classified according to their probability of infection based on the Centers for Disease Control and Prevention guidelines.

Results Among the 27 pregnancies at risk for CS, 48.2% ($n = 13$) of the women had a diagnosis during the 1st trimester, and the median gestational age at the end of the treatment was 28 weeks. Inadequate treatment was noted in 44.4% ($n = 12$) of the women. Adverse pregnancy outcomes were observed in 30.8% of the cases ($n = 8$), 5 of which had been adequately treated. We found 2 (7.7%) cases with "proven or highly probable CS," 10 (38.5%) with "possible CS," 12 (46.1%) with "less likely CS," and 2 (7.7%) with "unlikely CS." Among the infants, the treatment was successful, except for 1 neurosyphilis case.

Conclusion This study highlights many of the difficulties/concerns encountered in the maternal-neonatal management of syphilis. We highlight the importance of assuring the early detection of the infection as a way of guaranteeing the timely treatment, as well as a good compliance to the treatment and follow-up through a more efficient pregnant women surveillance network.

Keywords
- syphilis
- infection
- congenital syphilis
- prenatal diagnosis

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Resumo

Objetivo Avaliar a vigilância materno-fetal e o acompanhamento de crianças em risco de sífilis congênita (SC).

Métodos Estudo de coorte retrospetivo desenvolvido num hospital terciário de referência, cujo principal critério de inclusão foi a presença de serologia positiva para sífilis. O estudo incluiu todas as grávidas admitidas no nosso Hospital entre janeiro de 2004 e dezembro de 2013. Os recém-nascidos foram classificados de acordo com a probabilidade de infeção, com base nas recomendações do *Centers for Disease Control and Prevention*.

Resultados Entre as 27 gravidezes em risco de SC, 48,2% ($n = 13$) tiveram diagnóstico durante o 1° trimestre; a idade gestacional média no final do tratamento foi de 28 semanas. Em 44,4% ($n = 12$) das mulheres, o tratamento foi considerado inadequado. Em 30,8% dos casos ($n = 8$) houve algum evento adverso da gravidez, dos quais 5 foram adequadamente tratados. Em dois dos casos (7,7%) a SC foi provada ou considerada como altamente provável, 10 (38,5%) com SC provável, 12 (46,1%) com SC pouco provável, e 2 (7,7%) com SC improvável. Nos lactentes, o tratamento foi bem sucedido, com exceção de um caso de neurossífilis.

Conclusão Este estudo visa realçar muitas das dificuldades/preocupações encontradas na vigilância materno-neonatal dos casos com diagnóstico de sífilis. ublinhamos, não só, a importância de se assegurar a deteção precoce de infeção como forma de se garantir o tratamento atempado, mas também, uma adequada adesão à vigilância/tratamento, através de uma rede mais eficiente entre as diferentes instituições envolvidas no acompanhamento das grávidas.

Palavras-chave

- sífilis
- infecção
- sífilis congênita
- diagnóstico pré-natal

Introduction

Syphilis is a sexually transmitted infection caused by *Treponema pallidum* (Tp) that progresses through active and latent stages with different clinical presentations. Although fewer than 10% of syphilis cases are reported in developed countries,[1] several epidemiologic studies have shown an increase in early syphilis over the last decade. The annual report of the European Centre for Disease Prevention and Control (ECDC) found that the number of early-stage syphilis cases in Portugal increased by more than 50% between 2008 and 2012.[2] Accordingly, congenital syphilis (CS) has also reemerged despite systematic screening during pregnancy. Although the numbers were small, the ECDC reported the second highest incidence of CS in Europe (12.1/100,000 inhabitants) in Portugal.[3]

Adverse pregnancy outcomes of syphilis may occur in 66.5% of pregnant women with untreated syphilis, and include late spontaneous abortion, prematurity, small for gestational age (SGA) neonates, and stillbirth.[4] Thus, CS can manifest, according to the severity, as neonatal death, neonatal disease, or latent infection leading to later sequelae. Unfortunately, delivery at term of live infants who are fully asymptomatic may occur in approximately two-thirds of live born cases with untreated or inappropriately treated mothers. The early detection and adequate treatment of syphilis in pregnancy are the key points of this preventable condition.[5]

The aim of our study was to evaluate the maternal surveillance of syphilis and its clinical approach, the treatment and the follow-up of infants at risk for CS according to the most recent guidelines from the Centers for Disease Control and Prevention (CDC).[6]

Methods

This retrospective cohort study from a Portuguese Tertiary Referral Hospital is the result of a study of all cases with the International Classification of Diseases, Ninth Revision (ICD-9), codes of "maternal syphilis complicating pregnancy" and "congenital syphilis" over a period of 10 years. The maternal and infant medical records were thoroughly reviewed by the main researcher using maternal and pediatrics computer databases and paper clinical files.

The main inclusion criteria were positive non-treponemal tests (NTTs) and treponemal tests (TTs) among all pregnant women that had delivered at our hospital between January 2004 and December 2013.

The adverse pregnancy outcomes were defined as prematurity, SGA neonates ($<$ p10), perinatal death, or symptomatic CS in the newborn. Inadequate treatment in pregnancy was defined as untreated syphilis, undocumented therapy, the use of antibiotics other than benzathine penicillin, insufficient dose regimen, and inadequate serologic response to treatment (less than 4-fold decrease in NTT titers by 3 months) or therapy not taken until 1 month before delivery.

In Portugal, routine screening for syphilis is mandatory during the first and third trimesters of pregnancy.[7] This screening includes a quantitative NTT Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) and a TT - Treponema pallidum Particle Agglutination Assay (TP-PAA), Fluorescent Treponemal Antibody absorption (FTA-abs) or chemiluminescence assay (CLIA).[7] Non-treponemal tests are usually used for screening and monitoring therapy, while TTs are used to confirm the diagnosis.

The staging of maternal syphilis is complex; it is based on the combination of history, physical examination, epidemiologic features and serologic tests.[8] The quantitative maternal non-treponemal titer, especially if > 1:8, might be a marker of early infection and bacteremia. However, the risk for fetal infection is still significant in pregnant women with late latent syphilis and low titers. Latent syphilis is defined as having serologic proof of infection without the symptoms of the disease, while late latent syphilis is considered when the infection occurred more than 12 months before.[6]

All neonates whose mothers had a reactive NTT and TT were clinically examined and evaluated with serologic tests from peripheral blood. Maternal history of Tp infection and treatment for syphilis were considered when evaluating and treating the neonate for CS, except when the diagnosis of CS was proven or highly probable. In this context, we decided to classify our cases according to their probability of infection based on the 4 scenarios proposed by the CDC guidelines (1 - proven or highly probable CS; 2 - possible CS; 3 - less likely CS; 4 - unlikely CS).[6]

Intramuscular (IM) benzathine penicillin G regimens were used in the mothers' treatment according to the stage of infection (2.4 to 4.8 million units for early stage syphilis, and 7.2 million units in total, administered as 3 doses of 2.4 million units over 3 weeks, for latent syphilis or syphilis of unknown duration). For the neonates, the main regimens were IM benzathine penicillin G (50,000 units/Kg) in a single dose, or parenteral aqueous crystalline penicillin G (100,000–150,000 units/Kg/day) for a total of 10 to 14 days, according to their probability of infection.

The clinical and serologic follow-up of the seropositive infants was performed, including NTTs every 2–3 months, until there was a nonreactive result or a 4-fold decrease in antibody titers. In an uninfected or successfully treated infant, NTT titers are usually nonreactive by 6 months of age. Passively acquired syphilis antibodies may be present for longer, up to around 15 months of age.[9]

Results

Obstetric Surveillance

According to the selection criteria, between 2004 and 2013 we had 27 women with positive syphilis serologic results (►**Table 1**). The number of cases reported each year was similar between 2005 and 2010. However, between 2011 and 2013 we noticed an increase in the reported incidence, with 55.5% (15/27) of the cases occurring during this period of time. The median maternal age at delivery was 32 years (18-43); most patients were Caucasian (89%) and had poor education; 2 of them were co-infected with HIV. Out of the 9 cases without a proper pregnancy follow-up, 7 had irregular antenatal care, and 2 had no surveillance at all.

Among those 27 pregnancies at risk for CS, 7 of them had a previously known diagnosis of syphilis (5 with well-documented prior treatments). A total of 48.2% (13/27) had a positive diagnosis during the 1st trimester, 33.3% (9/27), at the 2nd trimester, 11.1% (3/27), at the 3rd trimester, and 7.4% (2/27), at delivery. All cases were classified as latent syphilis (5 early latent [18.5%], 7 late latent [25.9%], and 15 latent syphilis [55.6%] of unknown duration at the time of the diagnosis). One pregnancy resulted in a spontaneous abortion at 12 weeks, without fetal findings consistent with CS.

Table 1 Maternal and obstetric characteristics; evaluation, management and prevention of CS

Age at delivery (y) (mean ± 2σ)	32.5 ± 5.7 (18–43)
Number of previous gestations (median; range)	2 (0–8)
Parity (median; range)	1 (0–6)
Immigrant mothers	3/27 (11.1)
Unemployed	9/27 (33.3)
Inadequate pregnancy follow-up	12/27 (44.4)
Median RPR titers at treatment	1:16
Weeks of gestation at the end of the treatment (mean ± 2σ)[i]	27.9 ± 6.9
Adequate antenatal treatment[ii]	15/27 (55.6)
Median RPR titers at delivery	1:4
Gestational age at delivery (mean ± 2σ)	38.0 ± 1.9 (33–41)
Preterm delivery (< 37 WG)[iii]	5/26 (19.2)
Birth weight (g) (mean ± 2σ)	3087 ± 699 (1830–4700)
Small for gestational age (<p10)	5/26 (19.2)
Median RPR titer of neonate	1:4

[i]Excluding 12 women untreated or incorrectly treated, and 2 women with adequate treatment before pregnancy with stable NTT titers.
[ii]Including 2 women with adequate treatment before pregnancy with stable NTT titers.
[iii]Excluding one woman with spontaneous abortion at 1st trimester
Abbreviations: CS, congential syphilis; RPR, rapid plasma reagin.

Inadequate treatment was observed in 12 women (44.4%): 7 of them with the recommended treatment, but less than 4 weeks before delivery (3 needed a second bout of treatment due to insufficient serologic response), 4 had no treatment during pregnancy, and 1 was treated with erythromycin. Among the 15 women who were properly treated, only 8 had a well-documented treatment of their partners. Intramuscular benzathine penicillin G regimens were used in all cases, according to the stage of infection. None of our cases had prenatal ultrasonography findings suggestive of CS.

Neonatal Outcomes

The NTTs and TTs were positive in 26 newborns (►**Table 1**). The mean birth weight was 3,087 g, and 5 of them were SGA (19.2%). Twenty neonates were delivered at term, and 5 were late preterm (19.2%). No multiple births were reported.

Overall, adverse outcomes were observed in 30.8% of cases (8/26) (►**Table 2**), 5 of which had been adequately treated and had no other obstetric comorbidities. The main events were 2 cases of CS and 6 cases of preterm delivery and/or SGA neonates. Considering those 5 well-treated cases, the median gestational age at the end of the treatment was 28 weeks of

Table 2 Cases with adverse pregnancy outcomes: pregnancy follow-up and neonatal outcomes

Cases	Pregnancy follow-up				
	Maternal age/ Gravida/Para	Stage of disease/ Time of diagnosis	Neonatal outcomes	Maternal treatment	
1 (SGA + PTD)	27 years Primigravida	Early latent 2nd trimester	Adequate	Incorrectly treated (Incomplete 2nd treatment at 31 WG - inadequate serologic response)	
2 (SGA)	36 years Gravida 2/Para 1	Early latent 2nd trimester	Adequate	Properly treated[c]	
3 (PTD)	32 years Primigravida	Early latent 2nd trimester	Adequate	Properly treated[c]	
4 (SGA)	19 years Primigravida	Latent of unknown duration/1st trimester	Adequate	Properly treated[a] (2nd treatment at 28 WG - inadequate serologic response)	
5 (CS)	29 years Gravida 3 /Para 2	Latent of unknown duration/2° trimester	Irregular Surveillance	Properly treated[a]	
6 (CS)	19 years Primigravida	Latent of unknown duration/ At delivery	Without surveillance	Not treated	
7 (PTD)	29 years Gravida 4/Para 2	Late latent (Previously treated)	Irregular Surveillance	Properly treated[a]	
8 (SGA + PTD)	38 years Gravida 8/ Para 6	Late latent (Not treated)	Irregular Surveillance	Incorrectly treated	
Cases	Pregnancy follow-up				
	Other obstetric complications	Time at delivery/ Birth weight	RPR Titers (Newborn/ mother)	Probability of Developed CS[b]	CS
1 (SGA + PTD)	None	36 WG 2,030 g (p1)	1:16/ 1:16	Possible	No Aqueous penicillin G 10 days (100,000–150,000 units/Kg/day)
2 (SGA)	None	39 WG 2,660 g (p4)	1:16/ 1:16	Less likely	No
3 (PTD)	Thrombophilia	33 WG 2,130 g (p48)	1:32/ 1:32	Less likely	No Aqueous penicillin G 10 days (100,000-150,000 units/Kg/day)[d]
4 (SGA)	None	38 WG 2,260 g (p1)	1:4/ 1:4	Less likely	No
5 (CS)	None	40 WG 3,950 g (p85)	1:0/ 1:0	Proven or highly probable	Yes Aqueous penicillin G 10 days (100,000-150,000 units/Kg/day)
6 (CS)	None	36 WG 2,215 g (p4)	1:16/ 1:16	Proven or highly probable	Yes Aqueous penicillin G 14 days (100,000-150,000 units/Kg/day)
7 (PTD)	None	34 WG 2,220 g (p32)	1:4/ 1:8	Less likely	No
8 (SGA + PTD)	None	35 WG 1830 g (p1)	1:4/ 1:4	Possible	No Aqueous penicillin G 10 days (100,000–150,000 units/Kg/day)

Abbreviations: CS, congenital syphilis; p, percentile; PTD, preterm delivery; RPR, rapid plasma reagin; SGA, small for gestational age; WG, weeks of gestation.

Notes: [a] Three doses of intramuscular benzathine penicillin G - 7.2 million IU.

[b]Probability of developed CS based on the four scenarios proposed by the CDC guidelines.

[c]Two doses of intramuscular benzathine penicillin G - 4.8 million IU

[d]Treatment at 5 months after an elevation in the CLIA titers

gestation (WG); 2 were classified as early latent syphilis, 2 as latent of unknown duration, and 1 as late latent previously treated. Thus, ~ 60% (⅜) of the pregnancies with early latent syphilis, 28.6% (2/7) of the ones with late latent syphilis, and 20% (3/15) of the pregnancies with latent syphilis of unknown duration resulted in adverse fetal events.

Among the 18 remaining neonates, 2 were secondarily admitted before 6 months of age after an elevation in the TT titers, with a subsequent adequate treatment response.

According to the probability of developing CS based on the 4 scenarios proposed by the CDC guidelines, we found 2 cases of "proven or highly probable CS" (7.7%) (CDC scenario 1, ►**Table 3**), both with an abnormal physical examination consistent with CS, and both reported in 2011. In one case, the parents were properly treated in the 3rd trimester, and had a later, but weakly positive, RPR titer (1:1). The neonatal syphilis serology was compatible with the placental transfer of maternal antibodies; however, hypotonia, seizures and transfontanellar ultrasound findings suggested neurosyphilis. In the other case, the diagnosis was at the delivery, with an RPR titer of 1:16. Although the newborn had the same NTT titer as the mother, he presented signs of CS (anemia and thrombocytopenia, hepatosplenomegaly, rash, neurologic signs and radiographic signs of CS in the long bones).

From the 10 neonates with "possible CS" (38.5%) (CDC scenario 2), their mothers were not treated or underwent improper treatments, with serum quantitative NTT titers less than or equal to 4-fold the maternal titer. The mean birth weight was 3,236 g ± 848 g, and the mean gestational age at birth was 38.3 WG ± 2.0 WG, with 2 preterm deliveries (20.0%). All neonatal RPR serum titers were ≤ 1:16, and 2 of them were nonreactive.

Among the 12 neonates with "less likely CS" (46.1%) (CDC scenario 3) whose mothers were properly treated during pregnancy, the mean birth weight was 2,886 g ± 491 g, and the mean gestational age at birth was 37.6 WG ± 2.1 WG, with 2 preterm deliveries (16.7%).

There were 2 neonates with "unlikely CS" (7.7%) (CDC scenario 4) whose mothers' treatment was adequate before pregnancy, and their NTT titers remained low and stable before and during pregnancy. Both were born at term, and had an RPR < 1:4.

Table 3 Description of two cases with proven CS

Case	1	2
Maternal age/ Gravida/Para	**19 years Primigravida**	**29 years Gravida3 /Para2**
Pregnancy follow-up		
Time at diagnoses/ Stage of disease	At delivery/ Latent of unknown duration	28 WG/ Latent of unknown duration
Follow-up	None	Irregular
Maternal treatment	None	Properly treated: 3 doses of intramuscular penicillin G (7.2million IU)[i]
Time at delivery/ Type of birth/ Birth weight/ sex/ Apgar score	36 WG; Eutocic; 2,115 g (p4); Male; 5/7	40 WG; Vacuum-assisted; 3,950 g (p85); Male; 5/8
Neonatal outcomes and evaluation		
Clinical signs	Maculopapular rash; hepatosplenomegaly jaundice; upper gastrointestinal bleeding; seizures	Respiratory distress; hypotonia; seizures
RPR Titers (Newborn/ mother)	1:16/1:16[ii]	1:0/1:0 *Tp* PCR + (CSF)[iii]
Analytic findings	Anemia and thrombocytopenia; hyperglycemia; hyperbilirubinemia	Anemia and thrombocytopenia
Imaging findings	Transfontanellar ultrasound: bilateral intraventricular hemorrhage; hyperechogenic *corpus callosum* Long-bone X-ray: *periostitis*	Transfontanellar ultrasound: abnormalities on the ventricular lining and bilateral intraventricular strand, mild ventricular dilatation, and bilateral hypoechogenic area in the choroid plexus. MRI: subdural hemorrhage
Treatment	Aqueous penicillin G 14 days (100,000-150,000 units/Kg/day)	Aqueous penicillin G 10 days (100,000-150,000 units/Kg/day)

[i] Partner was properly treated too.
[ii] Lumbar puncture was not performed because the diagnosis of a grade I intraventricular hemorrhage contra-indicated the procedure.
[iii] Blood Tp PCR (mother and newborn) negative; CLF: Cerebrospinal fluid.
Abbreviations: CS, congenital syphilis; CSF, cerebrospinal fluid; MRI, magnetic resonance, imaging; PCR polymerase chain reaction; RPR, rapid plasma reagin; SGA, small for gestational age; Tp, Treponema pallidum; WG, weeks of gestation.

Neonatal Evaluation, Treatment and Follow-Up

Lumbar puncture was not performed in 1 of the 2 cases of "proven CS" (►**Table 3**), since the diagnosis of a grade I intraventricular hemorrhage contra-indicated the procedure. In the other case (suspicion of neurosyphilis), the cerebrospinal fluid (CSF) was analyzed using a real-time probe-based polymerase chain reaction (PCR) method, with a positive result. Nevertheless, in the 2 cases, Tp was not detected in the blood samples from either the mother or the newborn. Both were treated with intravenous aqueous crystalline penicillin G for 10 to 14 days. At follow-up, the RPR titers declined and were nonreactive between 6 and 2 months after birth respectively. At 6 months, a PCR of the CSF of the infant with proven neurosyphilis was performed, with a negative result. At 12 months, this child had a global developmental delay with a Griffiths developmental quotient of less than 85% and spastic diplegic cerebral palsy.

Among the 10 neonates with "possible CS", 1 underwent a lumbar puncture at 2 months of age after an elevation in the TP-PA titer, and 7 underwent long-bone radiographs. A complete blood count (CBC) was obtained for all children. The 2 neonates with nonreactive RPRs and normal clinic evaluations did not receive any treatment; 3 received a single dose of IM benzathine penicillin G, and in 5, aqueous crystalline penicillin G was administered for 10 days. Eight children continued with follow-up appointments, and RPR seroreversion was verified in all cases between 2 and 9 months.

Among the 12 infants with "less likely CS", only one was treated with parenteral aqueous crystalline penicillin G for 10 days due to an RPR titer of 1:8, 4-fold higher than the mothers' titer (1:2). The RPR became nonreactive at 12 months of age. All infants had adequate follow-ups, and their RPRs were nonreactive before 4 months of age. In one of these infants, a lumbar puncture was performed at 5 months, after an elevation in the CLIA titer. The result was negative, with a normal CBC and a normal long-bone radiograph. At that time, a 10-day course of aqueous crystalline penicillin G was administered with a successful outcome. Finally, of the 2 neonates with "unlikely CS," 1 received a single dose of IM benzathine penicillin (RPR 1:4), while the other did not receive any treatment at all (nonreactive RPR).

Discussion

Syphilis infection during pregnancy still represents a worldwide public health problem, with rates of CS rising in several parts of the world.[10] The annual report of the ECDC showed an increased number of early syphilis cases in Portugal of more than 50% between 2008 and 2012;[2] accordingly, a high rate of congenital syphilis was also reported. Our data reflect this reality, showing that 55.5% of neonates with positive syphilis serology were born between 2011 and 2013, with 2 cases of proven CS born in 2011. The highest seroprevalence in pregnant women was found in 2012, of 0.19%, and the lowest one in 2006, of 0.03%.

Effective prevention and identification of CS depends primarily on the identification of syphilis in pregnant women and, therefore, on the routine screening of all pregnant women for syphilis. With the re-emergence of syphilis in Portugal, universal screening of all pregnant women continues to be important, and remains the standard of care. Concerns about the cost-effectiveness of this screening in low-prevalence settings have been repeatedly proven.[11,12]

The infected women in our cohort were young (median age of 32 years old); 2 of them were co-infected with HIV, and apparently without high-risk behavior patterns; the rate of immigrant mothers was low (11.1%). These findings reinforce the importance of antenatal screening for syphilis even in developed countries.

Congenital syphilis is theoretically eradicable through antenatal care screening programs that assure the early identification and prompt treatment of women with a positive serology, ideally by the 24th WG.[3,13] However, coverage of the 1st trimester screening and timely antenatal treatment are still a problem.

In our study, 48.2% of the women were diagnosed during the 1st trimester, and the mean WG at the end of the treatment was 28 weeks among the well-treated women. Forty-four percent were women treated incorrectly, and the main cause seems to be maternal noncompliance to prenatal care, which can result in delayed treatment or undertreatment. Moreover, it is important to notice the lack of well-documented treatment of the partners.

The effectiveness of the treatment and the manifestations of CS are dependent on several variables, including the stage of maternal syphilis, the gestational age at the time of the infection, the severity of the fetal infection (the degree of maternal spirochetemia), the adequacy and timing of the maternal treatment, and the immunological response of the fetus.[14] Firstly, the staging of maternal syphilis is complex to determine; an accurate history, physical examination, epidemiologic features and serologic tests are needed.[8] In our series, all cases were classified as latent syphilis, but 55.5% of them were latent syphilis of unknown duration. Secondly, spirochetes can cross the placenta and infect the fetus by the 14th WG approximately, with the risk of fetal infection increasing with gestational age.[15] The direct damage caused by the spirochetes to both the placental (microvascular proliferation and inflammation) and the umbilical cord may compromise fetal growth.[16] Thirdly, regarding the treatment, although the majority of pregnancy adverse events are a consequence of undiagnosed, untreated or inadequately treated maternal syphilis, in our study we verified that, among the 8 cases with an adverse outcome (►**Table 2**), 5 had been adequately treated and had no other obstetric or maternal comorbidities. Despite the efficacy of penicillin, there are some factors that can justify these outcomes, especially an early stage of maternal syphilis/severity of fetal infection, gestational age at treatment or interval of time without treatment.[17] Overall, all studies showed a lower prevalence of adverse outcomes between women who had received an intervention in the first or second trimesters of pregnancy.[13] Of those who did not undergo syphilis screening and treatment until the 3rd trimester, Hawkes et al[13] observed different outcomes: from 2% of

"classical" CS to 68% of any reported adverse outcome (odds ratio [OR]: 2.24; 95% confidence interval [95%CI]: 1.28–3.93).

With regard to our well-treated CS case, the first penicillin administration was at 30 WG, although the exact time of infection was unknown (latent syphilis of unknown duration). On the other hand, regarding the other case of proven CS, the diagnosis was at delivery, and no treatment was instituted.

Inappropriate classification of neonates according to the CDC scenarios, due to erroneous interpretation of maternal-neonatal serologic test results or maternal treatment, easily occurs. The lack of well-documented information or incorrect pregnancy follow-up can lead to under-evaluation, under-treatment or even overtreatment in neonates. Of the neonates with "possible CS," two of them presented nonreactive NTTs, and the care provider determined that the mothers' risk of untreated syphilis was low, so no treatment was provided. However, treatment of these neonates with a single IM dose of benzathine penicillin G, in order to possibly incubate the syphilis, should be considered.[6] Before using a single dose of penicillin G, follow-up must be assured;[6] all of the infants in our study attended all of their consultations. Regarding neonates with "less likely CS," 10 of the 12 cases were not treated, because a close serologic follow-up was provided every 2–3 months for a period of at least 6 months. Finally, with regard to the 2 cases of "unlikely CS," no treatment was required in the case with a nonreactive NTT; however, in the other case, a single IM injection was administered.

Except for the neurosyphilis case (probably due to a faster sequester in the fetal central nervous system before 30 WG),[18] our study revealed no treatment failures in the infants that were followed-up, demonstrating that the risk-based approach of the CDC recommendations is relevant. In addition, a less aggressive treatment, like a single dose of benzathine penicillin G or abstention of treatment in "less likely CS" cases, seems to be acceptable in cases of adequate evaluation.

Strengths and Limitations

The extensive analysis of all cases, crossing information between obstetric and pediatric records, empowers our study, making it unlikely that any case was missed. Since it is a central university hospital, these cases tend to be referred to our center, making our sample more representative of the population from this region of Portugal. Moreover, our data are in agreement with the official rates reported by the ECDC.[2]

The retrospective design of the study is one of its main limitations, making it difficult to study some factors such as behavioral maternal characteristics, data concerning the treatments of some mothers and partners, and the reasons for noncompliance. The small number of detected cases also presents several challenges, in particular if we look at heterogeneity of the data, but it provides a detailed insight into the epidemiology of this rare disease. Lastly, the lack of well-documented information that must be conveyed between the health centers and hospitals was a further limitation.

Conclusion

Despite our good results, this study highlights many of the difficulties/concerns encountered in the maternal-neonatal management of syphilis. We highlight the importance of assuring the early detection of the infection, as well as a good compliance to treatment and follow-up, in order to avoid treatment failure. The features that contribute to this failure include the maternal stage of syphilis (early stage), advancing gestational age at treatment, higher NTT titers at treatment and delivery, and short interval from treatment to delivery.

Public health strategies aiming at the early detection of syphilis, at the treatment of infected partners, and at the promotion of access to sexual healthcare services should be reinforced. Better surveillance data are equally essential to understand where the antenatal screening programs are failing.

The proportion of syphilis-positive pregnant women treated ideally by the 24th week of gestation is considered by the ECDC as an important indicator that allows countries to estimate program effectiveness.[3] Consequently, encouraging all pregnant women to seek care in the first two trimesters of their pregnancies to avoid preventable adverse outcomes should be a priority of the health programs.

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Combined Effect of the PGR +331C > T, CYP17A1 -34A > G and CYP19A1 1531G > A Polymorphisms on the Risk of Developing Endometriosis

Efeito combinado dos polimorfismos PGR +331C > T, CYP17A1 -34A > G e CYP19A1 1531G > A no risco de desenvolvimento da endometriose

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Abstract

Purpose To evaluate the magnitude of the association of the polymorphisms of the genes *PGR, CYP17A1* and *CYP19A1* in the development of endometriosis.

Methods This is a retrospective case-control study involving 161 women with endometriosis (cases) and 179 controls. The polymorphisms were genotyped by real-time polymerase chain reaction using the TaqMan system. The association of the polymorphisms with endometriosis was evaluated using the multivariate logistic regression.

Results The endometriosis patients were significantly younger than the controls (36.0 ± 7.3 versus 38.0 ± 8.5 respectively, $p = 0.023$), and they had a lower body mass index (26.3 ± 4.8 versus 27.9 ± 5.7 respectively, $p = 0.006$), higher average duration of the menstrual flow (7.4 ± 4.9 versus 6.1 ± 4.4 days respectively, $p = 0.03$), and lower average time intervals between menstrual periods (25.2 ± 9.6 versus 27.5 ± 11.1 days respectively, $p = 0.05$). A higher prevalence of symptoms of dysmenorrhea, dyspareunia, chronic pelvic pain, infertility and intestinal or urinary changes was observed in the case group when compared with the control group. The

Keywords
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interval between the onset of symptoms and the definitive diagnosis of endometriosis was 5.2 ± 6.9 years. When comparing both groups, significant differences were not observed in the allelic and genotypic frequencies of the polymorphisms *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A*, even when considering the symptoms, classification and stage of the endometriosis. The combined genotype *PGR +331TT/CYP17A1 -34AA|CYP19A11531AA* is positively associated with endometriosis (odds ratio [OR] = 1.72; 95% confidence interval [95%CI] = 1.09–2.72).

Conclusions The combined analysis of the polymorphisms *PGR-CYP17A1-CYP19A1* suggests a gene-gene interaction in the susceptibility to endometriosis. These results may contribute to the identification of biomarkers for the diagnosis and/or prognosis of the disease and of possible molecular targets for individualized treatments.

Resumo

Objetivo Avaliar a magnitude de associação de polimorfismos nos genes *PGR, CYP17A1* e *CYP19A1* no desenvolvimento da endometriose.

Métodos Este é um estudo retrospectivo do tipo caso-controle, envolvendo 161 mulheres com endometriose (casos) e 179 controles. Os polimorfismos foram genotipados pela reação em cadeia da polimerase em tempo real utilizando o sistema TaqMan. A associação dos polimorfismos estudados com a endometriose foi avaliada pela regressão logística multivariada.

Resultados As pacientes com endometriose eram significativamente mais jovens do que os controles (36,0 ± 7,3 versus 38,0 ± 8,5, respectivamente, $p = 0,023$), apresentaram um índice de massa corporal menor (26,3 ± 4,8 versus 27,9 ± 5,7, respectivamente, $p = 0,006$), maior tempo médio de duração do fluxo menstrual (7,4 ± 4,9 versus 6,1 ± 4,4 dias, respectivamente, $p = 0,03$) e menor tempo médio do intervalo entre as menstruações (25,2 ± 9,6 versus 27,5 ± 11,1 dias, respectivamente, $p = 0,05$). Uma maior prevalência dos sintomas de dismenorreia, dispareunia, dor pélvica crônica, infertilidade, alterações intestinais e urinárias foi observada no grupo casos comparado ao grupo controle. O tempo médio entre o início dos sintomas e o diagnóstico definitivo de endometriose foi de 5,2 ± 6,9 anos. Comparando os dois grupos, não foram observadas diferenças significativas nas frequências alélicas e genotípicas dos polimorfismos *PGR +331C > T*, *CYP17A1 -34A > G* e *CYP19A1 1531G > A*, e nem considerando os sintomas, a classificação e o estadiamento da endometriose. O genótipo combinado *PGR +331TT/CYP17A1 -34AA|CYP19A11531AA* está associado positivamente com a endometriose (razão de possibilidades [RP] = 1,72; intervalo de confiança de 95% [IC95%] = 1,09–2,72).

Conclusões A análise combinada dos polimorfismos *PGR-CYP17A1-CYP19A1* sugere uma interação gene-gene na susceptibilidade à endometriose. Estes resultados podem contribuir para a identificação de biomarcadores para o diagnóstico e/ou prognóstico da doença, assim como de possíveis alvos moleculares para um tratamento individualizado.

Palavras-chave
- polimorfismos
- estrógenos
- endometriose
- biomarcadores

Introduction

Endometriosis is a benign gynecological estrogen-dependent disease characterized by the presence of endometrial tissue out of the uterine cavity, affecting nearly 10% of women of reproductive age. Symptoms may include dysmenorrhea, dyspareunia, chronic pelvic pain and infertility.[1] The pathogenesis and the molecular mechanisms that are involved in the development of endometriosis are not yet clear, and hereditary susceptibility is an area of growing investigation for the identification of genetic polymorphisms that may lead to an increased risk of developing the disease.[2,3]

Estrogen performs a fundamental role in endometriosis, which predominantly occurs in women of reproductive age who have high estrogen production.[4,5] An increase in enzyme expression is responsible for the estrogen synthesis and reduction of progesterone receptor (PGR) expression

observed in samples of endometrial injuries, but these phenomena are not found in controls.[6,7] As endometriosis is an estrogen-dependent disease, genetic polymorphisms involved in the biosynthesis and regulation of estrogens could be considered possible biomarkers for its diagnosis and/or prognosis. Cytochrome P450 17A1 (CYP17A1) is involved in the initial stages of estrogen synthesis, converting pregnenolone into 17α-hydroxypregnenolone and, subsequently, into dehydroepiandrosterone. Furthermore, cytochrome P450 19A1 (CYP19A1) acts in the final stage by converting androstenedione into estrone, and testosterone into estradiol.[4,8] The enzyme CYP17A1, also known as 17 α-hydroxylase, is encoded by the gene with the same name, located in chromosome 10q24.3.[8] The single nucleotide polymorphism (SNP) *CYP17A1 -34A > G* is located in the 5′ untranslated region (UTR) of the *CYP17A1* gene, and it causes a significant increase in the expression of 17 α-hydroxylase.[8] A different gene product, the aromatase enzyme, is encoded by the gene *CYP19A1*, which is located in chromosome 15q21. The SNP *CYP19A1 1531G > A* is found in the 3′UTR of this gene, and it causes a significant change in the levels of circulating estradiol.[8] Progesterone is also involved in the pathogenesis of endometriosis, as it is a strong antagonist of estrogen, and thus plays an essential role in the regulation of endometrial cell proliferation.[6] The *PGR* gene, located in chromosome 11q22–q23, is responsible for encoding both progesterone receptor isoforms (PR-A and PR-B) by transcribing from alternative promoters.[9] The SNP *PGR +331C/T*, located in the gene promoter region, creates an additional TATA box, and causes higher transcription of PR-B.[9]

As the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* are located near potential elements that regulate their respective genes, interfering with the levels of expression of the corresponding proteins, it becomes relevant to evaluate the influence of these SNPs in the development of endometriosis. To date, 12 studies have evaluated the association of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* in the development of endometriosis in different populations. However, the results of the analyses are controversial.[10–21] In this context, the objective of this study was to evaluate the magnitude of the association of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* with the development of endometriosis in women treated in two public reference hospitals in Brazil.

Methods

Study Design

This was a retrospective, case-control study approved by the Human Research Ethics Committees of two of our institutions (under protocols number 414/11 and 1.244.29 respectively), both located in the city of Rio de Janeiro, Brazil. All participating patients ($n = 340$) provided written informed consent, and visited one of the two institutions between March 2011 and October 2015. The research was conducted in accordance with the Declaration of Helsinki, which was revised in 2008. Patients with a surgical diagnosis (after laparoscopy or laparotomy) of endometriosis with histological confirmation of the disease, as well as those diagnosed by magnetic resonance imaging (MRI), were considered the case group ($n = 161$). The control group ($n = 179$) consisted of women with a negative diagnosis of endometriosis, after laparoscopy or laparotomy for tubal ligation ($n = 48$) or for the treatment of benign diseases, such as myoma ($n = 52$), ovarian cysts ($n = 30$), hydrosalpinx ($n = 5$), or for other reasons ($n = 44$). Women with any history or diagnosis of cancer or adenomyosis were excluded.[2]

The stage of the endometriosis was determined according to the revised American Fertility Society classification, which divides the disease into four stages: I (minimum), II (mild), III (moderate) and IV (severe).[22] Regarding the classification of the endometriosis, we considered the proposal of Nisolle and Donnez:[23] superficial endometriosis (SUP), ovarian endometrioma (OMA), and deep infiltrative endometriosis (DIE). Superficial endometriosis and ovarian endometrioma may be found in association with deep endometriosis,[24] and the cases in which this association was observed were considered DIE.

The body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Only severe and incapacitating symptoms of pain were included. Women who failed to conceive after one year of regular, contraceptive-free intercourse were considered infertile. Cyclical intestinal or urinary symptoms were defined as bowel and/or urinary pain and/or bleeding coinciding with menstrual periods.

Genotyping

Genomic DNA was extracted from the peripheral blood sample using a genomic DNA extraction kit (Genomic DNA Extraction, Real Biotech Corporation, Banqiao City, Taiwan), according to the manufacturer's instructions.

Genotyping of *PGR +331C > T* (rs10895068), *CYP17A1 -34A > G* (rs743572) and *CYP19A1 1531G > A* (rs10046) SNPs was performed by real-time polymerase chain reaction (PCR) using the TaqMan system. Oligonucleotides and probes specific to each SNP were obtained from Applied Biosystems: rs10895068 (C_27858738_10), rs743572 (C_2852784_30) and rs10046 (C_8234731_30). For all SNPs, PCRs were performed with 30 ng of template DNA, 1× TaqMan Universal Master Mix (Applied Biosystems, Foster City, CA, US), and with each primer and probe assay at 1× dilution, and H2O to 8μL. The PCR conditions were: 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds, and annealing at 60°C for 1 minute. Allele-detection was performed on a 7500 Real-Time System (Applied Biosystems, Foster City, CA, US), and the genotypes were then determined directly.

Statistical Analyses

The continuous variables were expressed as the mean ± standard deviation (SD), and the differences between means were evaluated using the Student's *t*-test. The categorical data were expressed as percentages, and evaluated by the Chi-square ($\chi 2$) test or Fisher's exact test, when applicable. For each SNP, the Hardy-Weinberg equilibrium (HWE) was calculated, and the allelic and genotypic

Table 1 Demographic and clinical characteristics of the study population ($N = 340$)

Variable	Controls ($N = 179$)	Cases ($N = 161$)	p^*
Age (years)	n (%)		
18–29	30 (16.8)	29 (18.0)	0.011
30–39	60 (33.5)	79 (49.1)	
≥ 40	86 (48.0)	48 (29.8)	
No information	3 (1.7)	5 (3.1)	
Marital status			
Married/partner	96 (53.6)	111 (68.9)	0.046
Single	53 (29.6)	38 (23.7)	
Divorced/Widow	5 (2.8)	1 (0.6)	
No information	25 (14.0)	11 (6.8)	
Level of Schooling			
Elementary education	38 (21.3)	24 (14.9)	< 0.001
High school	89 (49.7)	60 (37.3)	
Higher education	26 (14.5)	67 (41.6)	
No information	26 (14.5)	10 (6.2)	
BMI			
< 18.5	3 (1.7)	7 (4.4)	0.013
18.5–24.9	48 (26.8)	48 (29.8)	
25–29.9	50 (27.9)	63 (39.1)	
30–40	65 (36.3)	35 (21.7)	
> 40	13 (7.3)	8 (5.0)	
Infertility			
Primary	19 (10.6)	53 (32.9)	< 0.001
Secondary	3 (1.7)	16 (9.9)	
None**	133 (74.3)	58 (36.1)	
No attempt	20 (11.2)	32 (19.9)	
No information	4 (2.2)	2 (1.2)	
Parity			
0	19 (10.6)	53 (32.8)	< 0.001
1	23 (12.8)	37 (23.0)	
2	58 (32.5)	27 (16.8)	
3 or more	55 (30.7)	10 (6.2)	
No attempt	20 (11.2)	32 (20.0)	
No information	4 (2.2)	2 (1.2)	
Symptoms***			
Dysmenorrhea	29 (16.1)	77 (47.5)	< 0.001
Chronic pelvic pain	70 (38.9)	124 (76.5)	
Dyspareunia	50 (27.8)	102 (63.0)	
Cyclical urinary complaints****	9 (6.4)	41 (27.5)	
Cyclical intestinal complaints****	8 (6.0)	74 (49.7)	

Abbreviation: BMI, body mass index.
Notes: *p-value obtained by Pearson's Chi-squared ($\chi 2$) test. **Number of fertile women. ***The same woman can have more than one symptom. ****Pain or bleeding during the menstrual period.

distributions were compared between cases and controls by the $\chi 2$ test or Fisher's exact test. To evaluate the association between the SNPs and the development of endometriosis, as well as the presence of symptoms, the classification and staging of the disease were used to estimate the odds ratios (ORs) and their respective 95% confidence intervals (95% CIs), with adjustment for possible confounding factors, using a multivariate logistic regression. Values of $p < 0.05$ were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 20.0.

Results

The endometriosis cases were diagnosed through laparoscopy ($n = 90$, 55.9%), laparotomy ($n = 27$, 16.8%) or MRI ($n = 44$, 27.3%), and 87 (54%) were classified as DIE. Of the 117 surgery cases, 37 (31.6%) presented stages I-II diseases, and 80 (68.4%) presented stages III-IV. The most common locations of the endometriotic lesions were in the ovary (31%), followed by the intestine (19%), and the uterosacral ligaments (15%). The average age of the endometriosis patients at the time of diagnosis was 31.5 ± 7.5, and the average time for disease diagnosis, which was the time since the beginning of the symptoms until the definitive diagnosis, was 5.2 ± 6.9 years.

In ►**Table 1**, the demographic and clinical data from the study population are described. The patients with endometriosis were significantly younger than the controls (36.0 ± 7.3 versus 38.0 ± 8.5 respectively, $p = 0.023$), and presented a higher education level (41.6% versus 14.5%), as well as a lower BMI (26.3 ± 4.8 versus 27.9 ± 5.7 respectively, $p = 0.006$). The number of infertile women (primary or secondary) was significantly higher in the case group (42.9%) than in the control group (12.3%), and nearly 63% of the women from the control group had 2 or more children. The patients with endometriosis presented a higher prevalence ($p < 0.001$) of symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain, and urinary and intestinal changes. Considering the characteristics of the menstrual cycle, a significant difference was detected between cases and controls in relation to the average duration of the menstrual flow (7.4 ± 4.9 versus 6.1 ± 4.4 days respectively, $p = 0.03$) and the average interval between menstrual periods (25.2 ± 9.6 versus 27.5 ± 11.1 days respectively, $p = 0.05$).

When comparing the allelic and genotypic frequencies of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 G > A* between the cases and controls (►**Fig. 1**), no significant differences were detected, even when considering the staging and endometriosis classification (data not shown). The allelic distribution of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 G > A* in relation to the absence or presence of symptoms (dysmenorrhea, pelvic pain, dyspareunia, infertility, and urinary and intestinal problems, for example) in the endometriosis patients is summarized in ►**Fig. 2**. Considering the symptoms of the disease, no significant differences were found.

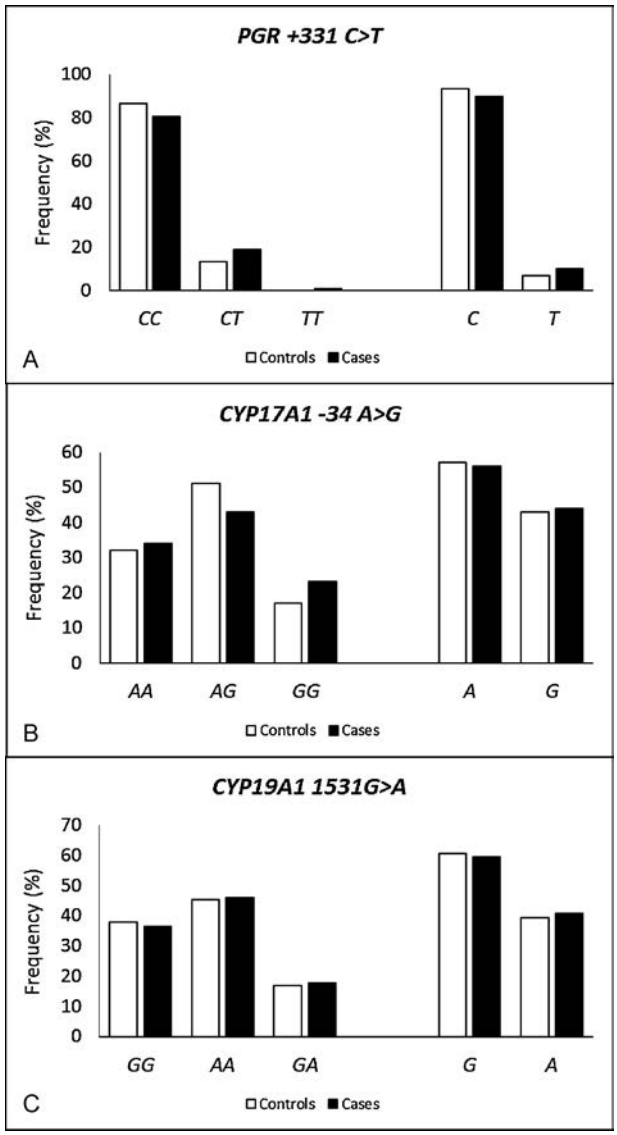

Fig. 1 Allelic and genotypic frequencies of the polymorphisms *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 G > A* in the study population.

A combined analysis of the three studied SNPs (*PGR +331C > T, CYP17A1 -34A > G* and *CYP19A1 G > A*), compared between the endometriosis cases and controls, was performed to investigate whether the presence of more than 1 SNP would increase the risk of developing the disease (►**Table 2**). It has been observed that relative to the combined wild-type genotype (*PGR +331CC*/*CYP17A1 -34AA*/*CYP19A11531GG*), the combined genotype *PGR +331TT*/*CYP17A1 -34AA*/*CYP19A11531AA* is associated with an increased risk of developing endometriosis. A combined analysis of the *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 G > A* genotypes was also performed in relation to the absence or presence of symptoms (dysmenorrhea, pelvic pain, dyspareunia, infertility, and urinary and intestinal problems, for example) in the endometriosis patients. However, no significant differences were found (data not shown).

In ►**Table 3**, we describe the variant allele frequencies of the SNPs *PGR +331 T*, *CYP17A1 -34 G* and *CYP19A1A* in

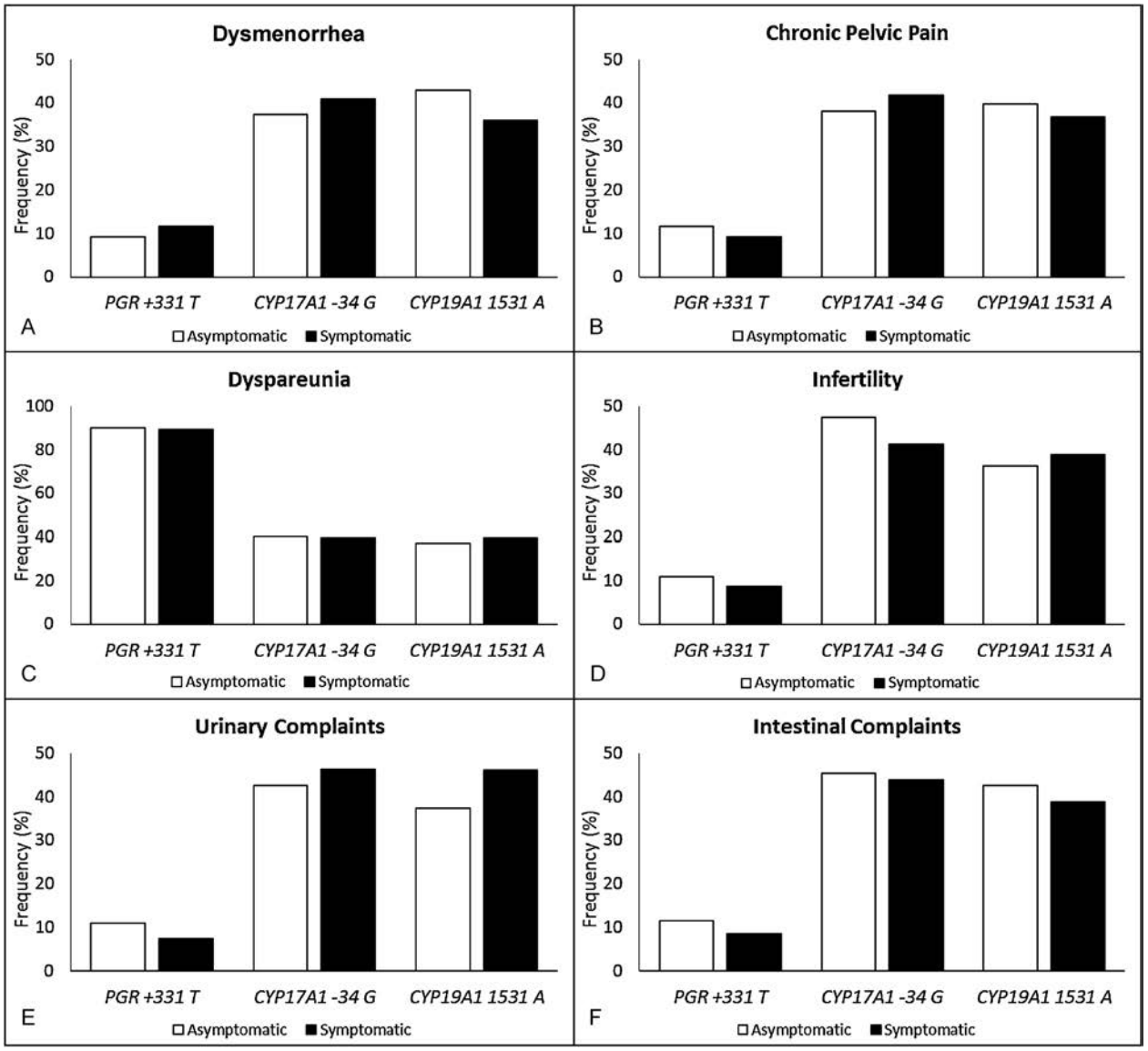

Fig. 2 Minor allelic frequencies of the polymorphisms studied among symptomatic and asymptomatic endometriosis patients.

different populations. The allele frequency *PGR +331 T* varied between 2% and 10% and 5% and 10% in the cases and controls respectively, based on 3 studies that have evaluated this SNP, including the present one. The SNP rs743572 has been evaluated in 7 studies, in addition to the present study, and the frequency of the *CYP17A1 -34 G* allele varied between 35% and 58% in the cases and between 31% and 63% in the controls. In addition to our study, 4 other studies also evaluated the SNP rs10046, and the allele frequency of *CYP19A1 1531A* varied between 35% and 58% and between 41% and 60% in the cases and controls respectively.

Discussion

Endometriosis is a complex multifactorial gynecological disease caused by the combination of hormonal, genetic and environmental factors, as well as immunological processes. Estrogen and progesterone are essential in the regulation of endometrial tissue growth, and, as such, they may play a central role in the pathogenesis of endometriosis.[5,6] In this study, a positive association between the combined genotype *PGR +331TT/CYP17A1 -34AA/CYP19A1 1531AA* and the development of endometriosis was observed.

Supporting our results, neither Lamp et al,[18] in Estonia, nor Trabert et al,[19] in the United States, could find an association with only the *PGR +331T* allele. However, van Kaam et al,[15] in the Netherlands, observed a protective effect (OR = 0.22; 95%CI = 0.06–0.77) for the development of endometriosis. In agreement with our findings, 5 studies from China,[13] Japan,[10] Turkey,[17] Italy[16] and the United States[19] failed to observe an association between the SNP *CYP17A1 -34G* and endometriosis. However, 2 studies in the Chinese population[11,12] found a positive association between endometriosis and the *CYP17A1 -34A* allele ($p = 0.046$ and $p = 0.009$). With relation to the SNP *CYP19A1 1531G > A*, none of the studies found an association with endometriosis,

Table 2 Combined genotype frequencies of the polymorphisms *PGR +331C > T, CYP17 -34A > G* and *CYP19 1531G > A* between controls and cases, and their association with the risk of endometriosis

Genotypes	Controls N (%)	Cases N (%)	*p* *	OR (95%CI)**
PGR +331C > T, CYP17 -34A > G and *CYP19 1531G > A*				
WT / WT / WT	23 (13.5)	11 (7.3)		1***
WT / WT / VAR	29 (17.1)	28 (18.6)	0.20	1.82 (0.73–4.57)
WT / VAR / VAR	70 (41.2)	60 (40.0)	0.17	1.35 (0.88–2.05)
VAR / WT / WT	2 (1.2)	4 (2.7)	0.18	1.57 (0.82–3.00)
VAR / VAR / WT	7 (4.1)	10 (6.7)	0.20	1.23 (0.90–1.67)
VAR / WT / VAR	1 (0.6)	7 (4.7)	0.02	1.72 (1.09–2.72)
WT / VAR / WT	25 (14.7)	22 (14.7)	0.15	1.13 (0.96–1.34)
VAR / VAR / VAR	13 (7.6)	8 (5.3)	0.87	1.02 (0.85–1.21)

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.
Notes: WT/WT/WT, *CC/AA/GG*; WT/WT/VAR, *CC/AA/GA* or *CC/AA/AA*; WT/VAR/VAR, *CC/GG/AA* or *CC/AG/GA* or *CC/AG/AA* or *CC/GG/GA*; VAR/WT/WT, *CT/AA/GG* or *TT/AA/GG*; VAR/VAR/WT, *CT/AG/GG* or *CT/GG/GG* or *TT/AG/GG* or *TT/GG/GG*; VAR/WT/VAR, *CT/AA/GA* or *CT/AA/AA* or *TT/AA/GA* or *TT/AA/AA*; WT/VAR/WT, *CC/GG/GG* or *CC/AG/GG*; VAR/VAR/VAR, *TT/GG/AA*; *p-value obtained through the Chi-squared test (Pearson *P*-value) or Fisher's exact test. **Adjusted by age and BMI. ***Reference group.

Table 3 Frequency of the studied polymorphisms among different populations (endometriosis patients and controls)

Polymorphism	Population	N*	Frequency among the controls (%)	Frequency among the cases (%)	Association with endometriosis	Reference
PGR +331 C > T (rs10895068)			*PGR +331 T*			
	Estonia	349	8.8	6.7	No association	Lamp et al[18]
	United States	823	4.8	5.1	No association	Trabert et al[19]
	Netherlands	165	9.7	2.3	Protective (T allele)	van Kaam et al[15]
	Brazil	179	6.6	10.1	No association	Present study
CYP17A1 -34 A > G (rs743572)			*CYP17A1 -34 G*			
	Turkey	93	30.8	57.6	No association	Bozdag et al[17]
	China	247	60.2	50.8	Risk (A allele)	Hsieh et al[11]
	China	227	62.9	50.8	Risk (A allele)	Hsieh et al[12]
	China	510	54.3	58.2	No association	Juo et al[13]
	Japan	317	39.8	42.9	No association	Kado et al[10]
	United States	823	39.3	34.8	No association	Trabert et al[19]
	Italy	190	37.2	42.3	No association	Vietri et al[16]
	Brazil	180	42.7	44.4	No association	Present study
CYP19A1 1531 G > A (rs10046)			*CYP19A1 1531 A*			
	Korea	412	55.9	55.8	No association	Hur et al[14]
	Estonia	349	59.8	55.0	No association	Lamp et al[18]
	China	371	56.4	57.5	No association	Wang et al[20]
	China	202	41.0	35.3	No association	Yang et al[21]
	Brazil	180	39.4	40.6	No association	Present study

Abbreviations: CYP17A1, cytochrome P450 17A1; CYP19A1, cytochrome P450 19A1; PGR, progesterone receptor.
Note: *N total number of individuals included in the study (cases + controls).

which is similar to our results.[14,18,20,21] To date, no study has investigated the combined effect of the SNPs *PGR +331TT*/*CYP17A1 -34AA/CYP19A1 1531AA* on the development of endometriosis.

The strength of the present study is that it is the first study performed in the Brazilian population that evaluated the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* in terms of endometriosis development, while considering the symptoms of the disease. All control patients were surgically evaluated to confirm a negative diagnosis of endometriosis; 27% of them had previously undergone sterilization, and 63% had already had 2 or more children. A limitation of this study was that the controls also included women with other gynecological diseases, providing lower risk estimations. Furthermore, considering the endometriosis patients, 27% were diagnosed by MRI. However, this has been a specific and accurate method for the detection of deep endometriosis.[25–28]

In conclusion, the combined analysis of the polymorphisms *PGR-CYP17A1-CYP19A1* suggests a gene-gene interaction in the susceptibility to endometriosis. The results may contribute to the identification of genetic biomarkers that are able to help in disease diagnosis and/or prognosis, as well as in the identification of possible molecular targets for individualized treatments.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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What do Infertile Women Think about Oocyte Reception, Oocyte Donation, and Child Adoption?

O que as mulheres inférteis pensam em relação a ovo recepção, doação de oócitos e adoção de crianças?

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Abstract

Purpose The views of infertile couples regarding oocyte donation by third parties and adoption are unknown, as these may be interpreted as a final closure of the available options for conception. This study aimed to determine the acceptance of oocyte donation, oocyte reception, and child adoption of infertile women who submitted to assisted reproductive technology (ART) treatment

Methods Sixty-nine women who were under treatment for infertility and submitted to ART procedures were included in this cross-sectional study. They were evaluated using semi-structured questionnaires administered during ovulation induction in a treatment cycle. Marital status, religion, years of schooling, occupation, type of infertility, age, duration of infertility, number of previous ART cycles, mean oocyte number per cycle, and mean number of embryos per cycle had no influence on a woman's acceptance of oocyte donation or oocyte reception.

Results More than 90% of the patients thought that the subject of "adoption" should be brought up during their ART treatments, although they preferred to discuss this topic with psychologists, not doctors. Women with occupations were more willing to consider adoption.

Conclusion The opinions of these patients on these issues seem to be based on personal concepts and ethical, religious, and moral values. Women preferred to discuss adoption with psychologists rather than doctors.

Keywords
- marital infertility
- oocyte donation
- adoption
- reproduction

Resumo

Objetivo Não se sabe ao certo o que os casais inférteis acham sobre doação de óvulos por terceiros e adoção, condições estas que podem ser interpretadas como um encerramento definitivo das opções disponíveis para concepção. Este estudo teve como objetivo determinar a aceitação da doação de oócitos, ovo recepção e adoção de crianças por mulheres inférteis submetidas a tratamento de reprodução assistida (RA).

Métodos Sessenta e nove mulheres em tratamento para infertilidade e submetidas a procedimentos de RA foram incluídas neste estudo transversal. Elas foram avaliadas por

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meio de questionários semiestruturados administrados durante a indução da ovulação em um ciclo de tratamento.

Resultados O estado civil, religião, escolaridade, ocupação, tipo de infertilidade, idade, duração da infertilidade, número de ciclos de RA anteriores, o número médio de oócitos por ciclo e de embriões por ciclo médio não tiveram influência sobre a aceitação da doação ou da recepção de oócitos. Mais de 90% das mulheres acha que o tema "adoção" deve ser discutido durante o tratamento de RA, porém preferem discutir este tema com psicólogos, e não com médicos. As mulheres com ocupações foram mais predispostas a considerar a adoção.

Conclusão As opiniões destas pacientes sobre estas questões parecem ser baseadas em conceitos pessoais e valores éticos, religiosos e morais. As mulheres preferiam discutir a adopção com psicólogos, em vez de médicos.

Palavras-chave
- infertilidade conjugal
- doação de oocitos
- adoção
- reprodução

Introduction

The worldwide incidence of couple infertility, which ranges from 3.5% to 16.7% in developed countries and from 6.9 to 9.3% in less-developed countries,[1] has been increasing in recent decades. Many men and women currently opt to postpone pregnancy because of professional or other responsibilities,[2] but fertility is currently a concern of many women who seek counseling regarding the postponement of pregnancy.[3] Advanced age has a negative impact on female fertility,[4] although other factors may also cause infertility in women (for example, malformations of the genital tract, infectious processes, endometriosis, myometrial and endometrial injuries, ovarian, pituitary or thyroid factors) and in men.

Many factors may cause infertility in men, and idiopathic oligoasthenoteratozoospermia (IO) is present in up to 30% of infertile men. Such condition may be linked to age, noninflammatory functional alterations in post-testicular organs, infective agents, alterations in gamete genome, mitochondrial alterations, environmental pollutants, and hormonal alterations.[5]

Infertile couples increasingly seek assisted reproduction (AR), although these services are not within reach of all couples, especially those in developing countries. Thus, fewer than 25% of infertile persons receive AR treatment worldwide.[1] When AR is not possible, or if AR fails, there are other resources such as a surrogate uterus, oocyte or embryo donation, and child adoption.[6]

Oocyte donation has been used since the 1980s,[7–9] and the results are comparable to those of patients who use their own oocytes in terms of the rate of embryo implantation, birth weight, gestational age at birth, perinatal mortality, and lactation.[10] Oocyte donation is indicated when there is premature ovarian failure, genetic anomalies with possible hereditary transmission, repeated failure of in vitro fertilization, poor response to ovarian stimulation, repeated spontaneous abortions,[11] and in other conditions. In some countries, restrictions limit the access to oocyte donation.[12] In countries where oocyte donation is widespread, there are ethical concerns about the possible abuse of donation by poor women. In addition, potential donors may falsify their health records to be accepted into these programs, and this may increase the risk of transmission of infectious diseases and hereditary defects. However, some research suggests that the characteristics of oocyte donors does not depend on remuneration.[13]

Adoption is another alternative that couples for whom AR treatment has failed should consider. However, adoption should not be seen as a treatment of infertility, but rather as an option for infertile couples who wish to be parents.[14] In Brazil, ~ 35% of all adoptions are sought by infertile couples.[15] In the United States, men tend to seek adoptions after they have already used infertility services and women tend to seek adoptions at the end of their reproductive periods and after unsuccessful AR treatment.[16] However, adoption may not satisfy a couple if they wish the physical experience of pregnancy, birth, and breastfeeding. Such couples may instead opt for gamete donation (GD). Indeed, many couples must decide between GD and adoption. For many couples, the reasons for choosing GD rather than adoption range from the practical to the emotional, and include the perceived negative aspects of adoption and perceived advantages of GD.[17] There is limited literature about the impact of different treatment approaches for couples who experience repeated AR failures. The views of these couples regarding oocyte donation by third parties and adoption are unknown, and these may be interpreted as a final closure of the available options.

In view of the limited research on this topic, the objective of the present study was to determine the acceptance of oocyte donation, oocyte reception, and child adoption of infertile women who submitted to AR treatment.

Methods

This cross-sectional study consecutively enrolled women who were under treatment for infertility and submitted to AR procedures in the Laboratory of the Sector of Human Reproduction, Department of Gynecology and Obstetrics, at the Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), over a period of 6 months (2013 to 2014). The women were recruited by a female gynecologist during the process of cycle monitoring for AR.

All women responded to a semi-structured questionnaire that had 14 questions about sociodemographic and clinical data. The questionnaire had open questions, and questions with optional replies or with the possibility of more than one reply regarding oocyte donation, oocyte reception, and adoption. The assayed sociodemographic characteristics included marital status (married, cohabiting, or single), religion (Catholic, Evangelical, Spiritualist, other), years of study in school (8, 12, or 17), and working status (remunerated worker or housewife). The type of infertility was classified as primary or secondary.

The questionnaire used to assess women's feelings and decisions on oocyte donation, oocyte reception, and child adoption contained the questions listed in ►**Table 1**.

The questionnaires were administered before the beginning of the AR cycle or during ovarian induction. This was predominantly a qualitative investigation. This study was approved by the Research Ethics Committee of the University Hospital, FMRP-USP, and all patients gave written informed consent to participate.

Statistical Analysis

The patients were divided into groups according to their responses (yes or no) to the following variables: oocyte donation, oocyte reception, and child adoption. The influences of sociodemographic and clinical characteristics on the responses to these questions were determined.

The Fisher exact test was used to determine the association between two qualitative variables using the PROC FREQ feature of SAS® 9.0 (Cary, NC, USA). The nonparametric Mann-Whitney test for independent samples (Conover, 1981) was used to compare two groups in terms of quantitative variables using the PROC NPAR1WAY feature of SAS® 9.0 (Cary, NC, USA). The level of significance was set at $p < 0.05$ in all analyses.

Results

We invited 112 women to participate in the study. Forty-three women refused to participate without stating the reasons for their decisions. Thus, 69 women (mean age: 34.5, SD: 4.2 years, range: 23–44 years) were included in the study (►**Table 2**).

Among the 69 participants, 4 (5.79%) had never heard about oocyte donation and 32 (46.4%) were not willing to donate their oocytes. Among these 32 patients, 21 (65.6%) stated they did not want other women to carry their biological offspring, 8 (28.12%) stated that they did not know the details of the technique and its implications, and 3 (6.25%) did not approve of the technique for religious reasons.

Marital status ($p = 0.99$), religion ($p = 0.49$), years of schooling ($p = 0.87$), occupation ($p = 0.50$), and type of infertility (primary versus secondary) ($p = 0.79$) had no influence on the decision to donate oocytes.

Table 1 Semi-structured questionnaire used to assess women's acceptance of oocyte donation, oocyte reception, and child adoption

Questions	Responses
Have you heard about oocyte donation previously?	Yes/no
Would you donate your oocytes?	Yes/no
If the response was "no" to the previous question, then why?	Religious factors/do not want children that are not mine to carry my genetic load/I am not familiar with the technique and its implications/others
If you are unsuccessful in your attempts at ICSI, would you accept the oocytes of a donor?	Yes/no
Why?	
If you became pregnant, would you donate your oocytes to another patient?	Yes/no
Have you ever thought about adoption?	Yes/no
Have you talked to your partner about adoption?	Yes/no
In your opinion, when should adoption be considered?	Never/after 1 attempt to treat infertility/after 2 attempts to treat infertility/after 3 attempts to treat infertility/after 4 or more attempts to treat infertility/only after entering menopause/when there are no more financial resources for treatment of infertility/when there are no more emotional resources for treatment of infertility/others
Do you think the health team that assists you during your AR treatment should discuss the topic of adoption?	Yes, always/no, always/only if the couple asks
If you answered yes to the previous question, respond to the next two questions	
When is the best time to discuss the possibility of adoption?	During the first visit/after a first treatment failure/after repeated treatment failures (state how many)
Who do you think should approach this topic?	Doctor/nurse/psychologist/other

Abbreviations: AR, assisted reproduction; ICSI, intracytoplasmic sperm injection.

Table 2 Characteristics of women undergoing assisted reproduction techniques who would donate oocytes, receive oocytes, and thought about adoption ($N = 69$)

Variable	Would donate oocytes?			Would receive oocytes?			Thought about adoption?		
	Yes ($N = 32$)	No ($N = 37$)	*p*	Yes ($N = 29$)	No ($N = 40$)	*p*	Yes ($N = 59$)	No ($N = 10$)	*p*
	Mean ± SD								
Age (years)	33.95 ± 4.42	34.81 ± 3.99	0.51	33.90 ± 4.71	34.68 ± .79	0.61	34.46 ± 4.20	33.70 ± 4.22	0.46
Years of infertility	5.88 ± 4.35	4.91 ± 2.73	0.77	6.43 ± 4.68	4.69 ± 2.61	0.37	5.67 ± 3.88	4.00 ± 1.91	0.37
N° of previous cycles	0 (0–1)	1 (0–1)	0.53	1 (0–1)	0 (0–1)	0.75	1 (0–1)	0 (0–1)	0.58
Oocytes in previous cycles	4.51 ± 4.90	7.86 ± 5.27	0.08	4.09 ± 3.24	8.01 ± 6.00	0.10	6.13 ± .99	7.42 ± 8.02	0.84
Embryos in previous cycles	2.21 ± 2.60	3.56 ± 3.03	0.24	2.16 ± 1.73	3.53 ± 3.14	0.35	2.82 ± 2.42	3.71 ± 4.50	0.99

Abbreviations: N, number; p, p-value; SD, standard deviation

A comparison between the women who said they would and the ones who said they would not donate oocytes indicated no significant differences in age, time of infertility, number of previous AR cycles (IVF and/or ICSI), mean number of oocytes retrieved per cycle, and mean number of embryos formed per cycle (►**Table 2**).

Forty of the 69 women (58.0%) stated that they would not receive oocytes from a donor and 10 (14.49%) said they did not think about adoption, even after unsuccessful treatment with their own oocytes. Comparisons between the women who said they would and the ones who said they would not receive oocytes and between the women who said they would or would not consider adoption also indicated no significant differences in age, time of infertility, number of previous cycles, number of oocytes obtained in previous cycles, or number of embryos formed (►**Table 2**).

Marital status, religion, amount of schooling, occupation, and type of infertility (primary or secondary) had no influence on the consideration of adoption in either subgroup, although women who worked outside the home thought about adoption more than those who were housewives ($p = 0.03$) (►**Fig. 1**).

Fifty-nine of the 69 women (85.51%) had already thought about adoption and discussed the topic with their partners, but only 5 (8.47%) were willing to adopt, and 54 (91.5%) stated that they would adopt only in the case of AR failure.

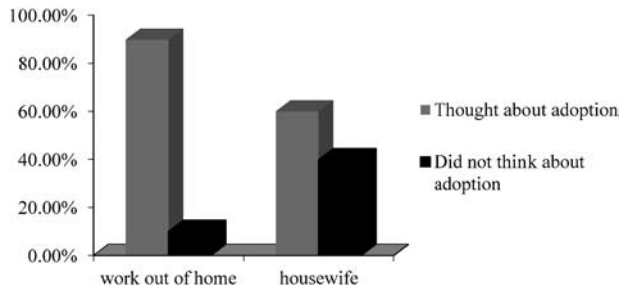

Fig. 1 Percentage of women receiving assisted reproduction techniques (ART) who worked outside the home or were housewives and considered adoption of a child.

Five (7.24%) women stated they would never consider adoption, 37 (53.6%) stated that adoption should always be considered, and 27 (39.1%) that it should be considered only when questioned by a professional. Among patients who said that adoption should be considered, 15 (23.4%) responded that a doctor should approach them on this topic, 10 (15.6%) that doctors and psychologists should jointly approach them on this topic, and 39 (60.93%) that only a psychologist should approach them on this topic.

Discussion

The objective of the present study was to evaluate the characteristics of women undergoing AR treatment regarding their acceptance of oocyte donation, oocyte reception, and child adoption and to determine the preferences of these women regarding which health professional should discuss the topic of adoption. The results demonstrated that almost half (46.4%) of the study population would not donate oocytes, mostly (65.6%) because they did not want another woman to carry their genetic offspring. None of the assessed sociodemographic or clinical characteristics of these patients was significantly associated with a willingness to donate oocytes. Most women's opinions on these matters were exclusively based on personal concepts of an ethical, religious, or moral nature. The women's most frequently mentioned reason for an unwillingness to donate oocytes is that they did not want another woman to carry their genetic offspring.

In the US, government regulations regarding oocyte donation focus on the dissemination of infectious diseases and rates of successful reproduction, and do not consider the psychological aspects of women undergoing the procedure.[18] However, previous studies have examined the ethical, economic, and psychological aspects of oocyte donation and reception.[19] A study of oocyte sharing in a sample of 48 donors and 38 recipients indicated that donors and recipients expressed divergent feelings. Some women maintained positive reciprocal feelings and were willing to keep a future relationship with their counterparts, but others did not intend to maintain this relationship and did not wish to learn about the results of the

conception.[20] Another study of couples stated that oocyte recipients preferred not to know about the origin of the oocytes, so that the child would be raised according to the family standards of the recipient.[21] Although most oocyte recipients do not think about the biological origins of their babies, oocyte donors frequently think about the babies born from their donated oocytes, whether these children are loved, if they have characteristics of the donors, and if they are happy.[19] Some women also express negative feelings about their biological child belonging to another person.[20] In our study, the second most frequent reason for not donating oocytes is a lack of knowledge about the technique and its implications. This suggests that educational measures that provide information about oocyte transfer and its implications during initial treatment would be useful to support the recruitment of potential oocyte donors.

An interesting finding of the present study is that women who received a larger number of oocytes or embryos in previous cycles did not favor the option of oocyte donation. On the contrary, women with a smaller number of oocytes in previous cycles were more likely to donate oocytes although this difference was not statistically significant. During our interviews on oocyte donation, some women stated that "they would donate because, like many other women, it was their dream to be a mother," or "they would donate to help women with the same wish as theirs to be mothers," or "they would donate to help a woman who is in the same situation as theirs."

When asked if they would receive donated oocytes, 53.0% of our women responded they would not because the child would not be their biological child, and that they would prefer to adopt. Karpel et al[22] reported contrary results in 2007. In that study, women who wanted to receive oocytes sought to have the experience of pregnancy, delivery, and breastfeeding above anything else. The possibility of semen being from the biological father may contribute to this decision, because both partners would play a role in conception. A previous study demonstrated that parents of children from female or male gametes think less about these children not being their biological children than the parents of adopted children.[23]

Most of the characteristics that we examined in the couples undergoing AR treatment were unrelated to the contemplation of adoption as an alternative to conception. However, women who held paying jobs thought more about adoption than women who were housewives. Previous studies demonstrated that women with a remunerated job who are able to develop a maternal role of good quality had better psychological well-being, although they were more susceptible to the stress associated with overwork.[24,25] Further research is needed to determine the reasons why housewives think less about adoption than working women. It may be that housewives create expectations about a family in which their ability to gestate and generate children is a key part of their primary role in their relationship.

In the present study, although patients who considered adoption as an option had already discussed it with their partners, only a small proportion of them (8.47%) appeared ready for adoption according to the questionnaire. Jones[16] reported that 84.5% of couples who opt for AR procedures think about adoption when they are informed that they are infertile, 29% initiate the adoption process, but only 18% really intend to adopt a child. Most couples do not wait for counseling with their doctors to become interested in adoption, but they need to hear that there are really no chances of successful AR treatment before they become interested in adoption.[22] This suggests that most patients seek successful AR, greatly wishing to obtain personal and/or social proof that they can generate a child. It is not simply the wish to be a mother, but the gestation of a baby that seems to play a fundamental role in this objective. In this respect, MacCallum[23] reported that the parents of children obtained by embryo donation (similar to oocyte donation) can more readily accept that their children are not biologically related than the parents of adopted children.[23] Thus, embryo or GD can be considered to be an important alternative to adoption. In the present study, most women stated that they only considered adoption as a possibility in cases of repeated treatment failure or when the financial or emotional resources involved in AR treatment were exhausted.

When the women were asked about being approached by a professional regarding adoption, most stated that the subject should be approached at some time (92.8%), but many (39.1%) felt that the subject should only be discussed when brought up by the patient. Most patients who thought that the topic should be discussed (60.9%), also thought that it should be raised by a psychologist. This may be because they believe psychologists are better equipped to approach the complex and conflicting topics regarding adoption or perhaps because discussion of this matter with a doctor may suggest to them that it is a "last option."

There are no well-established criteria in the literature about when a woman should consider the impossibility of gestation and stop AR treatment. This decision, which in principle should be made by the doctor, is somewhat subjective, and usually causes anguish and discomfort to the doctor. Although adoption is not a treatment for infertility, it is an option for couples who wish to have a child and may improve the quality of their lives.[26]

Conclusion

No previous studies have identified the clinical or demographic characteristics of women who would donate their oocytes, who would receive oocytes from another woman, or who would adopt a child. Instead, these decisions appear to be based on individual experiences and opinions. However, women who held jobs outside the home were significantly more likely to accept adoption than housewives.

Most of our patients thought that the topic of adoption should be mentioned during the AR treatment, although almost half of them believed that the patient herself–not the professional team – should begin discussion of this topic. About 60% of the patients stated that they preferred to discuss the topic of adoption with a psychologist without the participation of a doctor.

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Evaluation of the p16 and Ki-67 Biomarkers as Predictors of the Recurrence of Premalignant Cervical Cancer Lesions after LEEP Conization

Avaliação dos biomarcadores p16 e Ki-67 como preditores de recidivas de lesões pré-cancerígenas do colo do útero após conização por cirurgia de alta frequência

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Abstract

Objective To evaluate the expressions of biomarkers p16 and K_i-67 in low-grade (LG) or high-grade (HG) lesions, and to relate them to risk factors and the recurrence of these lesions.

Methods A retrospective case-control study of 86 patients with LG and HG lesions who underwent a loop electrosurgical excision procedure (LEEP) between 1999 and 2004. The control group was composed of 69 women with no recurrence, and the study group, of 17 patients with recurrence. All patients were followed-up over a two-year period after surgery, and screened every six months, including cytology and colposcopy. Biopsy samples collected from LEEP were submitted to immunohistochemical analysis for p16 and K_i-67. The statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, IBM-SPSS, Inc., Chicago, IL, US), with a significant $p < 0.05$.

Results The biomarkers p16 and K_i-67, separately or combined, showed no relation to recurrence on the total analysis. However, evaluating specifically HG lesions, the positive expression (2+ and 3 +) of p16/K_i-67 was associated with recurrence (0.010). In addition, p16 isolated was also more expressive in HG lesions (2+ and 3 + , $p = 0.018$), but it was unrelated to recurrence.

Conclusion Proteins p16 and K_i-67, both isolated and combined, are not reliable primary markers for the recurrence of cervical lesions in the majority of LG lesions. However, analyzing only the group with prior diagnosis of HG lesions, the expressions of p16 and of p16/K_i-67 were associated with recurrence, and they may be useful in monitoring these cases.

Keywords
- biomarkers
- conization
- cervical intraepithelial neoplasia
- recurrence

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Resumo

Objetivo Avaliar as positividades dos biomarcadores p16 e K_i-67 em lesões de baixo grau (BG) ou de alto grau (AG), e relacioná-las com os fatores de risco e com a recidiva dessas lesões.

Métodos Estudo retrospectivo caso-controle, com 86 pacientes com lesões de BG e AG, submetidas à conização por cirurgia de alta frequência entre 1999 e 2004. O grupo de controle foi constituído de 69 mulheres sem recidivas, e o grupo de estudo, de 17 pacientes que recidivaram. Todas as pacientes foram acompanhadas durante dois anos após a cirurgia, com controle a cada seis meses, incluindo citologia e colposcopia. As peças provenientes de cirurgia de alta frequência (CAF) foram submetidas a imunohistoquímica para p16 e K_i-67. A análise estatística foi realizada com o programa Statistical Package for the Social Sciences (SPSS, IBM-SPSS, Inc., Chicago, IL, EUA), com p significante quando $< 0,05$.

Resultados Isoladamente ou em conjunto, p16 e K_i-67 não se relacionaram com as recidivas quando analisados na totalidade dos casos. Entretanto, avaliando especificamente as lesões de AG, a positividade (2+ e 3 +) do conjunto p16/K_i-67 foi relacionada com recidiva (0,010). No mais, p16, isoladamente, foi também mais expresso nas lesões de AG (2+ e 3 + , $p = 0,018$), mas sem relação com recidiva.

Conclusão Quando testadas na totalidade dos casos, as proteínas p16 e K_i-67, separadas ou em conjunto, se mostraram ineficientes como marcadores primários de recidiva de lesões precursoras. Entretanto, quando avaliadas somente no grupo diagnóstico prévio de lesão de AG, as expressões das proteínas p16 e p16/K_i-67 têm relação com a recidiva, e podem ser úteis no acompanhamento desses casos.

Palavras-chave

- biomarcadores
- conização
- neoplasia intraepitelial cervical
- recidiva

Introduction

The search for markers to facilitate the diagnosis of diseases is a constant in scientific research to save resources, time and to prevent unnecessary treatments. Cervical cancer is the most common cancer among women in 45 countries of the world and, worldwide, 266 thousand women die of it each year;[1] it is preceded by cervical lesions that may or may not progress to invasion. They are associated with infection and with the persistence of the human papillomavirus (HPV) to progress to invasive carcinoma.[2] Through this process, the cells infected with high-risk oncogenic HPV alter the cell cycle, modifying the production of proteins p16 and K_i-67. The most common treatment for high grade (HG) lesions is cervical cone resection using the loop electrosurgical excision procedure (LEEP). A major concern of the treatment is the recurrence of the lesion, as it may reappear without symptoms and more severely.

Proteins p16 and K_i-67 are, respectively, cell progression and proliferation markers. Protein p16 is a tumor suppressor from the Ink4a family that induces the hyperphosphorylation of the retinoblastoma protein (pRb), and has low expression in normal tissues.[3] K_i-67 is a nuclear protein present in cells during the active proliferation stage, but it is not expressed when cells are in the quiescent state.[3] The expression of both molecules simultaneously already denotes some problem in the cell cycle.[4] The main objective of this study was to compare the expression of p16 and K_i-67, individually or combined, with the recurrence of cervical cancer precursor lesions after a LEEP procedure and, also, to verify whether other factors contributed to this.

Methods

The study was approved by The Ethics and Research Committee of Instituto de Ensino e Pesquisa, Santa Casa Belo Horizonte (no. 1.222.448), and only patients who agreed and signed the informed consent form (ICF) participated.

Sample Selection and Patient Monitoring

A total of 86 cases of cervical intraepithelial neoplasia (CIN) were evaluated, having been diagnosed by histopathology after LEEP surgery. The sample group was monitored from January 1999 to March of 2004 at a municipal healthcare center in the city of Belo Horizonte. All patients were re-evaluated every 6 months by oncotic cytology, colposcopy and cervical biopsy, when indicated, and followed-up during 2 years to assess whether or not there was lesion relapse.

The total sample of 86 patients consisted of 17 patients with CIN1, 11 with CIN2, and 58 with CIN3. Of the total, 17 presented lesion recurrence. The study group was composed of the 17 recurrences, and the control group, of the other 69 patients. Apart from the biomarkers, both groups were evaluated considering sociodemographic data, previous health status and histological variables.

Immunohistochemical Markers

To evaluate p16 and K_i-67 expression levels, immunohistochemistry was performed using monoclonal antibody MIB 1 (Dako) for the K_i-67 in the dilution of 1:100, and G175–405 (Zeta) in the dilution of 1:100 for the p16. Both antigens were detected using HiDef Detection System, HRP Polymer System (Cell Marque, Rocklin, USA). All immunohistochemical studies were performed in the laboratory of Instituto Moacyr Junqueira, in Belo Horizonte, according to standard protocols.

The readings were done by two independent examiners who classified the slides according to the percentage of positive cells, as described by Zhong et al[5] (►**Table 1**).

Statistical Analysis

Numerical variables were tested for normality (Kolmogorov-Smirnov test) and the Student's *t*-test was used in the calculations. At first, the analysis focused on the whole sample characteristics using tables of frequency for the categorical variables, and descriptive measures (mean, median, 25th and 75th percentiles, minimum-value, maximum-value and standard deviation) for the quantitative variables. Sociodemographic, health and histopathologic variables and their relationship with recurrence, p16 and K_i-67 positivity, the margin compromise in LEEP etc. were analyzed by the Chi-Square Test. When necessary, Fisher's Test was applied. In all tests, the significance level was of 5%. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM-SPSS, Inc., Chicago, IL, US) software, version 20.0.

Results

The sociodemographic variables evaluated were age, parity, first intercourse, number of partners and smoking. They were equally distributed in the two groups, and no statistical significance was detected.

The histological factors for glandular involvement and compromised surgical margins had increased expression in HG lesions ($p = 0.018$ and $p = 0.039$ respectively, ►**Table 2**). On the other hand, relevant associations with recurrence were found when evaluating the risk factors for human immunodeficiency virus (HIV) positivity (odds ratio [OR]: 0.31; 95% confidence interval [95%CI]: 0.135–0.937; $p = 0.033$) and glandular involvement in cervical lesions (OR: 4.44; 95%CI: 1.40–14.06; $p = 0.019$). Data are listed on ►**Table 3**.

When the expressions of p16 and K_i-67, isolated or combined, were evaluated considering the same risk factors, disregarding the presence or absence of recurrence, a significant correlation was only found on p16 positive in HG lesions (OR: 4.713; 95%CI: 1.091–20.23; $p = 0.018$, ►**Table 4**).

Specifically analyzing HG lesions that were p16/K_i-67 positive (2+ and 3 +), comparing the presence/absence of recurrence, a significant difference was found (OR: 0.19; 95% CI: 0.054–0.662; $p = 0.010$); however the percentage of positive cells was higher in the HG group with no recurrence. The other variables were not significant (►**Table 5**).

Table 1 p16 and K_i-67 positivity according to the percentage of positivity

Marker	Negative	Low positive	Moderately positive	High positive
		+1	+2	+3
p16*	< 5%	5–25%	26–50%	> 50%
K_i-67**	< 5%	5–25%	26–50%	> 50%

Notes: *Nuclear and cytoplasmic markers; **nuclear marker. Source: Zhong et al.[5]

Table 2 Relationship between lesion grade and histological risk factors

Lesion grade		Low grade	High grade	*p*
		n (%)	n (%)	
GI	Yes	0 (0)	19 (22.9%)	0.018
	No	15 (18.1)	49 (59)	
PM	Yes	1 (1.7)	1 (36.2)	0.039
	No	10 (17.2)	26 (46.8)	

Abbreviations: GI, glandular invasion; PM, positive margins.

Discussion

Most studies with biomarkers are limited to the correlation between percentage positivity and the presence and grading of pre-invasive lesions; nonetheless, few relate them to the recurrence of these lesions.[6] No literature was found with the same specific characteristics of this study. Therefore, the findings of this study were compared with each risk factor for which the markers were measured.

The group sample had a significant number of HIV+ patients (31.4%), and it is known that this pathology is directly related to CIN recurrence, mainly when there is a decrease in CD4 + , indicating low immunity and a poor control of the disease.[7–9] In the present study, it was observed that HIV+ women had a higher recurrence of CIN than HIV- women (52.9% and 26.1% respectively; $p = 0.033$). This finding is similar to that of Pantanowitz,[10] who found 50% recurrence rates for high-grade squamous intraepithelial lesion (HSIL) and 75% for low-grade squamous intraepithelial lesion (LSIL) over a 6-month period evaluation. Russomano et al[11] reported similar results, suggesting that CIN recurrence is 42% higher in HIV+ women. Tebeu et al[8] described the same findings in a meta-analysis study that evaluated the number of CIN recurrences in HIV+ women undergoing LEEP with clear surgical margins, in which the recurrence rate was of 20–75%. As in this study, they concluded that the presence of the HIV is a risk factor for CIN recurrence, even in the absence of any other important factors, such as compromised margins.

There was no significant increase of p16 expression in HSIL in women who were HIV+ compared with those who were

Table 3 Relationship between risk factors and recurrence of CIN

Variables		Cases n (%)	Recurrence n (%)		*p*
			Yes	No	
HIV	Negative	59 (68.6)	8 (9.3)	51 (59.3)	0.033*
	Positive	27 (31.4)	9 (10.5)	18 (20.9)	
Lesion grade	LG	17 (19.8)	3 (3.50)	14 (16.3)	1.000
	HG	69 (80.2)	14 (16.3)	55 (64)	
Glandular invasion	Yes	19 (22.1)	8 (9.6)	11 (13.3)	0.019 **
	No	64 (74.4)	9 (10.8)	55 (66.3)	
Positive margins	Yes	22 (25.5)	8 (13.8)	14 (24.1)	0.089
	No	36 (41.9)	6 (10.3)	30 (51.7)	

Abbreviations: CIN, cervical intraepithelial neoplasia; HIV, human immunodeficiency virus; LG, low-grade; HG, high-grade.
Notes: *OR: 0.31; 95%CI: 0.135-0.937; **OR: 4.44; 95%CI: 1.40–14.06.

HIV-, and that corroborates the findings of Nicol et al.,[12] who reported that the co-infection of HPV/HIV may result in alterations in the cervical cytokine profile, including factors such as interleukin-6, resulting in the decreased expression of p16. Although seropositivity for HIV has been proved to be a risk factor for recurrence,[10,13–15] the cervical lesions that recurred have not expressed more biomarkers in HIV+ women than in HIV- women ($p = 0.424$), showing that the markers cannot demonstrate if HIV+ women are more prone to recurrence.

Kodampur et al,[16] in a cohort study of 309 women with high-grade CIN who underwent LEEP, confirmed the increased need for further intervention when there was endocervical glandular involvement ($p = 0.024$), which is similar to our findings. Glandular involvement is closely related to HSIL,[17] and it was positively related to recurrence in the samples ($p = 0.019$), which corroborates the findings of Güdücü et al,[18] who observed that glandular extension is more present in HG lesions, thus demanding greater care when monitoring these cases.

A relationship was found between the histological risk factors, glandular involvement and compromised margins, to the high grade lesions ($p = 0.018$ and 0.039 respectively), confirming the severity and greater care that these lesions require. Similar results were found by Kir et al (2012),[17] who suggested a greater attention to the treatment of HG lesions whenever such risk factors were observed.

Jin et al[19] compared groups with CIN recurrence after LEEP (348 cases and 1,608 controls), and found that glandular involvement and positive surgical margins increased the risk of relapse. The glandular extension has shown to be a

Table 4 Risk factors of CIN recurrence and relationship with biomarkers

		p16 n (%)		*p*	K_i-67 n (%)		*p*	p16/K_i-67 n (%)		*p*
		Neg.	Pos.		Neg.	Pos.		Neg.	Pos.	
HIV	Neg.	9 (10.5)	50 (58.1)	1.000	3 (3.5)	56 (65.1)	0.252	4 (4.7)	23 (26.5)	0.199
	Pos.	4 (4.7)	23 (26.7)		5 (5.8)	22 (25.6)		3 (3.5)	56 (65.1)	
PM	Yes	2 (3.4)	20 (34.5)	0.697	2 (3.4)	20 (34.4)	0.697	1 (1.7)	31 (53.4)	0.235
	No	6 (10.3)	30 (51.7)		6 (10.3)	30 (51.8)		6 (10.3)	20 (34.4)	
GI	Yes	1 (1.2)	18 (21.7)	0.280	1 (1.2)	18 (21.6)	0.675	1 (1.2)	18 (21.7)	0.314
	No	12 (14.5)	52 (62.7)		7 (8.4)	57 (68.6)		6 (7.2)	58 (69.9)	
LG		6 (7.0)	11 (12.8)	0.018*	3 (3.5)	14 (16.3)	0.189	3 (3.5)	14 (16.3)	0.189
HG		7 (8.1)	62 (72.1)		5 (5.8)	64 (74.5)		4 (4.7)	65 (75.6)	

Abbreviations: CIN, cervical intraepithelial neoplasia; GI, glandular invasion; HG, high-grade; HIV, human immunodeficiency virus; LG, low-grade; Neg., negative; PM, positive margins; Pos., positive.
Note: *OR: 4.713; 95%CI: 1.09–20.23.

Table 5 Relationship between recurrence and p16/K_i-67 expression (positive 2+ and 3 +) and risk factors

Risk factor	Recurrence n (%)		*p*
	Yes	No	
High-grade lesion			
p16/K_i-67 positive			
Yes	5 (7.2)	41 (59.4)	0.010*
No	9 (13)	14 (20.3)	
HIV presence			
p16/K_i-67 positive			
Yes	3 (11.1)	10 (37)	0.420
No	6 (22.2)	8 (29.6)	
Positive margins			
p16/K_i-67 positive			
Yes	3 (13.6)	9 (40.9)	0.378
No	5 (22.7)	5 (22.7)	
Glandular Involvement			
P16/K_i-67 positive			
Yes	5 (26.3)	9 (47.4)	0.603
No	3 (15.8)	2 (10.5)	

Abbreviation: HIV, human immunodeficiency virus.
Note: *OR: 0.19; 95%CI: 0.054–0.662.

primary risk factor; however, compromised margins were not found to be a reliable predictor of recurrence, as opposed to several studies,[20–22] and this may be because of the less expressive number of positive margin patients included in this study.

The main question of the current research was whether CIN recurrence could or could not be related to p16 and K_i-67 positive, data still unknown in literature. A study that resembles this was recently published by Fonseca et al.[6] They evaluated the markers p16 and p53 in 83 conization specimens, analyzing the recurrence predictors of high-grade CIN. They compared the grade of positive markers with relapse, and concluded that they could not foresee the disease's recurrence after conization. The findings of that paper were supported by the findings of this study, as the presence of p16 and K_i-67 could not be related to glandular involvement, positive margins or recurrence in the samples, suggesting that the dosage of p16/K_i-67 cannot be seen as effective in predicting the recurrence of these risk factors. A significant relation was found though, between p16 positive and HG lesions, leading to the conclusion that in HG lesions, changes in the cell cycle stand out, and that the increased expression of p16 reflects the subsequent inhibition of the pRb. This inhibition of the pRb induces cell immortalization and transformation, a main factor in the evolution of cancer lesions. The same was observed by Calil et al[23] in a study of 174 biopsies of the cervix. A strong positive correlation between the expression of p16 and the severity of premalignant lesions was found. In contrast, p16 and K_i-67 (2+ and 3+), analyzed together in HG lesions, were significantly associated with recurrence, suggesting that a strong positive HG lesion protein expression would possibly have higher risks of recurrence and, therefore, more attention should be given to these patients, as opposed to the negative or low expressions (1+), which would be less prone to recurrence.

Conclusion

The high positivity of p16/K_i-67 was a predictor of recurrence only in patients with HG lesions, suggesting that patients who fit the profile should be monitored closely. In addition, but independently, the research showed that HIV seropositivity and glandular invasion were recurrence risk factors, and also that compromised margins and glandular involvement are more common in severe lesions.

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Long-Acting Reversible Contraception*

*Contracepção reversível de longa ação**

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Abstract

Unwanted pregnancy is a major public health problem both in developed and developing countries. Although the reduction in the rates of these pregnancies requires multifactorial approaches, increasing access to long-acting contraceptive methods can contribute significantly to change this scenario. In Brazil, gynecologists and obstetricians play a key role in contraceptive counseling, being decisive in the choice of long-acting reversible methods, characterized by intrauterine devices (IUDs) and the contraceptive implant. The vast scope due to the reduced number of situations to indicate long-acting methods should be emphasized in routine contraceptive counseling. On the other hand, gynecologists and obstetricians should adapt the techniques of insertion of long-acting methods, and engage in facilitating conditions to access these contraceptives through public and private health systems in Brazil. This study is part of a project called *Diretrizes e Recomendações FEBRASGO* (*Guidelines and*

Keywords
- contraception
- contraceptive agents
- contraceptive devices
- intrauterine devices
- progestins

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Recommendations of the FEBRASGO – Brazilian Federation of Gynecology and Obstetrics Associations from the Portuguese acronym). It aims to review the main characteristics of long-acting contraceptives and critically consider the current situation and future prospects to improve access to these methods, proposing practical recommendations of interest in the routine of gynecologists and obstetricians.

Resumo

A gravidez não planejada representa importante problema de saúde pública tanto em países desenvolvidos quanto naqueles em desenvolvimento. Embora a redução das taxas dessas gestações requeira abordagens multifatoriais, o aumento no acesso aos métodos contraceptivos de longa ação pode contribuir de forma expressiva na mudança desse cenário. No Brasil, os ginecologistas e obstetras têm papel fundamental no aconselhamento contraceptivo, sendo decisivos na escolha dos métodos reversíveis de longa ação, caracterizados pelos dispositivos intrauterinos (DIUs) e pelo implante anticoncepcional. A grande abrangência decorrente do pequeno número de situações que contraindicam os métodos de longa ação deve ser enfatizada no aconselhamento contraceptivo de rotina. Por outro lado, os ginecologistas e obstetras devem se adaptar às técnicas de inserção dos métodos de longa ação, bem como se engajar na facilitação de condições para o acesso a esses contraceptivos por meio do sistema de saúde pública e privada no Brasil. Este estudo, parte do projeto denominado "Diretrizes e Recomendações FEBRASGO", tem por objetivo revisar as principais características dos contraceptivos de longa ação, além de considerar de forma crítica o panorama atual e as perspectivas futuras, visando melhorar o acesso a esses métodos, com recomendações práticas de interesse na rotina do ginecologista e obstetra.

Descritores
- anticoncepção
- anticoncepcionais
- dispositivos anticoncepcionais
- dispositivos intrauterinos
- progestógenos

Introduction

Prevalence and Social-medical Impact of Unintended Pregnancy

Unwanted pregnancies affect a large number of women in the world and in Brazil. Surveys have observed an average worldwide pregnancy rate of 133 in every 1,000 women aged 15–44, but ~ 40% of them, 53 in every 1,000, are unintended.[1] The highest incidence is in Latin America, the Caribbean and Africa, reaching rates above 60% of pregnancies.[1]

More than 200 million women living in developing countries want to avoid pregnancy, but unfortunately do not use any contraceptive method.[2] In Brazil, in 2006, data from the National Survey on Demography and Health of Children and Women showed that only 54% of women had planned their pregnancies, and 18% of pregnancies were unwanted.[3] More recently, it was observed that 55.4% of Brazilian pregnant women did not want to be pregnant at that time.[4] Unintended pregnancy is defined as untimely or unwanted at the time of conception.[1] Knowledge about the pregnancy is important because it can result in adverse effects for both the mother and the fetus.[5] These data may help especially developing countries, where maternal morbidity and mortality are higher.

Despite the difficulty of establishing causal relationships, some studies have found an association between unwanted pregnancy and negative repercussions in the maternal and fetal health sphere, as well as in the economic and social health spheres.[5] These are considered risky pregnancies for their frequent association with some type of habit or obstetrical disorder.[6] The most frequently observed alterations are inadequate prenatal care or delayed start of prenatal care, no reduction or interruption of smoking/alcohol use, increased incidence of abortion, prematurity, low birth weight and lower chance of breastfeeding.[6]

Studies have shown a strong association between altered or poor quality mental health in women and unwanted pregnancies. Especially in those situations in which the couple already had the desired number of children.[7] The prevalence of psychiatric illnesses, such as depression, is twice as high among women who did not plan their pregnancies when compared to those who planned them.[7] Studies suggest that unwanted pregnancy reduces the opportunities of education and work, contributing to reduced socioeconomic growth and, consequently, the worsening of social inequalities. This issue is considered one of the great challenges for the public health system, because it is responsible for a significant financial and social cost to society.[5]

Unwanted pregnancies can be reduced through quality of life improvement programs. The most effective programs and with the best socioeconomic results are those acting in the training and education of individuals. The implementation of preventive measures, such as promoting health information, improving and adapting care systems, and expanding techniques for women's treatment and follow-up is also necessary. Prevention through contraceptive methods is an effective way that can bring good results. One of the main causes of unwanted pregnancy is the unmet need for contraception. The lack of contraceptive methods, the

existence of few options, and the incorrect use of the contraceptive system lead to unwanted pregnancy. Thus, the chosen method and the frequency and type of use over time can reduce this risk. Among the available contraceptive options, long-acting methods are the main interventions for reducing unwanted pregnancies, especially in the groups that are at risk, given their high efficacy. By definition, long-acting reversible contraceptives (LARCs) last for three years or more, and are represented by intrauterine devices (IUDs, such as copper IUDs and the levonorgestrel intrauterine system [LNG-IUS]) and the contraceptive implant.[8]

Methods

This literature review has the objective of offering theoretical and practical knowledge about long-acting reversible contraceptive methods. The selected topics are related to effectiveness, safety, ethical-legal aspects and practical applicability.

PubMed was the searched database by using Medical Subject Headings (MeSH) that suggested treatment outcome for contraceptives, *contraceptive agents*, *female* or *contraceptive agents*, *female (pharmacological action)*. Other related terms included *intrauterine devices* or *intrauterine device*s, *medicated* and *3-keto-desogestrel (supplementary concept)*. The generic keyword *long-acting reversible contraceptive* was also used. The Brazilian legislation was also consulted, including the Brazilian Civil Code and the Statute of the Child and Adolescent (ECA, in the Portuguese acronym), as well as resolutions from the government and specialties societies, which were verified by bibliographical survey or quotes on the internet.

All relevant studies published until October 2016 were included. The bibliographic references of the selected articles were also used. The classification of the studies followed the classification of the Brazilian Medical Association (AMB, in the Portuguese acronym) regarding the degree of recommendation: (A) observational or experimental studies of better consistency (meta-analysis or randomized clinical trials); (B) less consistent observational or experimental studies (other non-randomized clinical trials or observational studies or case control studies); (C) reports or case series (uncontrolled studies); and (D) opinion devoid of critical evaluation based on consensus, physiological studies or animal models.

Results and Discussion

Principles of Long-Acting Reversible Contraceptives

Effectiveness

Compared with short-acting methods, LARCs are superior in terms of efficacy, providing pregnancy rates of less than 1% per year in perfect and typical use (A).[8] One of the main advantages of LARCs in relation to short-acting reversible contraceptives is the maintenance of their high efficacy regardless of the user's motivation. Long-acting reversible contraceptives are independent of the physicians' or the user's action to maintain their efficacy, and have the highest rates of satisfaction and continuity of use among all reversible contraceptives.

The etonogestrel contraceptive implant is the only available type in Brazil, and it has a failure rate of 0.05% and duration of 3 years(A).[9] The copper IUD is very effective as a contraceptive, with a failure rate ranging from 0.6 to 0.8% in the first year of use, and up to 10 years of action (A).[9] Recent studies confirm the high efficacy of the LNG-IUS, which has been associated with pregnancy rates ranging from 0 to 0.6% of women/year (D).[10]

Indications

Long-acting reversible contraceptives are recommended for all women who desire effective contraception, including adolescents, nulliparous, women in the postpartum or post-abortion periods, and in comorbidities that may characterize contraindications to estrogen-containing methods (D).[11] Thus, the great scope of LARCs can be attested by the small number of contraindications of these methods. ►**Fig. 1** shows both the conditions in which LARCs are recommended and not recommended (D).[12]

Acceptance and Continuity

Long-acting reversible contraception methods maintain their high efficacy regardless of the users' motivation, unlike short-acting reversible contraceptive methods, which rely on correct use to achieve high efficacy. Because of their typical ease of use, LARCs were dubbed 'get it and forget it' (B).[13]

Contraception experts believed the high rates of unwanted pregnancies could be reduced by increasing access to LARCs (D).[14] The Contraceptive CHOICE Project was conducted with this objective. It is a prospective cohort that broke the main barrier to use LARCs: the cost. The purpose of the CHOICE Project was to evaluate the satisfaction and continuity rates among all reversible contraceptive methods, including LARCs (B).[15]

The CHOICE results coincided with the experts' thinking: continuity and satisfaction rates were higher among LARC users (in all age groups) when compared with short-acting contraceptive methods (86.2% versus 54.7%, and 83.7% versus 52.7% respectively). It is important to note that most participants of the CHOICE Project had low income, were at high risk for unwanted pregnancies, and 41.8% of the study participants had had at least one abortion (B).[15] The overall discontinuity rate was higher among adolescents (14–19 years of age) compared with adult women (> 25 years of age). In addition, for two years, two-thirds of adolescent LARC users continued with their method, while only a third of short-acting method users continued to use their method in the same period. Adolescents in the CHOICE study had a lower rate of satisfaction with short-acting methods compared with adult women. However, satisfaction rates among LARC users were high and similar among adolescents and adult women (B).[16]

►**Table 1** shows the higher continuity rate among LARC users compared with users of short-acting methods for two years (B).[17,18]

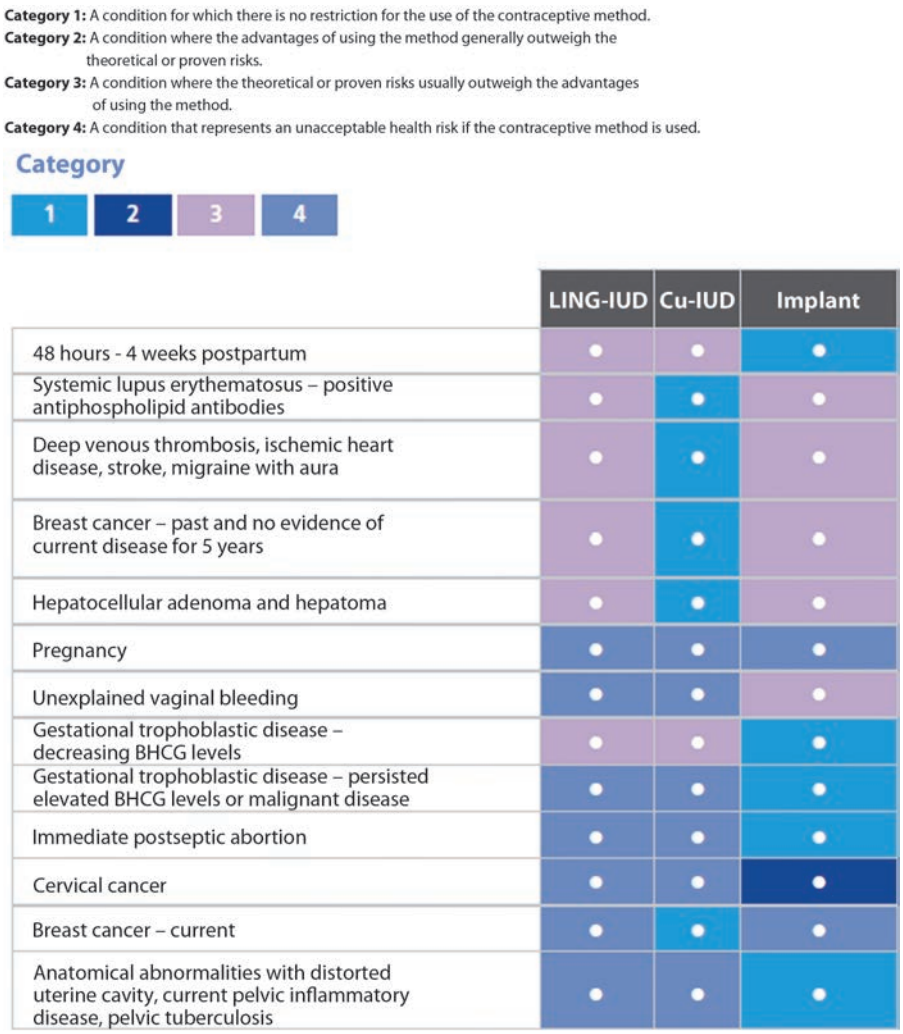

Fig. 1 Clinical conditions represented by categories of Medical Eligibility Criteria for contraceptive use.

Continuity rates above 80% in the first year of use are also reported in other populations, always associated to adequate prior counseling on all contraceptive methods (B).[19] A Brazilian study has observed a trend in the past 15 years of more women continuing to use LARCs and depot medroxyprogesterone acetate (DMPA) until menopause rather than undergoing surgical sterilization, either in them or in their partners. There was also a reduction in female and male sterilization rates in the service. The authors attribute the high continuity rate of LARCs and DMPA observed in the study to the appropriate orientation regarding the high efficacy of these methods (B).[20]

Table 1 Continuity rate of reversible contraceptive methods in the first and second year of use according to different studies

Method	WHO[18] – 1st year %	CHOICE[13] – 1st year %	CHOICE[13] – 2nd year %
Pills	67	59	43
Ring	67	56	41
Patch	67	49	39
Injectables	56	57	38
Copper IUD	78	85	77
LNG-IUS	80	88	78
Implant	84	83	68

Abbreviations: IUD, intrauterine device, LNG-IUS, levonorgestrel intrauterine system; WHO, World Health Organization.

Higher continuity rates were associated to the beginning of the use of a LARC method in the postpartum period and to higher satisfaction rates (C).[21] A study with American students found higher acceptance rates of LARCs among adolescents with previous history of vaginal intercourse and younger age (C).[22]

Counseling and Barriers to Access to Long-acting Methods

There are numerous advantages to LARCs, but their use is still below what is expected due to myths among patients and health professionals.

Counseling is critical to increase the continuity rate of the method. A national study evaluating the efficacy of conventional counseling versus intensive counseling among women who chose LARCs did not observe a difference in discontinuity rates between groups. In this study, conventional counseling

consisted of verbal guidance on mechanism of action, safety, efficacy, how and when fertility returns, adverse effects of the chosen method, and its non-contraceptive benefits.

For intensive counseling, in addition to information from conventional counseling, a leaflet was provided with a picture of the pelvic anatomy, further explanation of changes in bleeding patterns that could occur during the use of the chosen method, the mechanism of action of menstrual irregularities, and the possibilities of treatment. The authors concluded that routine counseling appears to be sufficient among the majority of women to help improve the rates of continuity and satisfaction among new LARC users (A).[23]

On the other hand, a study comparing the acceptance of LARCs among post-abortion women undergoing a motivational interview versus common counseling (control) found that more than twice as many women in the intervention group chose and continued to use LARCs (60% versus 31%). Motivational interviewing is a kind of patient-centered counseling that includes reflective listening, open discussion about the advantages and disadvantages of contraceptive methods, always avoiding confrontation, to promote the patients' own motivation for behavior change. Women in the intervention group also reported higher rates of satisfaction with counseling than those in the control group (92% versus 65%) (A).[24]

Studies have shown that the continuity and satisfaction rates with the contraceptive method are greater when the decision is made by the patient. Women prefer to decide on their contraceptive method autonomously, with less influence of the health professional, and after appropriate advice (B).[25]

Thus, it is important to explain about all methods clearly and objectively, so patients make an informed decision. Women selected for the CHOICE study received brief information from a trained professional on the duration, efficacy, and site of implantation of all LARCs (B).[26] After this orientation and eliminating the cost of medications, of the 5,087 women included in the study, 68% chose LARCs, 23% chose combined hormones, and 8% chose medroxyprogesterone acetate (B).[13] The training of health professionals is also fundamental to reduce barriers and increase access to LARCs. A study was conducted in 40 family planning services for low-income population in several American cities. It found the training of service providers had increased the counseling, selection and initiation of LARCs among adolescents and young adults compared with women in service settings that did not receive training (start of LARCs: 27% versus 12% for adolescents, and 28% versus 18% for young adults). The intervention was a continuing education course that lasted for half a day based on eligibility criteria and clinical cases, and a practical training to insert IUDs and implants (A).[27] The American College of Obstetricians and Gynecologists (ACOG) recommends that health professionals provide guidance on LARCs in all consultations with sexually active adolescents. Long-acting reversible contraceptives should be the first line of contraceptive option for them, due to the high risk of unwanted pregnancy in this age group (D).[28] The experience and training of health professionals with LARCs is directly proportional to their supply. A study with more than 1,000 American gynecologists and obstetricians has shown that 95% of the interviewees offer IUDs to patients, while only half of those interviewed offer contraceptive implants. During medical residency, 92% were trained for IUDs, while only 50% were trained for their implantation. Continuing education in the last two years was the most associated variable with provision of contraceptive implants, and 32% of interviewees reported lack of training on insertion as a barrier (B).[29]

A study with over 200 gynecologists and obstetricians in Latin America on the knowledge of IUDs found deficiencies and contradictions regarding their knowledge and attitudes. Of the participants, 10% did not recognize the high efficacy of LARCs, 80% answered they did not offer IUDs for nulliparous women, and almost 10% did not offer them for adolescents, even though 90% of respondents reported that nulliparous women are candidates for LNG-IUS (B).[30] In addition to the importance of appropriate counseling to increase access to LARCs, other barriers need to be overcome, such as the high cost of the medications. Studies have shown that LARCs are the most cost-effective reversible methods, although they are still inaccessible to the low-income population (B).[31]

The most commonly mentioned barrier for the use of LARCs is the cost of the medications (63%), followed by the women's lack of knowledge about their safety, acceptability, and expectations. The shortage of trained health professionals was a commonly cited barrier, especially among primary health care providers (49%) (D).[32]

Clinical Features, Indications and Clinical Management with Long-acting Reversible Methods

Levonorgestrel Intrauterine System

The LNG-IUS has a reservoir containing 52 mg of levonorgestrel, measures 32 mm in length, and releases 20 µg of levonorgestrel per day. Through the control membrane, the system releases levonorgestrel, which starts circulating in the plasma 15 minutes after insertion. The release rate of 20 µg/day drops throughout use, stabilizing at around 12–14 µg/day, until finally reaching 11 µg/day at the end of 5 years, the recommended time for using LNG-IUS (D).[33] According to Luukkainen and Toivonen (D),[34] the main mechanisms of action that collaborate to obtain a contraceptive with fewer side effects and high effectiveness are the following:

- thick cervical mucus hostile to sperm penetration, inhibiting the sperm's motility in the cervix, endometrium and fallopian tubes, preventing fertilization;
- high levonorgestrel concentration in the endometrium, preventing response to circulating estradiol;
- strong anti-proliferative effect in endometrium;
- inhibition of mitotic activity in the endometrium; and
- maintenance of estrogenic production, enabling good vaginal lubrication.

As a result of these various contraceptive actions, the effectiveness rate of LNG-IUS is very high, and in several clinical studies representing over 100,000 women/year/use, a Pearl index of 0.1 was obtained (A).[35] Thus, the LNG-IUS has excellent contraceptive efficacy and equivalent performance

for both 'correct' and 'habitual' use (B) (A).[36] Its satisfaction rate showed indexes higher than 75% in the first year (A).[37]

One of the main points of the LNG-IUS is its local action on the endometrium, leading to endometrial atrophy. This endometrial atrophy allows the appearance of clinical effects such as amenorrhea and/or oligomenorrhea, which differentiate it from patients using copper IUDs (A).[36] Simply put, the beneficial effects of the LNG-IUS are the following:

- increased hemoglobin concentration;
- it is an effective treatment for menorrhagia;
- it is an alternative to hysterectomy and endometrial ablation;
- it prevents anemia;
- it can be used in endometrial protection for hormone replacement therapy; and
- it minimizes the effects of tamoxifen on the endometrium.

With these non-contraceptive effects, LNG-IUS can offer alternatives to the treatment of menorrhagia, endometrial hyperplasia and adenomyosis. It offers good results in improving symptoms and menstrual pattern in women with endometriosis and uterine fibroids (C).[38]

Clinical Management

The use of LNG-IUS may present some complications and, although not so frequent, these possibilities should be discussed before insertion. Anticipatory guidance on possible side effects helps to achieve better user acceptance, good results and, consequently, a higher rate of continuity of use of LNG-IUS. In addition, anticipatory guidance allows a greater understanding of the method by the users, and leads to a faster search of professionals or services, in case any complication is perceived. The most common side effects are:

- expulsion;
- pain or bleeding;
- perforation;
- infection;
- ectopic pregnancy; and
- topical pregnancy.

Signs of possible complications that may lead to the return of patients to the doctor are the following:

- significant bleeding or abdominal pain within the first three to five days after insertion may indicate perforation at the time of insertion or the possibility of infection or displacement of the LNG-IUS;
- irregular bleeding or pain in all cycles may correspond to displacement or partial expulsion of the LNG-IUS;
- fever or chills with or without vaginal discharge may indicate the presence of infection;
- persistent pain during sexual intercourse may relate to infection, perforation or partial expulsion;
- menstrual delay with pregnancy symptoms or expulsion of the LNG-IUS may indicate intra or extrauterine pregnancy, although rarely observed; and
- longer or non-visible LNG-IUS string may indicate displacement of the device or even gestation.

LNG-IUS and Infections

Bacterial infections may appear because of endometrial cavity contamination at the time of LNG-IUS insertion, and although acute pelvic inflammatory disease (PID) is quite rare, when it occurs, it is more common in the first 20 days after insertion (C).[39] Administration of doxycycline (200 mg) or azithromycin (1 g) an hour before insertion of the IUS may protect against pelvic infections, but the prophylactic use of antibiotics should not be indicated for women at low risk for sexually transmitted diseases who are candidates for LNG-IUS insertion. On the other hand, in women with a potential risk for bacterial endocarditis, antibiotic prophylaxis should be used an hour before insertion or removal of the LNG-IUS.

During the first year of use, the infection rate is low for both the LNG-IUS and TCu-380A. After three years, the rate of acute PID in LNG-IUS users is lower than that of TCu-380A users (0.5% and 2.0%, respectively). The low rate of acute PID in young women under 25 years of age stands out. In patients aged between 17 and 25 years, the difference is quite significant, with an index of 5.6% in TCu-380A users, and 0.3% in LNG-IUS users (C).[39] In conclusion, the risk of developing pelvic inflammatory disease associated with IUDs is quite low and related to the moment of insertion (B).[40]

LNG-IUS and Perforations

Perforations are rare complications occurring in 1.3 times per 1,000 insertions. The careful insertion technique is the main form of prevention (B).[40] Perforation usually occurs when the LNG-IUS is not inserted in the direction of the uterine cavity, or when the cavity length (hysterometry) is not measured correctly.

At the time of perforation, patients experience severe pain, and the insertion procedure must be interrupted immediately. The LNG-IUS must be removed through delicate traction of the strings, which solves the vast majority of cases. Perforation may be partial or complete. Pelvic ultrasonography, particularly the transvaginal one, is of great value for the diagnosis of perforations, enabling a more appropriate conduct in each case.

In cases of partial perforation, hysteroscopy is indicated to remove the device when traction maneuvers of the strings are not successful.

In complete perforations or beyond the uterine serosa, laparotomy or laparoscopy are indicated to locate the LNG-IUS and remove it (C).[41]

LNG-IUS and Ectopic Pregnancy

Anderson, Odlind and Rybo (A)[36] found an ectopic pregnancy rate of 0.2 women/year after 5 years of LNG-IUS use, compared with 2.5 women/year in Nova-T (Bayer, Leverkusen, Germany) users. Other studies have not observed the occurrence of ectopic pregnancies in patients using LNG-IUS. These numbers represent a reduction of 80% to 90% in ectopic pregnancy risk when compared with women not using contraception. For ectopic pregnancy, the approximate Pearl index is 0.02 per 100 women/year (D).[33]

Thus, the risk of ectopic pregnancy in LNG-IUS users is less than 0.25% in 5 years of use (B).[40]

LNG-IUS and Topical Pregnancy

Although pregnancy rates are extremely low, its occurrence in women using the LNG-IUS requires adequate conduction according to the location of the gestational sac in relation to the LNG-IUS and the gestational age at the time of the diagnosis (C).[42]

If the device strings are visible on specular examination (gestation not greater than 12 weeks), they should be gently removed by continuous and gentle traction. If the strings are not visible on the specular examination, hysteroscopy performed by an experienced and careful professional usually solves most cases.

In cases of more advanced gestation, with the LNG-ISU distant from the internal bore of the cervix, removal attempts should be avoided, as the occurrence of failure is very high. In these cases, advice for the pregnant woman is key, bearing in mind it is a pregnancy with increased risk of abortion, preterm labor and infections. In addition, it should be monitored and examined frequently in the prenatal routine or in the presence of any sign or symptom of hemorrhagic and/or infectious complications.

LNG-IUS and Acne

The occurrence of acne (12%), weight gain (7%), depressive mood (5%) and headache are minor side effects, and most often do not require LNG-IUS removal for their treatment (D).[43] Severe cases are rare, and the user should be advised to remove the LNG-IUS only when there is no clinical improvement with the use of spironolactone (100 mg/day for 3 months) in mild and moderate cases, and/or Roaccutane (Hoffman-La Roche, Basel, Switzerland) in cases of more intense symptomatology (C).[44]

Copper Intrauterine Device

Intrauterine devices are the most known long-acting methods, and copper IUDs are the most widely used in the world (D).[45] The device's mechanism of action is the alteration of sperm motility and decrease of its viability caused by cervical mucus with high copper concentrations (C).[46,47] In addition, increased leukocytes and cytokines in the uterine cavity drastically reduce the likelihood of fertilization (A).[48] Despite being scarcely used in Brazil (less than 5% of sexually active women use IUDs), these methods are highly effective, low cost, and easy to use (B).[49,50]

Copper-containing IUDs do not contain hormones, and the most widely used types nowadays are the TCu-380 IUD and the Multiload R375 IUD. They are more effective than other models with lower copper concentrations that were used in the past. They are easily inserted or removed and, at the same time, do not require that the women or their partners remember to use or apply them daily, enhancing the contraceptive effect (B).[49]

The TCu-380 IUD is probably the most widely used in the world. It has a ten-year durability, and very low Pearl index (one pregnancy or less in every 100 users in the first year of use, and accumulating the rate of 3 out of every 100 users after 5 years) (B).[49] The cumulative pregnancy rate throughout 20 years in a Brazilian clinic was 4 in every 100 women/year (B).[51] Large randomized clinical trials have shown copper IUDs remain effective for 12 to 13 years (A).[52]

Insertion of Copper IUD

Traditionally, IUDs are inserted during the menstrual period, because the uterine cervix is believed to be discretely dilated. However, the advantage of this practice is the exclusion of pregnancy. Although unusual, IUDs can be inserted at any point in the menstrual cycle if the pregnancy is safely excluded. In addition, IUDs can be inserted immediately after miscarriage, or in the immediate postpartum period (A).[52]

For a long time, nulliparity was a reason for contraindicating IUD use. However, recent studies have demonstrated no greater difficulty in IUD insertion into nulliparous women (failure rates of insertion are similar to those of multiparous women), as well as similar acceptance, tolerability and pain compared with women with previous pregnancies (B).[53] Though this group is known to have a slight increase in expulsion rates in the first 6 months (B),[53] the World Health Organization (WHO) currently considers it category 2 of the eligibility criteria, that is, the benefits outweigh the possible harm (D).[12]

Medications to Facilitate IUD Insertion

One of the main limiting factors for IUD use is pain during insertion. Medications such as misoprostol (prostaglandin inhibitor), non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics have been used to try to minimize this pain. A recent systematic review found 15 randomized clinical trials (A).[54] The evidence did not show the insertion was easier, neither a reduction in the need for techniques to dilate the uterine cervix, nor higher success rates (A).[54] Only a study with women who underwent a failed insertion procedure showed higher success rates in the group that used misoprostol prior to the procedure compared with the placebo group (A).[55] The use of diclofenac plus 2% intracervical lidocaine also showed no positive effect on insertion (A).[56]

Acceptability of the TCu-380 IUD

A recent Australian study followed a cohort of TCu-380 IUD users to learn more about which women used the method. Between 2009 and 2012, 211 women were monitored. One third of the women were under 30 years of age, 36.5% had never been pregnant, and the main reasons to choose the method were effectiveness and not wanting to use hormonal methods. The continuity rate was 79.1% and 61.3% at the end of 1 and 3 years respectively (B).[57]

IUD and Pelvic Inflammatory Disease

A classic concern of health professionals was the risk of developing PID and consequently infertility in users of any IUD. Because of this 'myth,' many felt it would be inappropriate to offer the method to women without a steady partner, or to those who had never been pregnant. However, studies have shown no correlation between the use of intrauterine methods and a greater chance of developing

PID. Therefore, the method can be offered to patients previously considered outside the eligible group for their use (D).[58,59]

Irregular Bleeding with Copper IUD

It is unclear why copper IUDs increase uterine bleeding. This may occur due to increased subendometrial vascularization in users of this method (D).[60] A comparative study between users of TCu-380 and LNG-IUS showed greater uterine bleeding in the first month after insertion of the TCu-380 with subsequent decrease until the third month, when the menstrual pattern stabilizes (C).[61] No study has shown satisfactory results in the treatment of irregular bleeding with copper IUD. Empirically, in an attempt to avoid premature removal of the IUD, clinicians have used NSAIDs (to try to decrease vascular proliferation factors) or combined oral contraceptives to stabilize the endometrium. One of the causes of this bleeding may be infection and, if early-stage PID is suspected, the use of broad-spectrum antibiotics can improve irregular bleeding because they treat subclinical endometritis.

Etonogestrel Implant

Implants are plastic devices placed under the skin that continuously release progestogens. In Brazil, the only approved implant is IMPLANON, which is a single rod, $\sim$ 4 cm long by 2 mm thick, containing 68 mg of etonogestrel (ENG) (3-ketodesogestrel), the active metabolite of desogestrel, involved in a non-radiopaque ethylene vinyl acetate (EVA) membrane (B).[62]

The contraceptive effect is achieved mainly through consistent ovulation inhibition (C).[4] Alongside ovulation inhibition, ENG also causes alterations in the cervical mucus that hinder sperm passage, as well as alterations in the endometrium, making it less suitable for nidation (C).[63,64] On the other hand, after the removal, the users' serum levels become undetectable within a week, then most women show ovulation and are able to conceive within a few days after implant removal (B).[65]

Indications for ENG implantation depend on the women's preference, on comorbidities in which estrogens cannot be used, and on vulnerable groups such as adolescents, drug addicts and women with HIV.

Management of Events and Adverse Events

A follow-up of more than 900 women for 3 years (C)[66] showed that among general events, complaints of headache (in 15% of patients) are more frequent during the first 6 weeks, when ENG release has a higher concentration (60 to 70 mcg/day) (B).[67,68] The headache usually occurs at the end of the day without hemicrania characteristics and, when necessary, common analgesics are effective (C).[69] Another characteristic complaint of estrogenic action is mastalgia (10%). However, in cases of implants, it is also more frequent in the initial six-week period, generally well-tolerated, requiring mostly the reassurance of no risk of malignancy. If needed, common analgesics are effective (C).[69]

A meta-analysis study found complaints regarding weight gain from 12% of the patients. Importantly, this gain with isolated progestogen methods is similar to that found in women using other hormonal and non-hormonal contraceptive methods (A).[70] The CHOICE study showed no difference in weight gain among LARC (copper IUD, LNG-IUS and ENG implant) users during the first year of follow-up (B).[71] Therefore, if there is weight gain, women should be consulted about any changes in lifestyle and diet (C).[69]

Acne as an adverse event was reported by 11% of the users. The most likely women to complain about acne are former users of the combined hormonal method. Because of ethinyl estradiol (EE), such method greatly increases the sex hormone-binding globulin (SHBG), considerably decreasing free testosterone (B).[72] The ENG-releasing implant, on the other hand, has a neutral effect on the SHBG (C).[63] Therefore, the replacement of the EE method by the implant causes SHBG levels to fall rapidly, increasing free testosterone. There is no study evaluating the use of anti-androgenic drugs in the acne of the users of progestogen-only methods. However, for the management of this adverse event, it is possible to initially use 100 to 200 mg/day of spironolactone and, if there is no improvement, 25 mg/day of cyproterone acetate for 15 days/month or throughout the month, for about 6 months (D).[73]

As the ENG-releasing implant does not inhibit the follicle-stimulating hormone (FSH) (C),[63,64] follicular cysts can occur in $\sim$ 25% of the users after 12 months (C),[74] but these ovarian cysts are benign, with no repercussion for the women, and tend to disappear in 12 weeks. Usually, they are occasional findings, and do not cause symptoms. However, if there is abdominal pain, the use of non-steroidal analgesics or anti-inflammatory drugs may be indicated (C).[69]

The main adverse event of the ENG-releasing implant, as of any progestogen-only contraceptive, is the change in the bleeding pattern and also the main cause for abandoning the method.[23,75] To discuss irregular bleeding, it is important to know the patterns of vaginal bleeding induced by the contraceptive methods (C),[76] taking into account the number of days and the intensity of the vaginal bleeding or spotting (spotting/bleeding of small quantity with use of at most one pad or tampon/day) for a 90-day period, called reference period (RP). The following are considered: 1) amenorrhea: absence of bleeding in the RP; 2) infrequent bleeding: up to three episodes (days) of bleeding in the RP; 3) normal frequency: between three and five episodes of bleeding in the RP; 4) frequent bleeding: more than five episodes in the RP; 5) prolonged bleeding: more than 14 days of bleeding (uninterrupted) in the RP.

Studies show these bleedings are usually well-tolerated by women, provided they are well-oriented prior to insertion (B).[23,75] Amenorrhea, infrequent bleeding and regular bleeding are considered a favorable bleeding pattern, while frequent and prolonged bleeding is considered unfavorable. As shown in ►**Table 2**, the great majority of women presented a favorable bleeding pattern, and only 20–25% presented an unfavorable pattern (frequent or prolonged bleeding) (C) (►**Table 2**).[77,78]

Table 2 Bleeding pattern with use of ENG-releasing implant

Bleeding pattern	ENG implant%
Amenorrhea	22-40
Infrequent	30-40
Regular	20
Unfavorable pattern	6.7 frequent + 17.7 prolonged

Abbreviation: ENG, etonogestrel.

How to Manage Irregular Bleeding?

- Guidance regarding the expected bleeding pattern prior to the insertion (B).[23,75]
- Patience in the first 6 months is key, since ~ 50% of women with an unfavorable pattern have a chance to improve their bleeding pattern (C).[78]
- Rule out all other bleeding causes if the pattern remains unfavorable after six months or associated pain appears (B).[79]
- Treat as often as necessary, and with medications that can be used and demonstrated in studies to be better than placebo, though with different strength of evidence:[79,80]
  - 30 mcg of EE + 150 mcg of LNG for 1 to 3 cycles with or without pause between cartons (A).
  - Tranexamic acid 500 mg - 1,000 mg every 8 hours for 5–7 days (A). The treatment can be repeated as many times as necessary, as long as they do not exceed 7 days.
  - Doxycycline 100 mg every 12 hours for 5–7 days (C). Here, the action is of decreasing metalloproteinases, and not the known antibiotic action.
  - Non-steroidal anti-inflammatory drugs (C). The most studied were:
    - Ibuprofen: 400 mg, every 8 hours for 5 days.
    - Mefenamic acid: 500 mg, every 8 hours for 5 days.
    - Celecoxib: 200 mg/day for 5 days.

  - Estrogens (C): they have not shown to be better than placebo at usual doses. Because of the decrease in estrogen receptors, their action is difficult. Ethynil estradiol 50 mcg/day was effective to decrease bleeding in users of LNG-releasing implants.[78]
  - Progestogens-only (D): even though to date there are no studies comparing them to placebos, they have been increasingly used:
  - Desogestrel 75 mcg/day for 1–3 cycles.
  - Norestisterone 10 mg every 12 hours for 21 days.
  - Medroxyprogesterone acetate (MPA) 10 mg every 12 hours for up to 21 days.

Special Situations for Use of Long-acting Contraceptive Methods

Adolescents and Nulliparous Women

After a decline in the past 15 years, the rate of teenage pregnancy returned to grow for the first time in 2006 in the USA, an increase of ~ 3% over the rate of 2005 in women aged between 15–19 years (B).[1] Part of this can be explained by the fact that the most popular contraceptive methods used by adolescents depend on correct use for their effectiveness.

Adolescents want a safe and effective contraception method, but find barriers to know and access the different options, often because of the high initial cost.

Guidance to adolescents about contraception should include information on all available methods, including IUDs and implants as first-line methods. However, many doctors do not feel safe inserting IUDs and implants in adolescents because they are not trained to do so. A study with predominantly medical professionals concluded that only 31% of them considered IUDs an appropriate method for adolescents; 50% would insert an IUD in a 17-year-old girl with a child, and only 19% would insert it in an adolescent with the same age without children, which goes totally against the available guidelines (B).[81]

Currently, the most popular forms of contraception in adolescents are condoms and the withdrawal method (coitus interruptus), followed by contraceptive pills (B).[82] Only 3.6% of women aged 15–19 years use IUDs. The use of less reliable methods probably contributes to the 80% rate of unwanted pregnancy among adolescents aged 15–19 years.

Age and parity are not contraindications to use LARCs. Thus, they are indicated to adolescents and nulliparous women (D).[12]

There are few studies of implants in adolescents. In a retrospective study (2010–2013), Obijuru et al (B),[83] evaluated 116 records of adolescents using etonogestrel implants who were in follow-up in an adolescent clinic.

Although in this group 39% of the participants reported previous use of oral contraceptives, and 27% previous use of DMPA, only 14% of the patients were using the method at the time of implant insertion.

Among them, 35% used only condoms, 42% did not use any contraceptive method, only 3% used IUDs, and 3% used implants. This means the majority of sexually active adolescent (77%) patients were at risk of gestation, considering the low efficacy of condoms as a contraceptive method.

Of the 116 participating patients, 94% were nulliparous, and complete follow-up was available for 81% of them. The authors considered as early removal of the implant if it happened in less than 32 months. The implant continuity rate at 12, 24 and 32 months was 78%, 50% and 40% respectively.

Removal in less than 32 months occurred in 35% of the cases. Early removal because of uncomfortable bleeding occurred in 18% (17/94) of the patients. There was no significant association between body mass index, uncomfortable bleeding and early removal of the implant. The results indicate the continuity rate is high at 12 and 24 months, with 40% of patients reaching 32 months of implant use, a significant period of pregnancy protection (B).[83]

There are different guidelines for IUD use in adolescents. In 2007, the committee of the American College of Obstetricians and Gynecologists (D)[84] recommended considering IUDs as first-line options for contraception in adolescents with or without children. The WHO also supports the use of IUDs in adolescents by providing eligibility criteria 2

(benefits superior to risk) for women at menarche aged 20 years (D).[12] The American Academy of Pediatrics (D)[85] also considers IUDs to be safe in nulliparous adolescents, not causing tubal infertility. Their removal is followed by the rapid return of fertility.

Health professionals often do not identify adolescents as potential candidates for using intrauterine methods. Part of this thought results from the old fear that IUDs caused pelvic inflammatory disease (PID) and tubal infertility, which would be particularly worrying in childless adolescents. Current evidence discards this association. The use of IUDs does not increase the risk of pelvic inflammatory disease of the upper genital tract above the baseline risk expected for women.

In addition to the unfounded fear of tubal infertility, the IUD is often avoided in adolescents because of the thought of its greater risk of expulsion and adverse effects in nulliparous women compared with multiparous women. A study of 129 nulliparous LNG-IUD users found an expulsion rate of less than 1% per year in women who had never been pregnant (B).[36] Other studies also found no increased risk of expulsion in nulliparous women, nor a relationship with endometrial cavity size measured by hysterometer or ultrasonography (regardless of parity) (B).[86]

Immediate Postpartum Period and Post-abortion

Usually, the prescription of contraceptives in the puerperal period occurs around six weeks after delivery (A).[87] On the other hand, the rates of missed postpartum consultations are high, ranging from 10 to 40%, which makes many women exposed to a new gestation (C).[69] Despite the contraceptive effectiveness of lactation and amenorrhea, in Brazil, the average period of exclusive breastfeeding is around 50 to 60 days (median of 54 days) (C).[88] Thus, it seems opportune that some women initiate contraception still in the maternity, particularly among drug users, distant dwellers, and those who would not have access to puerperium consultations. Long-acting reversible contraceptives are alternatives for these women. The WHO recommends the use of all LARCs in the first 48 hours after delivery, provided there are no contraindications to these methods (D).[12] In this situation, continuity rates at 12 months are high, and, in adolescents who used LARCs in the immediate postpartum period, there was more than 80% reduction in the risk of a new pregnancy in 1 year (B).[89]

The expulsion rates of copper IUD and LNG-IUS are higher at immediate postpartum insertion, and higher than the rates observed in users of implants inserted in the postpartum period (39% versus 14% respectively) (B).[90] Long-acting reversible contraceptives inserted in the immediate postpartum period appear not to affect lactation, growth, and neonatal and infant development (A).[91] The insertion of LARCs after abortion is released if the woman wishes to become pregnant (WHO), since ovulation occurs in more than 90% of women in the month following the abortion (D).[12]

Drug Addiction

In Brazil, there are $\sim$ 370,000 people who use crack or similar drugs, of which 21% are women (78,000) and, of these, 13% are pregnant (10,000) (C).[92]

Crack consumption has been directly associated with HIV infection. The prevalence among women is double that of men (C).[92] In Cracolândia, an area in the central region of the city of São Paulo where crack users gather, 9% of women have positive serology for HIV (B).[93] The most frequent risk behaviors in this population are the high number of partners, unprotected sex, and the exchange of sex for drugs or money to buy drugs, especially among sex workers (B).[94–96]

Compared with the general population, morbidity is increased among female drug users with regard to abortions (16.1%), fetal intrauterine death (1.7%) and prematurity (20.6%) (B).[93] Female drug users in Brazil had 3.4–3.8 pregnancies/woman, and birth rates of 2.6–2.9 live children/woman (B).[95]

All these reasons determine the need to avoid pregnancies in this vulnerable population due to the damages caused by drugs, and because they are high-risk pregnancies. Much has been written about the consequences of substance use during pregnancy, but there has been much less focus on preventing these unwanted pregnancies in women with disorders with the use of opioid substances and their derivatives.

The studies demonstrate the unmet contraception demand, especially for the most effective methods, compared with non-user women, such as long-acting reversible contraception, and barriers to easier access and use. A way to alleviate the problem would be for institutions to treat the use of substances in conjunction with services providing contraception to promote the use of those methods (A).[97,98]

Approximately 35% of women who use drugs do not use any contraceptive method (B).[93] In a systematic review performed in 2015 (6 studies), when opioid-user women took contraception, they did it less frequently than non-users (56% versus 81% respectively). The percentages of use varied as follows: IUDs, 7%; implants, 15%; tubal ligation, 17%; oral hormonal contraceptives, 17%; and quarterly injectable, 8%.

No study evaluated the vaginal ring or transdermal patch. The use of moderately effective methods was observed as follows: condom, 62%; diaphragm, 10%; sponge and natural methods, $\leq$ 4%; and less effective methods, such as foam (3%) and vaginal shower (23%). The condom is the most widely used method because of its dual function of preventing sexually transmitted diseases (STDs) (A).[97] In Brazil, the efficacy of the methods should be adjusted with the availability of safe methods that do not depend on the willingness of female drug users to use them, given the difficulty in tracing this population.

With regard to very effective methods, tubal ligation can be performed as long as it is available in the basic health network, within established clinical criteria, and with informed and signed consent, avoiding the criticisms of the movements contrary to the 'sterilization' process (D).[99] Despite the difficulties in access and the rapid return of fertility after the time of use, LARCs can be offered (A).[98]

When using copper or levonorgestrel IUDs, the risk of pelvic inflammatory disease should be considered, given the difficulty of performing pre-insertion examinations and tracking patients (B).[100] The etonogestrel implant can be

used, and it promotes safe protection against unwanted pregnancy (B).[93]

As short-duration methods are difficult to use in drug users and have a 9% real failure rate, they should be avoided (A).[9] Although the quarterly injectable method has up to 3% of failure rate, it can be an option, but it needs active control of health agencies (A).[9] Condoms should always be recommended and offered, given the risks of sexually transmitted diseases.

Ethical and Legal Aspects for the Procedure of Inserting Long-acting Methods in Adolescents

In Brazil, the use of the informed consent form (ICF) in studies involving human beings was first proposed by Resolution number 01/88 of the Brazilian National Health Council, and the entire chapter IV of Resolution 196/96-CNS/MS is dedicated to it.[101] Although the ICF was more widely used in clinical trials, the value of consent was extended to routine medical care situations. Thus, in article 1 of January 21 2016 (Federal Council of Medicine recommendation 1/2016), it is emphasized that physicians should consider the ICF in decisions about patient health care.[102]

The insertion of LARCs is characterized as a medical procedure; hence, it could follow the precepts of establishing the informed consent. Age is the main controversial point, because there are differences in the interpretation of laws involving adolescents. The WHO characterizes adolescence as the second decade of life (10 to 19 years), and youth as the period between 15 and 24 years of age. The Brazilian Statute of the Child and Adolescent, in Article 2, considers people aged up to 12 incomplete years as children, and those aged between 12 and 18 years as adolescents. The Brazilian Civil Code, in turn, considers the age of 18 years for the practice of all acts of civil life. People older than 16 years can reach civilian majority for certain acts (emancipation, marriage, exercise of effective public employment, etc.).[103]

The Brazilian Statute of the Child and Adolescent preserves privacy, confidentiality and informed consent as fundamental rights. The 'family power' (old parens patriae) of the parents or legal guardians is not an absolute right.[104]

However, in Brazil, according to the new article 217-A of the penal code modified by law 12.015/2009, article 3, the age of consent for sex is 14 years. Article 217-A of the Criminal Code defines as 'rape of a vulnerable' the act of 'having carnal conjunction' or practicing libidinous acts with somebody aged under 14 years, regardless if real violence has occurred. That is, if a minor under 14 years of age engages in any sexual act, it may be considered sexual violence, even if the act was performed on one's own free will.[105]

Article 228 of the Brazilian Federal Constitution establishes that "minors under 18 years of age are criminally unimputable, subject to the norms of a special legislation," and, in accordance with the constitutional norm, the Statute of the Child and Adolescent infraction regime does not follow the typical system of Criminal Law based on criminal types and minimum and maximum penalties for each offense. The Statute of the Child and Adolescent does not refer to penalties or crimes practiced by adolescents, mentioning only infractions and social and educational measures that are not individualized for each specific conduct. There is no reference to "criminal liability" in the Statute of the Child and Adolescent.[103]

The Brazilian Pediatric Society (SBP, in the Portuguese acronym) and the Brazilian Federation of Gynecology and Obstetrics Societies (FEBRASGO, in the Portuguese acronym) have prepared a document stating that the "prescription of contraceptive methods" should take into account the adolescents' request, and respect medical eligibility criteria regardless of age. The prescription of contraceptive methods for adolescents younger than 14 years of age is no unlawful act of the physician, as long as the aforementioned criteria are respected. In the care of sexually active adolescents younger than 14 years, there is no longer the presumption of rape, as long as there is professional knowledge that it is not happening, based on information provided by the adolescent and careful evaluation of the case, all of which must be duly recorded in the patients' medical record (D).[106]

As this is a difficult issue, the Women's Health Reference Center (in the city of São Paulo) provided an alternative to this situation by adopting a term of consent for adolescents aged younger than 15 years using an etonogestrel subdermal implant as contraceptive. The document is signed by the adolescent, and has the same guidelines contained in the ICF, although more appropriate to that age, in addition to the regular ICF signed by the legal guardian (B).[93]

In conclusion, since there are many doubts in this situation, the consent of the adolescents and the legal guardians are considered for the use of LARCs, reinforcing the contraceptive counseling and suggesting the use of the ICF. These aspects still need further debate among the involved societies and public bodies.

Final Recommendations

1. Long-acting reversible contraceptives include the copper IUD, the LNG-IUS and the etonogestrel implant (D).
2. Long-acting reversible contraceptives have greater contraceptive efficacy compared with short-duration methods (B).
3. Long-acting reversible contraceptives have greater acceptance and continuity rates, and less contraindications compared with short-duration methods (A).
4. Anticipatory guidance about the bleeding pattern in each method is key, because, although low, discontinuity of the use of LARCs is mainly due to irregular bleeding (B).
5. Intrauterine methods do not increase the risk of PID (B).
6. Intrauterine methods may be indicated to women with history of ectopic pregnancy (B).
7. The LNG-IUS and the etonogestrel implant may be indicated for lactating women, including during the immediate postpartum period, because they are not related to thromboembolic events, and do not affect milk production and the infants' growth and development (A).
8. The postpartum insertion of intrauterine methods is associated with a higher expulsion rate (B).

9. Long-acting reversible contraceptives can be indicated to adolescents and nulliparous women (B).
10. Intrauterine methods and the etonogestrel implant do not increase the risk of venous thromboembolism (A).
11. The etonogestrel implant plays an important role in the contraception of vulnerable groups, such as drug users and homeless people (B).
12. The insertion of LARCs in adolescents should be performed after consent of the legal guardian as well, and the ICF can be used (D).
13. The main barriers for the use of LARCs are related to access and cost. Training the health professionals, providing proper guidance in particular, is also fundamental to reduce the barriers and expand the access to LARCs (B).

Conclusion

Long-acting reversible contraceptives are more effective contraceptive methods than short-acting contraceptive methods. They present a higher continuity rate, and have a small number of contraindications. Irregular bleeding is the main cause of discontinuation. They can be indicated for nulliparous women and adolescents, and can be inserted in the postpartum or immediate post-abortion. Intrauterine methods are not associated with increased risk of PID, provided that the technical rigors of insertion are observed. The main barriers to the use of LARCs are access and cost. Health professionals involved in contraceptive measures should prioritize appropriate guidance and training to offer and recommend LARCs.

Note

This study is part of the Guidelines and Recommendations of the FEBRASGO, and its authors are members of the Brazilian National Specialized Commission in Contraception.

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Prenatal Diagnosis of Galen Vein Aneurysm Using Ultrasonography and Magnetic Resonance Imaging and Perinatal and Long-Term Neurological Outcomes: A Case Series

Diagnóstico do aneurisma de veia de Galeno por meio de ultrassonografia e ressonância magnética e resultados perinatais e neurológicos: série de casos

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Abstract

Objective To describe the prenatal diagnosis of Galen vein aneurysm (GVA) based on ultrasonography and magnetic resonance imaging (MRI) in a series of cases, as well as its postnatal outcomes and follow-up until 4 years of age.

Methods A retrospective longitudinal study was performed, analyzing a database comprising seven cases of prenatal diagnosis of GVA at two Brazilian institutions from February of 2000 to May of 2012. The following data were evaluated: gestational age at diagnosis, GVA dimensions on ultrasonography, associated fetal changes, findings on fetal echocardiography, gestational age at delivery, type of delivery, birth weight, Apgar score at the 1st and 5th minutes, neonatal outcomes, and survival with follow-up until 4 years of age.

Results The mean gestational age ± standard deviation on the prenatal diagnosis of GVA based on ultrasonography was 25 ± 4.9 weeks. The mean length of GVA was 3.2 ± 0.4 cm. The mean gestational age at birth was 37.5 ± 0.7 weeks, and a cesarean section was performed in 85.7% of the cases (6/7). The mean birth weight was 3,070 ± 240.4 g. The total survival rate was 42.8% (4/7), with three neonatal deaths. Of the four survivors, three presented with normal neuropsychomotor development until 4 years

Keywords
- Galen vein aneurysm
- prenatal diagnosis
- ultrasonography
- magnetic resonance
- perinatal outcomes

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of age and only one showed serious neurological sequelae. Ultrasonography and MRI showed similar findings for all seven cases.

Conclusions Galen Vein Aneurysm is associated with a high neonatal death rate. Therefore, its prenatal diagnosis is essential for parent counseling and follow-up at tertiary care institutions.

Resumo

Objetivo Descrever o diagnóstico pré-natal de uma série de casos de aneurisma de veia de Galeno (AVG) por meio de ultrassonografia e ressonância magnética (RM), bem como os resultados pós-natais e acompanhamento até 4 anos de vida.

Métodos Realizou-se um estudo retrospectivo longitudinal com análise de banco de dados de sete casos de diagnóstico pré-natal de AVG em dois serviços brasileiros entre fevereiro de 2000 e maio de 2012. Foram avaliados a idade gestacional ao diagnóstico, dimensões do AVG na ultrassonografia, alterações fetais associadas, achados da ecocardiografia fetal, idade gestacional ao parto, tipo de parto, peso ao nascimento, índice de Apgar no 1° e 5° minutos, resultados neonatais, e sobrevida com acompanhamento até 4 anos de idade.

Resultados A idade gestacional média ± desvio-padrão ao diagnóstico pré-natal do AVG pela ultrassonografia foi de 25 ± 4,9 semanas. O comprimento médio do AVG foi 3,2 ± 0,4 cm. A idade gestacional média ao nascimento foi 37,5 ± 0,7 semanas, sendo que, em 85,7% dos casos (6/7) o parto foi cesáreo. O peso médio ao nascimento foi de 3.070 ± 240,4 gramas. A sobrevida total foi de 42,8% (4/7), com três óbitos neonatais. Dos quatro sobreviventes, três apresentaram desenvolvimento neuropsicomotor normal até a idade de 4 anos, sendo que apenas um apresentou sequelas neurológicas graves. Ultrassonografia e RM apresentaram achados semelhantes nos sete casos.

Conclusões O AVG está associado à elevada taxa de óbito neonatal, sendo, portanto, fundamental o seu diagnóstico pré-natal precoce para aconselhamento dos pais e seguimento em serviço terciário.

Palavras-chave
- Aneurisma da veia de Galeno
- Diagnóstico pré-natal
- Ultrassonografia
- Ressonância magnética
- Resultados perinatais

Introduction

Galen vein aneurysm (GVA) is a rare congenital malformation arising because of the presence of multiple arteriovenous shunts that drain to a median prosencephalic vein.[1] There is usually only a single malformation corresponding to ~ 1% of all vascular cerebral malformations. However, it may be associated with congenital heart disease, hydrops, and cystic hygroma.[2] Its etiology is unknown, and there is no described familial inheritance. Heart failure is the most common symptom in the neonatal period, but seizures and other neurological signs may also be observed.[3,4]

Because GVA has a low incidence rate but high morbidity and mortality rates, a prenatal diagnosis is necessary for adequate follow-up, delivery, and parent counseling. In general, the condition is prenatally diagnosed based on conventional ultrasonography when a cystic image that confirms dilation of the vein, located either in the middle region or slightly deviated from the central region, below the third ventricle on the middle supratentorial line is identified.[5] Color Doppler imaging shows a turbulent flow inside the cyst, which may be associated with secondary ventriculomegaly.[6] Magnetic resonance imaging (MRI) helps to confirm the diagnosis and also reveals complications such as hemorrhagic injury in the white matter of the brain.[7] Other prenatal diagnostic methods such as ultrasonography in the 3-dimensional power Doppler mode have been described, but these have shown no advantages over conventional ultrasonography and MRI.[8,9] Fetal echocardiography may help detect early signs of heart failure, which, together with hydrops, is the most common consequence of GVA.

Here we present a series of seven cases of prenatal diagnosis of GVA with their main findings based on conventional ultrasonography and MRI as well as their postnatal outcomes.

Methods

A retrospective longitudinal study was performed, analyzing a database of seven cases of prenatal diagnosis of GVA from February of 2000 to May of 2012 at two Brazilian institutions: Centro Integrado de Saúde Amaury de Medeiros da Universidade de Pernambuco (UPE) and Clínica de Diagnóstico por Imagem (CDPI). This study was approved by the Committee on Ethics in Research of the Universidade de Pernambuco (UPE). Five cases were from UPE and 2 from CDPI.

The following data were evaluated: gestational age (in weeks) at diagnosis, GVA dimensions on ultrasonography, associated fetal changes, findings on fetal echocardiography,

gestational age at delivery, type of delivery, birth weight, Apgar score at the 1st and 5th minutes, neonatal outcomes, and survival with follow-up until 4 years of age. In addition, we have described the main findings based on color Doppler ultrasonography and MRI.

Results

The mean gestational age ± standard deviation on prenatal diagnosis of GVA by ultrasonography was 25 ± 4.9 weeks. The mean length and width of the GVA on diagnosis were 3.2 ± 0.4 cm and 2.2 ± 1.6 cm, respectively. The mean gestational age at birth was 37.5 ± 0.7 weeks, and a cesarean section was performed in 85.7% of cases (6/7). The average birth weight was 3,070 ± 240.4 g. Mean Apgar scores at the 1st and 5th minutes were 8.5 ± 0.7 and 9.5 ± 0.7, respectively. The overall survival rate was 42.8% (4/7), with three neonatal deaths. Of the four survivors, three presented with normal neuropsychomotor development until 4 years of age and only one showed serious neurological sequelae. ►**Table 1** presents the description of the pre- and postnatal data of the seven cases of GVA. ►**Fig. 1** shows the pre- and postnatal imaging findings of case #7. ►**Table 2** presents the description of the main findings based on conventional color Doppler ultrasonography and MRI in the seven cases of the prenatal diagnosis of GVA.

Discussion

Here we present a series of cases of prenatal diagnosis of GVA based on ultrasonography at an average gestational age of 25 weeks; our diagnosis agrees with the findings reported in most publications.[8–10] Magnetic resonance imaging is used to evaluate associated neurological findings that may be of prognostic value. In our case series, MRI showed no diagnostic advantages over ultrasonography. In a series of 18 cases of GVA, MRI identified 3 cases of neuronal migration abnormalities that had not been identified by ultrasonography.[2]

In our series, associated findings were present in 71% of the cases (5/7) and cardiomegaly was the most frequent finding. However, in only two cases, a therapeutic preterm delivery was performed owing to congestive heart failure in the fetus. The mean gestational age at delivery was 37.5 weeks, and the mean birth weight was adequate in terms of the gestational age. In a series of 21 cases, the mean gestational age at birth was high (38.7 weeks) and the mean birth weight was also adequate in terms of the gestational age (3096 g).[2] The most frequent type of delivery in our case series was cesarean section (86%), which is in accordance with the high incidence of this type of delivery in Brazil, both in public and private institutions, regardless of fetal malformations.[11]

Associated anomaly is a proven factor of adverse perinatal outcome in cases of GVA and termination of the pregnancy is indicated in countries where this procedure is legal.[2] Regarding the type of delivery, in the absence of fetal cardiac dysfunction and isolated GVA, normal delivery is the best choice. In the presence of fetal cardiac dysfunction and isolated/associated GVA, there is no consensus in the literature and the choice should be based on the gestational age and the neonatal intensive care.

Table 1 Prenatal outcomes of fetuses diagnosed with Galen vein aneurysm

Case#	1	2	3	4	5	6	7
GA at diagnosis (weeks)	33	36	32wk, 1d	35	30	24	26
Associated findings	cardiomegaly, slight pericardial effusion	polyhydramnion, ventriculomegaly, cardiomegaly, cervical vascular congestion	Polyhydramnion	ventriculomegaly, cardiomegaly, cervical vascular congestion	ventriculomegaly, pericardial effusion, cardiomegaly, cervical vascular congestion	None	None
Fetal echo.	cardiomegaly,	pulmonary hypertension, heart failure	Normal	cardiomegaly, pericardial effusion, heart failure	cardiomegaly, tricuspid failure, pericardial effusion	Normal	Normal
GVA (cm)	2.9 × 1.1	3.2 × 1.8	2.2 × 1.8	7.0 × 2.5	4.2 × 2.5	3.0 × 2.3	3.5 × 3.4
Type of delivery	Vaginal	Cesarean	Cesarean	Cesarean	Cesarean	Cesarean	Cesarean
GA at birth (weeks)	37	39	38	36wk, 1d	34wk, 4d	38	39
Apgar score, 1st & 5th min	8 and 9	3 and 6	7 and 9	5 and 4	6 and 4	8 and 9	9 and 10
Birth weight (g)	2900	2940	3180	2980	2550	3060	3240
Neonatal outcome	GVA embolization at 6mth	ICU, digoxin, furosemide	discharge 4d after birth	ICU for 28d	heart failure	3wk in the ICU	seizures, hydrocephalus, heart failure 2wk after birth
Survival up to 4yr of age	Normal	death at 48h	spontaneous thrombosis at 4yr, normal development	serious neurologic sequelae	death on 4th day	death during surgery	Normal

Abbreviations: d, day(s); echo., **echocardiography**; GA, gestational age; GVA, Galen vein aneurysm; ICU, intensive care unit; mth, month(s); wk, week(s); yr, year(s).

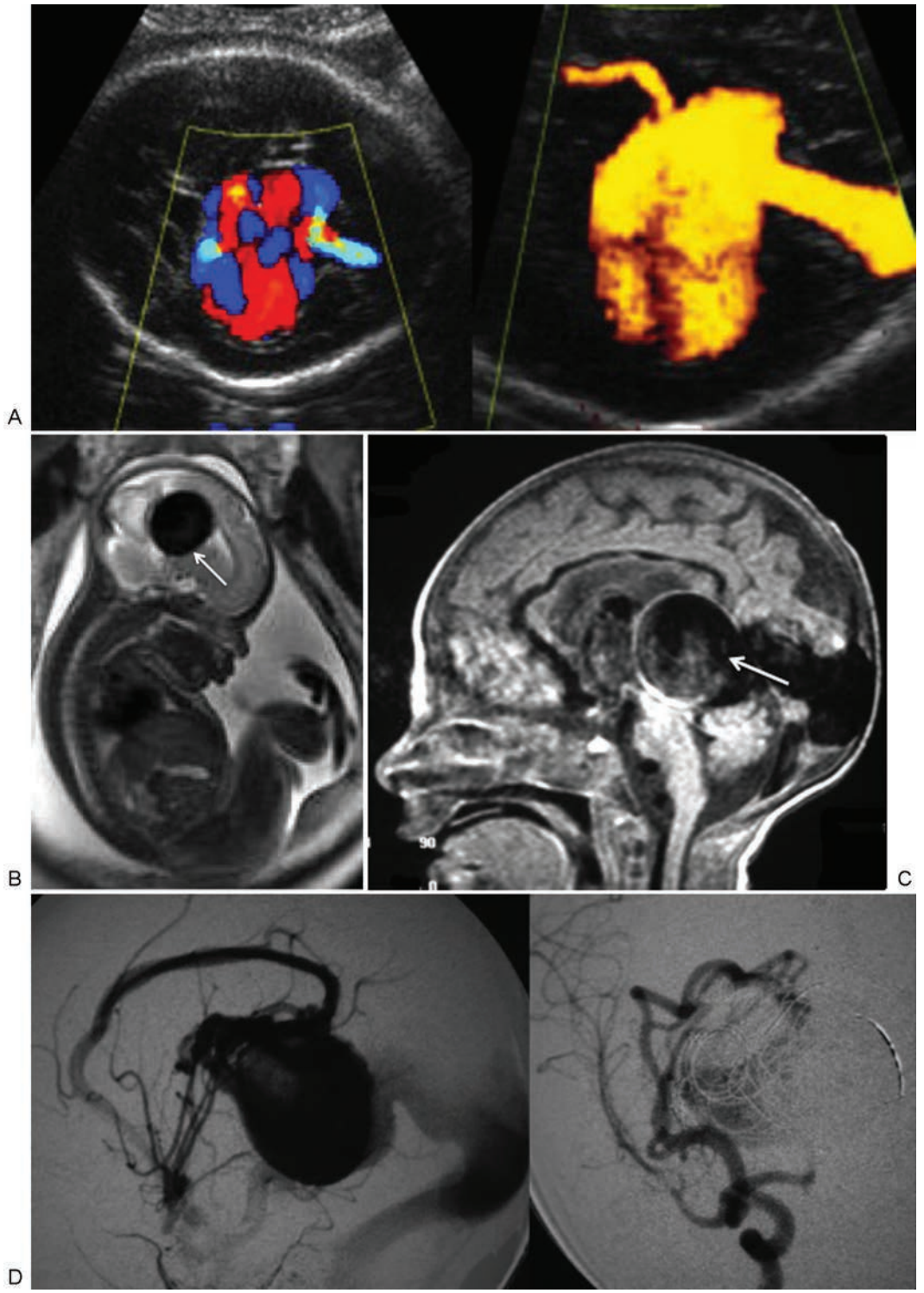

Fig. 1 (A) Two-dimensional ultrasonography in the axial plane based on color and power Doppler ultrasonography at the 28th week of pregnancy, confirming the Galen vein aneurysm. **(B)** Fetal sagittal T2 magnetic resonance image confirming the Galen vein aneurysm with a hypointense signal (arrow). **(C)** Postnatal sagittal T2 magnetic resonance image confirming the Galen vein aneurysm (arrow). **(D)** Angiography performed on the 23rd day after birth. Pre- and post-embolization images, showing reduction in the Galen vein aneurysm.

Despite advancements in prenatal diagnosis, neonatal mortality is high in GVA, with three neonatal deaths (43%) observed in our case series, as well as a case of serious neurological sequelae in the 4-year follow-up (14%). In all these neonatal deaths, the fetuses showed cardiomegaly in the fetal echocardiography. In a case series in which termination of the pregnancy was performed in fetuses with GVA, 89% of them showed cardiomegaly in the fetal echocardiography.[2] There are no studies regarding the best fetal echocardiography follow-up in cases with cardiac dysfunction/cardiomegaly.

Table 2 Findings on magnetic resonance imaging and ultrasonography in our cases of prenatal diagnosis of Galen vein aneurysm

Case #	Magnetic resonance imaging	Ultrasonography
1	Ellipsoid expansive formation, ~ 2.0 cm in its largest diameter at the level of the middle line in the tentorial region, posterior to the pituitary, hypointense T1 and T2 signals, suggesting a flow void, communicating with the sinus rectus, consistent with aneurysmal dilation of the Galen vein, with no signs of ventriculomegaly.	An elongated cystic image, measuring ~ 2.9 × 1.1 cm, was observed in a location posterior to the thalamus, continuing on the middle line and spreading superiorly between the hemispheres. On the color Doppler, a low-resistance flow was observed, with an arterial pattern prevailing. The echographic aspect and the flow pattern are consistent with Galen vein aneurysm. Enlarged cardiac area and slight pericardial effusion.
2	Slight ventriculomegaly and expansive ellipsoid formation in a middle line location, spreading to the posterior fossa, consistent with arteriovenous malformation (Galen vein aneurysm).	Slight ventriculomegaly and an elongated anechoic image in a middle line location, spreading to the posterior fossa. On the color Doppler, an abundant flow of very low resistance, consistent with an arteriovenous malformation (Galen vein aneurysm). Enlarged cardiac area with slight pericardial effusion.
3	Intracranial ellipsoid expansive formation, 3.0 × 2.1 cm in size, located on the middle cerebral line (supratentorial), consistent with Galen vein aneurysm.	A homogeneous intracranial cystic area, measuring 2.2 × 1.8 cm, localized on the middle line (supratentorial). On color Doppler, intense arteriovenous flow. Normal heart size and shape.
4	Ellipsoid expansive formation measuring 7.0 × 2.5 cm, supratentorial, slight dilation of the posterior horn of the brain ventricle and the 3rd ventricle, consistent with Galen vein aneurysm associated with ventriculomegaly.	A cystic area with a tubular aspect, measuring 4.1 × 3.7 cm, on the middle line (supratentorial), being confirmed based on color Doppler as an arteriovenous flow within, consistent with Galen vein aneurysm. Slight ventricular dilation. Slightly enlarged cardiac area. Vascular congestion of the cervical region.
5	Ventricular dilation and ellipsoid expansive formation, measuring ~ 6.0 × 4.0 cm, on the middle line (supratentorial), consistent with Galen vein aneurysm.	A cystic area with a tubular aspect, measuring ~ 5.5 × 4.0 cm, on the middle line (supratentorial), confirmed based on color Doppler as an arteriovenous flow within, consistent with Galen vein aneurysm. Slight ventricular dilation.
6	Expansive lesion with lobulated contours and well-defined limits, with a hypointense T2 signal and an iso/hypointense T1 signal, measuring 3.0 × 1.8 × 2.3 cm, interhemispheric, posterior to the 3rd ventricle, with no compressive effect.	Anechoic image measuring 34 × 28 mm, located posteriorly above the thalamus. Slightly dilated lateral ventricles. Color Doppler with turbulent flow. Normal 3rd and 4th ventricles.
7	Expansive lesion with lobulated contours and well-defined limits, with a hypointense T2 signal and an iso/hypointense T1 signal, measuring 3.5 × 3.4 × 2.6 cm, interhemispheric, posterior to the 3rd ventricle, no compressive effect.	Anechoic Image measuring 26 × 24 mm, posterior to the 3rd ventricle. Normal lateral, 3rd, and 4th ventricles. Color Doppler with turbulent flow.

In a systematic review of 90 cases of prenatal diagnosis of GVA, the mortality rate was 54%, and serious neurological sequelae were found in 14% of the cases[2]; this was consistent with the findings of our study. Postnatal treatment of GVA will depend on its size; small GVAs with low flow may undergo spontaneous thrombosis, as observed in case #3. Patients with neurological and cardiac symptoms must be treated by a radiological or surgical intervention.[5] When GVA is not life threatening, the vascular malformation is best embolized after 5 months from birth,[12] as performed in cases #1 and #7, which showed good postnatal outcomes and normal neurological development in the 4-year follow-up.

In summary, we have presented a series of cases of prenatal diagnosis of GVA based on ultrasonography and MRI. Because GVA is associated with high rates of neonatal death, its prenatal diagnosis is essential for parent counseling and follow-up at tertiary care institutions.

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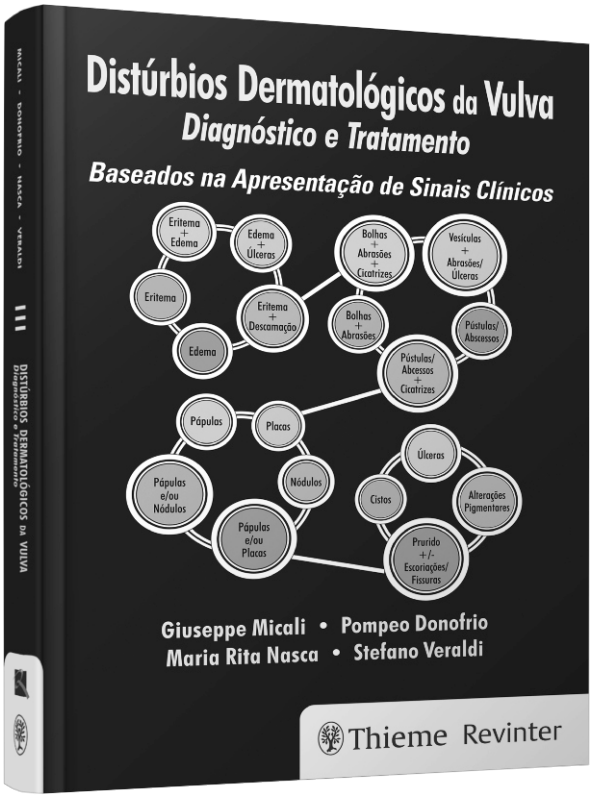
Porque o conhecimento médico está em constante evolução!



Mais do que classificar os transtornos vulvares por categorias padronizadas como lesões neoplásicas, inflamatórias ou infecciosas, esta obra descreve os distúrbios dermatológicos da vulva através da apresentação das lesões elementares que determinam os principais sinais morfológicos como: eritemas, bolhas, placas, cistos ou úlceras. ***Diagnóstico e Tratamento dos Distúrbios Dermatológicos da Vulva - Diagnóstico Baseado na Apresentação de Sinais Clínicos*** combina imagens clínicas com descrições curtas e objetivas, a fim de facilitar a identificação imediata e correta de vários transtornos vulvares. Ricamente ilustrada, com centenas de fotografias coloridas de altíssima qualidade, esta obra apresenta cada distúrbio com a seguinte abordagem:descrição clínica, definição, etiologia, epidemiologia, desenvolvimento, diagnóstico, diagnóstico diferencial e tratamento. Décadas de experiência clínica de renomados médicos e cientistas reconhecidos internacionalmente foram condensadas neste único volume. Trata-se de um recurso valioso e útil tanto para ginecologistas e dermatologistas experientes quanto para residentes nestas especialidades.

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- **Acknowledgements:** restricted to people and institutions that contributed to research development in a relevant way. Any financial support provided by development agencies or private companies should be mentioned in the section Acknowledgments. For Brazilian authors, RBGO requests the citation of CNPq, Capes, FAPESP and other financing agencies, together with the number of research process or granted scholarships.
- **Contributions:** according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit must be based on three conditions met in full: 1. Substantial contributions to conception and design, data collection or analysis, and interpretation of data; 2. Writing of the article or critical review of the intellectual content; and 3. Final approval of the version to be published.

Manuscript

Instructions to Authors

The Brazilian Journal of Gynecology and Obstetrics publishes the following categories of manuscripts:

Original Articles, complete prospective, experimental or retrospective studies. Manuscripts containing original clinical or experimental research results have priority for publication.

Case Reports, of great interest and well documented from the clinical and laboratorial point of view. In the letter of referral, authors should indicate new or unexpected aspects in relation to already published cases. The text of Introduction and Discussion sections should be based on an updated bibliographic review.

Review Articles, including comprehensive reviews, meta-analysis or systematic reviews. Spontaneous contributions are accepted. The methods and procedures adopted for obtaining the text should be described, and based on recent references, including the current year. As this subject is still subject to controversy, the review should discuss the trends and lines of research under way. In addition to the text of the review, there should be an abstract and conclusions. See the 'Instructions to Authors' section for information on the text body and title page;

Letters to the Editor, dealing with editorial matters or not, but presenting relevant information to readers. Letters can be summarized by the editor, but maintaining the main points. In case of criticism to published works, the letter is sent to the authors so their reply can be published simultaneously;

Editorial, only at the publisher's invitation.

Title

When writing a scientific article, the researcher should focus on the manuscript title, which is the business card of any publication. It should be elaborated very carefully, and preferably written only after the article finalization. A good title adequately describes the manuscript content. Generally it is not a phrase, because it does not contain the subject, only verbs and arranged objects. Titles rarely contain abbreviations, chemical formulas, adjectives, names of cities, among others. The title of manuscripts submitted to RBGO must contain a maximum of 18 words.

Abstract

The abstract should provide the context or basis for the study, establish the objectives, basic procedures, main outcomes and key findings. It should emphasize new and important aspects of the study or observations. Since the abstract is the only substantive part of the article indexed in many electronic databases, authors should ensure it reflects the article content in an accurate and highlighted manner. Do not use abbreviations, symbols and references in the abstract. In case of original articles from clinical trials, authors must inform the registration number at the end of the text.

Informational abstract of structured type of original articles

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

Objective: What was done; the question posed by the investigator.

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

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

Conclusion: The conclusions; the answer to the question asked.

Informational abstract of structured type of systematic review articles

Among the included items are the review objective to the question asked, data source, procedures for selecting the studies and data collection, the results and conclusions. The abstracts of systematic review articles submitted to RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: Declare the main purpose of the article.

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

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

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

Data synthesis: State the main results of the review and the methods used to obtain them.

Conclusions: Indicate the main conclusions and their clinical usefulness.

Informational abstract of unstructured type of review articles, except systematic reviews and case studies

It shall contain the substance of the article, covering the purpose, method, results and conclusions or recommendations. It exposes enough details so readers can decide on the convenience of reading the full text (Limit of words: 150).

Keywords

The keywords of a scientific paper indicate the thematic content of the text they represent. The main objectives of the aforementioned terms are the thematic content identification, indexing of the work in databases, and rapid location and retrieval of contents. The keyword systems used by RBGO are DeCS (Health Sciences Descriptors - Lilacs Indexer) and MeSH (Medical Subject Headings - MEDLINE-PubMed Indexer). Please choose five descriptors that represent your work on these platforms.

Manuscript body (Manuscripts submitted to RBGO must have a maximum of 4000 words. Note that tables, charts and figures in the Results section and References are not counted).

Introduction

The **Introduction** section of a scientific article has the purpose of informing what was researched and the reason for the investigation. This part of the article prepares the reader to understand the investigation and justification of its realization. The content informed in this section should provide context or basis for the study (i.e. the nature of the problem and its importance); state the specific purpose, research objective, or hypothesis tested in the study or observation. The study objective usually has a more precise focus when formulated as a question. Both the primary and secondary objectives should be clear, and any analyzes in a pre-specified subgroup should be described; provide strictly relevant references only and do not include data or conclusions of the work being reported.

Methods

According to the Houaiss dictionary, **Methods** "is an organized, logical and systematic process of research". The method comprises the material and procedures adopted in the research in order to respond to the central research question. Structure the Methods section of RBGO starting with the study design; research scenario (place and period in which it was performed); sample of participants; data collection; intervention to be evaluated (if any) and the alternative intervention; statistical methods used and the ethical aspects of the study. When thinking about the writing of the study design, reflect if it is appropriate to achieve the research objective, if the data analysis reflects the design, and if what was expected with use of the design was achieved to research the theme. Following, the guidelines used in clinical or epidemiological research that should be included in the section Methods of manuscripts sent to RBGO:

Types of study (adapted from Pereira, 2014*):

Case Report (Case study): In-depth investigation of a situation in which one or a few people are included (usually up to ten);

Case series: A set of patients (for example, more than ten people) with the same diagnosis or undergoing the same intervention. In general, these are consecutive series of patients seen in a hospital or other health institution for a certain period. There is no internal control group formed simultaneously. The comparison is made with external controls. The name of external or historical control is given to the group used to compare the results, but that was not constituted at the same time within the study: for example, the case series is compared with patients from previous years.

Transversal (or Cross-sectional) study: Investigation to determine prevalence; examine the relationship between events (exposure, disease, and other variables of interest) at any given time. Cause and effect data are collected simultaneously: for example, the case series is compared with patients from previous years.

Case-control study: Particular form of etiological investigation of retrospective approach in which the search of causes starts from the effects. Groups of individuals, respectively with and without a particular health problem are compared in relation to past exposures in order to test the hypothesis that exposure to certain risk factors is the contributing cause of the disease. For example, individuals afflicted with low back pain are compared with an equal number of individuals (control group) of the same sex and age, but without low back pain.

Cohort study: Particular form of investigation of etiological factors in which the search of effects starts from the cause; therefore, the opposite of case-control studies. A group of people is identified, and pertinent information on the exposure of interest is collected, so the group can be monitored over time, checking those who do not develop the disease in focus, and if the prior exposure is related to occurrence of disease. For example, smokers are compared to nonsmoker controls; the incidence of bladder cancer is determined for each group.

Randomized study: This has the connotation of an experimental study to evaluate an intervention hence the synonym of *intervention study*. Can be performed in a clinical setting; sometimes referred to simply as clinical trial or clinical study. It is also conducted at the community level. In clinical trials, participants are randomly assigned to form groups called study (experimental) and control (or testimony), whether submitted or not to an intervention (for example, a drug or vaccine). Participants are monitored to verify the occurrence of outcome of interest. This way, the relationship between intervention and effect is examined under controlled observation conditions, usually with double-blind evaluation. In the case of a **randomized study**, inform the number of the Brazilian Registry of Clinical Trials (REBEC) and/or the number of the International Clinical Trials Registration Platform (ICTRP/OMS) on the title page.

Ecological study: Research performed with statistics: the unit of observation and analysis is not constituted of individuals, but of groups of individuals hence the synonyms: study of groups, aggregates, clusters, statistics or community. For example, research on the variation of mortality coefficients for diseases of the vascular system and per capita consumption of wine among European countries.

Systematic Review and Meta-analysis: Type of review in which there is a clearly formulated question, explicit methods are used to critically identify, select and evaluate relevant research, and also to collect and analyze data from the studies included in the review. There is use of strategies to

limit bias in the localization, selection, critical evaluation and synthesis of relevant studies on a given topic. Meta-analysis may or may not be part of the systematic review. Meta-analysis is the review of two or more studies to obtain a global, quantitative estimate of the question or hypothesis investigated; and employs statistical methods to combine the results of the studies used in the review.

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

Script for statistical review of original scientific papers

Study objective: Is the study objective sufficiently described, including pre-established hypotheses?

Design: Is the design appropriate to achieve the proposed objective?

Characteristics of the sample: Is there a satisfactory report on the selection of people for inclusion in the study? Has a satisfactory rate of responses (valid cases) been achieved? If participants were followed up, was it long and complete enough? If there was a pairing (eg. of cases and controls), is it appropriate? How did you deal with missing data?

Data Collection (measurement of results): Were the measurement methods detailed for each variable of interest? Is there a description of comparability of the measurement methods used in the groups? Was there consideration of the validity and reproducibility of the methods used?

Sample size: Has adequate information on sample size calculation been provided? Is the logic used to determine the study size described, including practical and statistical considerations?

Statistical Methods: Was the statistical test used for each comparison informed? Indicate if the assumptions for use of the test were followed. Was there information about the methods used for any other analysis? For example, subgroup analysis and sensitivity analysis. Are the main results accompanied by accuracy of the estimate? Inform the p value and confidence interval. Was the alpha level informed? Indicate the alpha level below which the results are statistically significant. Was the beta error informed? Or indicate the statistical power of the sample. Has the adjustment been made to the main confounding factors? Were the reasons that explained the inclusion of some and the exclusion of others described? Is the difference found statistically significant? Make sure there are sufficient analyzes to show the statistically significant difference is not due to any bias (eg. lack of comparability between groups or distortion in data collection). If the difference found is significant, is it also relevant? Specify the clinically important minimal difference. Make clear the distinction between statistically relevant difference and relevant clinical difference. Is it a one- or two-tailed test? Provide this information if appropriate. What statistical program is used? Inform the reference where to find it, and the version used.

Abstract: Does the abstract contain the proper article synthesis?

Recommendation on the article: Is the article in acceptable statistical standard for publication? If not, can the article be accepted after proper review?

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

IMPORTANT!

RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, which are aimed to improve the presentation of research results. Check the following international guides:

Randomized clinical trial:
http://www.consort-statement.org/downloads/consort-statement

Systematic reviews and meta-analysis: http://www.scielo.br/pdf/ress/v24n2/2237-9622-ress-24-02-00335.pdf

Observational studies in epidemiology: strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf

Qualitative studies: http://intqhc.oxfordjournals.org/content/19/6/349.long

Results

The purpose of the Results section is to show the study findings. It is the original data obtained and synthesized by the author with the aim to answer the question that motivated the investigation. For the writing of the section, present the results in logical sequence in the text, tables and illustrations, first mentioning the most important findings. Do not repeat all information of the tables or illustrations in the text. Emphasize or summarize only important observations. Additional or supplementary materials and technical details may be placed in an appendix where they will be accessible without interrupting the flow of the text. Alternatively, this information may be published only in the electronic version of the Journal. When data are summarized in the results section, provide numerical results not only in derived values (eg. percentages), but also in absolute values from which the derivatives were calculated, and specify the statistical methods used for their analysis. Use only the tables and figures necessary to explain the argument of the work and evaluate its foundation. When scientifically appropriate, include data analysis with variables such as age and sex. Do not exceed the maximum limit of five tables, five charts or five figures. Tables, charts and/or figures should be included in the body of the manuscript and do not count the requested limit of 4000 words.

ATTENTION!

In Case Studies, the Methods and Results sections should be replaced by the term Case Description.

Discussion

In the **Discussion** section, emphasize the new and important aspects of the study and the conclusions derived therefrom. Do not repeat details of data or other information presented in the introduction or results sections. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, comparing and contrasting the results with other relevant studies, stating the limitations of the study, and exploring the implications of the findings for future research and clinical practice. Avoid claiming precedence and referring to incomplete studies. Do not discuss data not directly related to the results of the presented study. Propose new hypotheses when justifiable, but qualify them clearly as such. In the last paragraph of the Discussion section, cite which information of your work contributes relatively to advancement of knowledge.

Conclusion

The **Conclusion** section has the function of relating the conclusions to the objectives of the study, but authors should avoid unfounded statements and conclusions not adequately supported by data. In particular, authors should avoid making statements about economic benefits and costs unless their original includes economic analysis and appropriate data.

References

A study is based on the results of other research that preceded it. Once published, it becomes support for future work on the subject. In the report of their research, authors state the references of prior works consulted that they deem pertinent to inform readers, hence the importance of choosing good References. Properly chosen references lend credibility to the report. They are a source for convincing readers of the validity of facts and arguments presented.

Attention! For manuscripts submitted to RBGO, authors should number the references in order of entry into the manuscript and use those numbers for text citations. Avoid excessive references by selecting the most relevant for each statement and giving preference to the most recent work. Do not use hard-to-reach quotations, such as abstracts of papers presented at congresses, theses or restricted publications (non-indexed). Seek to cite the primary and conventional references (articles in scientific journals and textbooks). Do not use references such as 'unpublished observations' and 'personal communication'. Authors' publications (self-citation) should be used only if there is a clear need and relationship with the topic. In this case, include in bibliographical references only original works published in regular journals (do not cite chapters or revisions). The number of references should be 35, in exception review articles. Authors are responsible for the accuracy of data contained in the references.

Please check the American Medical Association (AMA) Citation Style to format your references.

*The Instructions to Authors of this journal were elaborated based in the literary work ***Artigos Científicos: Como redigir, publicar e avaliar de Maurício Gomes Pereira, Editora Guanabara Koogan, 2014.***

Submission of papers

The articles must, necessarily, be submitted electronically, according to the instructions posted on the site: http://mc04.manuscriptcentral.com/rbgo-scielo

There is no fee for submission and review articles.

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BURGHARDT – COLPOSCOPIA E PATOLOGIA CERVICAL

Texto e Atlas – 4ª Edição

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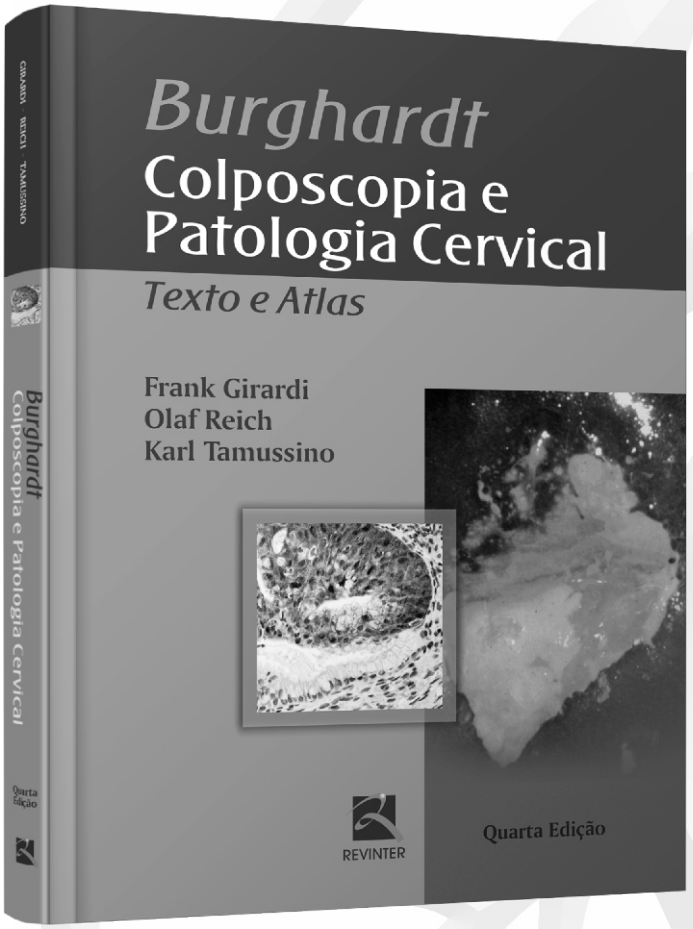

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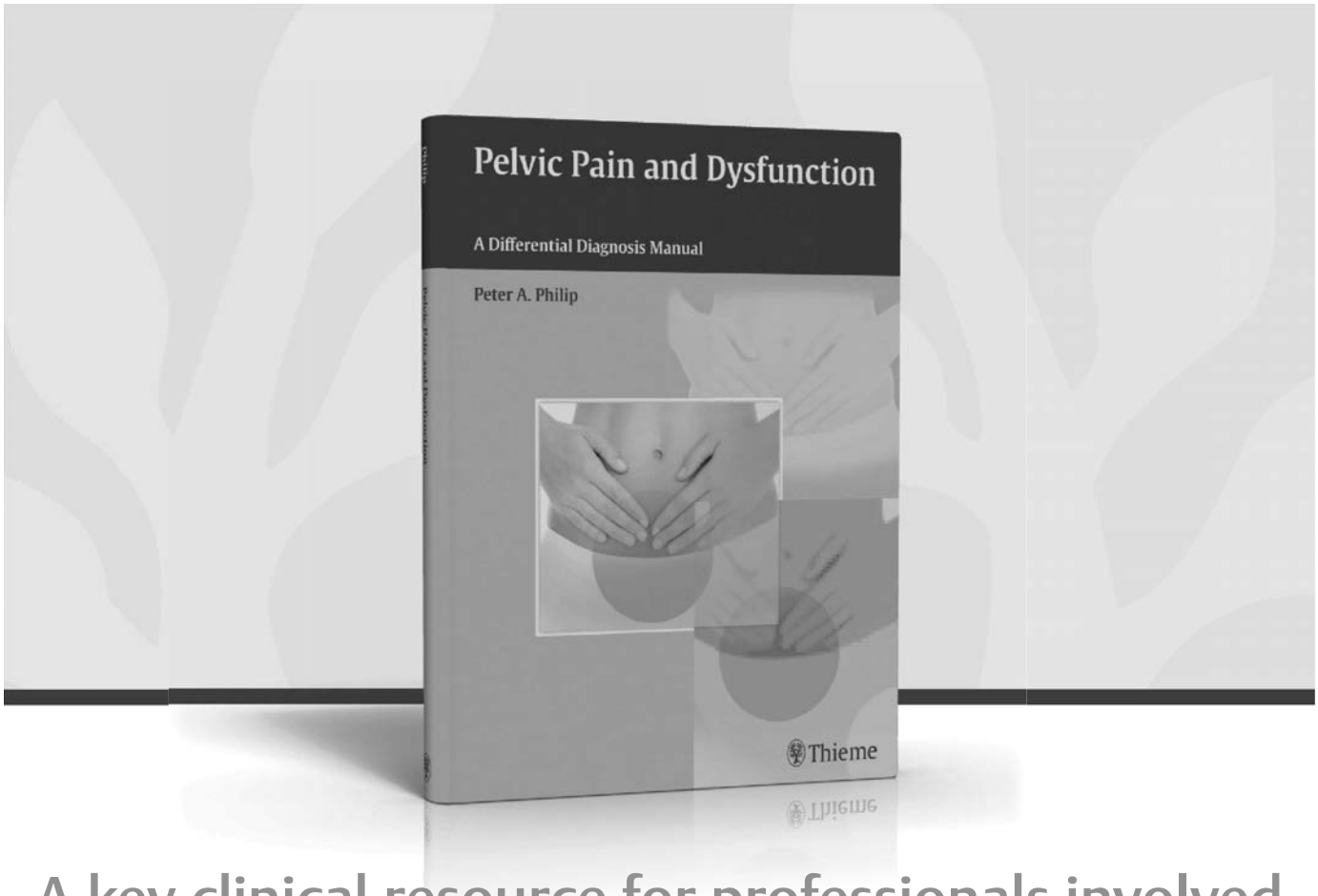
Completamente revisado e atualizado, o texto sobre colposcopia e patologia cervical, que marcou a época de Bughardt, estabelece um novo padrão no campo. Oferece aos especialistas informações completas sobre os procedimentos colposcópicos, bem como os fundamentos histopatológicos necessários para realizar um diagnóstico preciso. Abrangendo desde equipamento e técnicas, à detecção de achados normais e anormais, ao diagnóstico diferencial e diretrizes terapêuticas, este livro não encontra rival na literatura. Focado na apresentação integrada dos achados colposcópicos com a sua patologia subjacente, este livro oferece uma compreensão completa dos aspectos morfológicos do diagnóstico clínico. É essencial para os ginecologistas, obstetras, oncologistas ginecológicos, patologistas, residentes, *fellows*, *trainees* e outros profissionais que trabalham na prevenção e detecção precoce para alcançar os melhores resultados possíveis no manejo do carcinoma cervical.



A key clinical resource for professionals involved in the treatment of pelvic pain and dysfunction

Pelvic Pain and Dysfunction
A Differential Diagnosis Manual

Peter A. Philip

2016/120 pp./80 illus./hardcover
ISBN 978-3-13-173221-7
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Pelvic Pain and Dysfunction: A Differential Diagnosis Manual is a comprehensive guide on the management of patients suffering from pelvic pain as well as dysfunction of the bowel and bladder systems. It integrates differential diagnosis concepts with orthopedic medicine and helps clinicians learn how to apply these concepts when treating patients suffering from pelvic pain.

KEY FEATURES:

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Junte-se à luta

FORÇA AMIGA

contra o câncer de colo do útero

Dê o próximo passo e lute por esta paciente.

Há muito a ser feito por ela.

DOUTORES, CONVIDAMOS TODOS VOCÊS
A FAZEREM PARTE DA CAMPANHA **#FORÇAAMIGA.**

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