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Editorial

Enhanced Recovery After Surgery (ERAS): New Concepts in the Perioperative Management of Gynecologic Surgery

Programa Enhanced Recovery After Surgery (ERAS): novos conceitos de manejo perioperatório em Cirurgia Ginecológica

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What is ERAS?

The Enhanced Recovery After Surgery (ERAS) program is a paradigm shift from traditional perioperative management initiated by Kehlet in 1997[1] as a multidisciplinary approach to the care of the surgical patient.[1–3] The program is based on perioperative medical optimization, including preoperative counseling, pain relief, carbohydrate loading, thromboembolism prophylaxis, standard anesthetic protocol and intraoperative fluid, recovery of normal gastrointestinal function, and early mobilization (►**Table 1**). The primary goal of the protocol is to minimize the response to the stress of the operation by maintaining homeostasis, avoiding catabolism with consequent loss of protein and muscle strength, and cellular dysfunction.[3]

The main objectives of the ERAS program are to accelerate functional recovery, improve postoperative outcomes, shorten the length of stay (LOS) in the hospital, reduce the overall health care costs, and improve the satisfaction of the patients without increasing complications and/or hospital readmission rates.[4] The ERAS protocols resulted in a 30% to 50% reduction in the LOS and similar reductions in complications, as well as lower costs and readmission rates.[3] The protocols were developed for colorectal surgery, and variations are being adopted for surgical procedures of various specialties, including Gynecology.[5,6]

The ERAS Society is an international nonprofit professional society that promotes, develops, and implements ERAS programs, publishes updated guidelines for many operations, and was officially registered in 2010 in Sweden (http://erassociety.org). Its mission is to develop perioperative care and to improve recovery through research, education, auditing and implementation of evidence-based practices. Throughout its history, the ERAS Society has developed and published numerous evidence-based protocols and implementation programs worldwide to enhance recovery after surgery. This society conducts structured implementation programs that are currently in use in more than 20 countries. The ERAS Society group published in 2016 the guidelines for pre- and intraoperative care in gynecologic oncology surgery.[7,8] In 2005, the Department of Surgery of The Faculty of Medical Sciences of Universidade Federal do Mato Grosso, Brazil, adapted the ERAS program to our reality and created the Accelerating the Total Postoperative Recovery (ACERTO, in the Portuguese acronym) project. The application of the ACERTO multimodal protocol determined a significant improvement in morbidity and mortality in general surgery.[9]

Why should an ERAS pathway be adopted in gynecologic surgeries?

Most of the data on the ERAS program that is available in the literature refers to colorectal surgeries. Variations of the protocol are being adopted for gynecologic procedures despite the limited population and procedure-specific outcome data.[5] Studies comparing the ERAS program to conventional practices in gynecologic surgery have shown a faster patient recovery, as well as a significant reduction in the LOS without an increase in readmission rates and complications in patients submitted to the practices recommended by the program.[2–4,10] In addition, the incidences of urgent clinic

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Table 1 Enhanced Recovery After Surgery (ERAS) program principles

Enhanced Recovery After Surgery (ERAS) program		
What does it promote?	**Why should it be implemented?**	**What is necessary for the implementation?**
– Minimization of the stress response to the operation by controlling the perioperative physiology – Operative medical optimization: preoperative counseling, pain relief, carbohydrate loading, thromboembolism prophylaxis, standard anesthetic protocol and intraoperative fluid, recovery of normal gastrointestinal function, and early mobilization	– Shorter length of hospital stay – No increase in readmissions and/or reoperations and/or complications rates – Faster and safer patient recovery – Improved quality of life and patient satisfaction – Reduction in overall healthcare costs	– Program coordinator (doctor/nurse) – Involvement of all units dealing with the surgical patient – Multidisciplinary team working together around the patient – Multimodal approach to resolving issues that delay recovery and cause complications – Scientific, evidence-based approach to care protocols – Change in management through interactive and continuous audits – Whenever possible, minimally invasive surgery

Source: Adapted from Kehlet (1997)[1] and Carey and Molder (2018).[2]

and emergency room visits, readmissions, and reoperations within 90 days of the surgery were similar for patients who were discharged on the day of the surgery compared with those admitted for more than 24 hours.[11]

Introducing the ERAS protocol for abdominal hysterectomy reduced the LOS without increasing complications or readmissions.[10] For benign vaginal hysterectomies, ERAS has been associated with a reduction in the LOS of 51.6%, and it enables more women to be discharged within 24 hours, with no increase in patient readmissions rates.[12] Establishing the program for vaginal hysterectomy also resulted in a reduction in costs, coupled with increased patient satisfaction and no rise in morbidity.[13]

In Urogynecology, ERAS implementation has been associated with a greater proportion of same-day discharges and high patient satisfaction, but with slightly increased hospital readmissions within 30 days.[5] The implementation of ERAS protocols in gynecologic surgeries has been associated with a substantial reduction in the administration of intravenous fluids and morphine, as well as a reduction in the LOS in open procedures associated with improved patient satisfaction and decreased hospital costs.[14]

Regarding minimally invasive surgeries (MISs), increased American Society of Anesthesiologists (ASA) physical status, being African American, and increased length of procedure were significantly associated with readmissions after laparoscopic hysterectomies for benign and malignant conditions performed following an ERAS pathway.[15] Even in gynecologic oncology MISs in, ERAS is associated with a decreased LOS without increases in morbidity or readmission rates.[11]

The implementation of ERAS protocols for women undergoing major gynecologic surgery has been associated with a substantial decrease in intravenous fluid and morphine administration combined with a reduction in the LOS, improved patient satisfaction, and decreased hospital costs.[14] Despite the lack of high quality studies evaluating the benefits of enhanced recovery programs in comparison to conventional care for gynecologic cancer patients, this approach is considered a safe perioperative management strategy. The LOS is reduced, without affecting the rates of complications or readmission.[6,16–18]

The ERAS principles are applied across all surgical specialties, and ongoing innovation must continue to enable the processes to improve.[3] A successful ERAS program can lead to a reduction in overall healthcare costs, faster and safer recovery, and improved quality of life and patient satisfaction. In addition, for patients with gynecologic cancer, returning to or getting close to the baseline physiological level enables the accomplishment of the planned adjuvant therapies without delay, resulting in better oncologic outcomes.[4]

How should an ERAS program be implemented?

The essential aspect in changing the practice and implementing an ERAS pathway is forming a team composed of key individuals from each involved unit.[3] As illustrated in ►**Table 1**, the ERAS program has several principles.[2,3] The approach to the care of the surgical patient through the various parts of the hospital must be multimodal and multidisciplinary.[3] The process of implementation of an ERAS program involves a team consisting of surgeons, anesthetists, an ERAS coordinator (often a nurse or a physician assistant), nurses, dieticians, and physiotherapists from units that care for the surgical patient.[3] No single element by itself will improve the outcomes of surgery. Adherence to the program is crucial, and continuous auditing of the care process enables the team to have a comprehensive view of the patient outcomes.[3] Minimally invasive surgery is a vital component of an ERAS program, and should be the preferred surgical approach whenever possible.[2]

The program brings together best practices, organization of care and clinical management.[6] The care protocol is based on published evidence, and it is important to

implement additional changes in light of new evidence. An important goal for the ERAS Society is to build a network of hospitals around the world. Successful implementation of an ERAS program requires a multidisciplinary team effort and active participation of the patient in the goal-oriented functional recovery program.[4] The ERAS program focuses on patients who actively participate in their own recovery process, and ensures they receive adequate postoperative care.

The implementation ERAS in gynecologic surgery involves four essential stages: the preadmission, preoperative, intraoperative, and postoperative stages.[2] The strategies include preadmission counseling, avoidance of preoperative bowel preparation, use of opioid-sparing multimodal perioperative analgesia (including locoregional analgesia), intraoperative goal-directed fluid therapy, and avoidance of routine use of nasogastric tubes, drains and/or catheters.[4] Postoperatively, it is important to encourage early feeding, early mobilization, timely removal of tubes and drains, if present, and opioid-sparing analgesia regimens.

The recommendations of the perioperative enhanced recovery pathway for gynecologic surgeries are shown in ►**Table 2**.[2,4,7,8,17] Smoking and alcohol consumption (alcohol abusers) should cease four weeks before surgery. Anemia should be actively identified, investigated, and corrected preoperatively. Mechanical bowel preparation should

Table 2 Main recommendations of the perioperative enhanced recovery pathway for gynecologic surgeries

Enhanced Recovery After Surgery (ERAS) program recommendations for gynecologic surgeries		
Preadmission stage	Prevention of complications	Appropriate preoperative risk stratification, timely risk modification, and medical optimization have to be performed. Screen and treat anemia
	Counseling	Preoperative counseling of patients and caregivers
Preoperative stage	Bowel preparation	Elimination of mechanical bowel preparation and rectal enema for most procedures
	Diet	No solids after midnight; clear liquid diet 2–4 hours before surgery; 100-g carbohydrate-loaded drink the night before surgery; and a 50-g carbohydrate-loaded drink 2–4 hours before surgery
	Premedication	Avoid long- or short-term sedative agents (Tramadol ER, Pregabalin, Celecoxib, Acetaminophen IV)
	IVF therapy	Saline lock until going to the OR
Intraoperative stage	Analgesia immediately before going to the OR	Acetaminophen 1,000 mg PO; Gabapentin 600–1,200 mg PO once or Pregabalin 100–300 mg PO once; Celecoxib 200–400 mg PO once
	Nausea and vomiting prophylaxis	Scopolamine transdermal patch 2 hours preoperatively; Dexamethasone 4 mg IV once at induction
	Analgesia	Total intravenous anesthesia; regional anesthesia if appropriate; Acetaminophen 1,000 mg IV once (if not oral); local wound infiltration: preincisional or postincisional bupivacaine hydrochloride or postincision liposomal bupivacaine
	Fluid balance	Goal-directed fluid therapy with a net zero balance at the end of the surgical case; Lactated Ringer's over normal saline for electrolyte balance
Postoperative stage	IVF therapy	IVF 40 ml/h; saline lock when tolerating 500 ml oral
	Analgesia	Opioid-sparing analgesia; Acetaminophen or Ibuprofen; Pregabalin, 75 mg every 12 hours (for 48 hours)
	Nausea and vomiting management	Ondansetron 4 mg PO every 6 hours prn nausea and vomiting, or Prochlorperazine 10 mg IV every 6 hour prn nausea and vomiting
	Diet	Regular diet on POD0; oral hydration; gum chewing
	Foley catheter	Remove on POD1
	Activity	Ambulate 8 times a day; eat all meals sitting in a chair; stay out of bed 8 hours a day
	Transfusion	Restrictive; only for hemoglobin level > 7

Abbreviations: ER, endorectal; IV, intravenous; IVF, intravenous fluids; OR, operating room; PO, postoperative; POD, postoperative day; PRN, pro re nata (when necessary).
Source: Adapted from Miralpeix et al. (2015);[4] Nelson et al. (2016);[7,8] Ljungqvist et al. (2017);[3] and Carey and Molder (2018).[2]

not be used routinely even when bowel resection is planned. The intraoperative prevention of intraoperative hypothermia with suitable active warming devices should be used routinely. Very restrictive or liberal fluid regimes should be avoided in favor of euvolemia. The intraoperative stage recommendations include the standard anesthetic protocol, avoidance of nasogastric tubes or removal at the end of surgery, and infusion of local anesthetic (bupivacaine) in the wound (deep and superficial injections) prior to closure.[4,7]

The prophylaxis against thromboembolism includes well-fitting compression stockings and intermittent pneumatic compression. Extended prophylaxis (28 days) should be given to patients after laparotomy for abdominal or pelvic malignancies. The key postoperative protocol elements are early feeding (limiting the administration of intravenous fluids when the patient tolerates oral intake greater than 500 ml), early mobilization and opioid-sparing analgesia. A multimodal approach to postoperative nausea and vomiting with antiemetic agents should be used for patients undergoing gynecologic procedures. The patient should ambulate 8 times per day, have all meals sitting in a chair, and stay out of bed at least 8 hours per day.[4,7]

Final considerations

The implementation of the ERAS program represents a paradigm change in the perioperative management of the surgical patient, and is a multidisciplinary approach based on scientific evidence management.[3] The program is clinically effective and has impacts on the outcomes of the patients, offering a safe, high-quality and cost-effective/cost-saving perioperative care. Therefore, the ERAS program should become the standard practice for all women undergoing elective gynecologic surgeries.[16] Implementation challenges have been attributed to a variety of contextual factors, such as perceived lack of resources and resistance to change among providers. The number and combination of ERAS elements varied considerably across the studies. In Brazil, the challenge is to define strategies to adopt perioperative enhanced recovery programs in different scenarios. Compliance by the staff and the patients to the protocol elements of the ERAS is crucial to ensure a well-established and successful program.

Conflicts of interest
The authors have no conflicts of interest to disclose.

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Hazards of Repeat Pregnancy during Adolescence: A Case-control Study

Riscos da repetição da gestação na adolescência: um estudo de caso-controle

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Abstract

Objective To evaluate the social, obstetric and psychological risk factors related to repeat pregnancy in teenagers.

Methods A case control study conducted at Centro de Atenção à Saúde Integral da Mulher (Caism, in the Portuguese acronym), in Campinas, Brazil, from 2015 to 2017. Three groups were selected: a case-group of adolescents who had repeat pregnancy and two control-groups, one consisting of adolescents who had delivered at first time and another one of adult women with more than one deliveries. Participants were asked about habits, socio-demographics characteristics, reproductive and obstetric history and assessed psychological issues.

Results Ninety women were enrolled, 30 in each study group. Adolescents with repeat pregnancy have lower self-esteem scores and more ineffective contraceptive use. When compared with teens at first delivery, they had less schooling level (odds ratio [OR] 4.03 [1.37–11.8]), more school abandon (OR 8.16 [2.36–28.2]) and drugs use (OR 4.97[1.39–17.8]). Non-white skin color (OR 6.2 [1.15–41.0]), drugs use (OR 17.5 [2.62–116.6]) and first sexual intercourse under 15y (OR 18.0[2.82–115.0]) were found as higher risk factors for repeat pregnancy when comparing adolescents and adults. Moreover, adolescents with more than one gestation had lower self-esteem and greater susceptibility to unplanned pregnancy.

Conclusion There was an association between repeat pregnancy among adolescents and lower education, early onset of sexual activity, non-white skin color, low use of contraception and increased use of drugs.

Keywords

- adolescence
- pregnancy
- vulnerability
- contraception

Resumo

Objetivo Avaliar a associação entre fatores de risco sociais, obstétricos e psicológicos relacionados a repetição da gravidez em adolescentes.

Métodos Estudo caso-controle realizado num Hospital Universitário de Campinas, Brasil, de 2015 a 2017. Foram selecionados três grupos: um grupo-caso de adolescentes com repetição de gravidez, e dois grupos controles, um de adolescentes primíparas

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e outro de mulheres adultas com mais de um parto. Foram coletados dados referentes a aspectos sociodemográficos, história reprodutiva e obstétrica e fatores psicológicos.

Resultados Foram incluídas 90 mulheres, 30 em cada grupo de estudo. Adolescentes com repetição de gravidez apresentaram menor autoestima e mais uso inadequado de contraceptivos. Quando comparadas a adolescentes primíparas, tiveram menor nível escolar (razão de probabilidades [RP] 4.03 [1.37–11.8]), maior interrupção dos estudos (RP 16.3 [3.61–73.6]) e maior uso de drogas (RP 4.97[1.39–17.8]). A comparação entre adolescentes com repetição de gestação e mulheres adultas revelou maior risco para cor da pele não-branca (RP 6.2 [1.15–41.0]), uso de drogas (RP 17.5 [2.62–116.6]) e primeira relação sexual com menos de 15 anos 15y (RP 18.0 [2.82–115.0]). Além disso, as adolescentes com segunda gravidez apresentam menor autoestima, baixo uso de contracepção e maior suscetibilidade a gravidez não planejada.

Conclusão Houve associação entre repetição de gravidez na adolescência e menor tempo de estudo, início precoce de atividade sexual, cor da pele não branca e maior uso de drogas.

Palavras-chave
- adolescência
- gravidez
- vulnerabilidade
- contracepção

Introduction

Adolescent pregnancy is a global health problem and can be associated with high rates of maternal death and adverse newborn outcomes. The World Health Organization (WHO) defines adolescents as those between the ages of 10 and 19 years old.[1] In the United States, it is estimated that 35% of adolescents will have a second pregnancy in less than 2 years, and most of those are unintended.[2]

Teenagers tend to postpone the beginning of prenatal care and need careful attention to detect common conditions in this age group, such as use of alcohol, drugs and smoking, besides the higher risk of sexually transmitted infections.[3] For these young girls, pregnancy means a higher risk during prenatal care and childbirth, as they are at higher risk of preeclampsia and other hypertensive disorders, like anemia, inadequate nutrition, sexually transmitted diseases, low birth weight, fetal growth restriction and prematurity.[4] Therefore, the infant mortality rate is higher among children born from adolescent mothers compared with those born from young adult women, aged from 20 to 24 years old.[5]

Adolescent pregnancy constitutes a social problem, as there are social factors involving and determining pregnancy at a young age and the consequences related to childbirth at this age. Childbearing during this period feeds a cycle of deprivation that can compromise young mothers and their children's lives, leading to social disadvantage, with higher rates of unemployment, poverty and discrimination. Up to 40% of adolescent mothers feel depressive and stigmatized by the pregnancy; furthermore, low self-esteem is very common among them.[4]

There are several risk factors that can be associated with teenage pregnancy.[3,6] Apparently, socioeconomic characteristics are the major risk factor, although some may argue that socioeconomic status is more related to a prognostic evaluation of those women. Some studies have not been able to identify factors that are related to incidence of a second pregnancy during adolescent stage. Therefore, there is no evidence of predictors for a higher risk of repeat pregnancy under age of 20.[5] Some studies have shown obstetric outcomes as an independent determining factor in the incidence of adolescent repeated pregnancies, observing longer inter-pregnancy intervals among women who experienced prenatal and/or childbirth complications.[7] However, it has been also observed the opposite, as many women with history of poor outcomes during their first pregnancy tend to have a rapid repeat pregnancy, with a less than 12 months between deliveries interval.[8]

It appears that, to reduce adolescent pregnancy rates in developed and developing countries, actions should be focused on a multifaceted and interdisciplinary management that address not only the risk factors and risk-behavior, but also aims for social and cultural factors that influence young people's decision making.[9] It means that contraception promotion (especially the use of long-acting reversible contraceptives), and sexual orientation should be considered when counseling adolescents,[10] but those alone may not be enough to decrease adolescent pregnancy rates. A single component action could not be the solution.

This study aimed to evaluate social, obstetric and psychological risk factors related with repeat pregnancy among adolescents in comparison to those of adolescents after their first delivery and adult women with more than one delivery.

Methods

This case control study was conducted at Centro de Atenção à Saúde Integral da Mulher (Caism, in the Portuguese acronym), at Universidade Estadual de Campinas (UNICAMP) from August of 2015 to August of 2017.

We considered three groups: a case-group of adolescents ($\leq$ 19 years) who had given birth for the second time, that is, as a result of repeat adolescent pregnancy, hereby referred to as repeat pregnancy teenagers, (RPTeens), and two control groups; the first one composed of teenagers who had given birth for the first time (1stPTeens), and the control-group of

adult women with repeat pregnancy (adults). For each one of these groups, 30 patients were enrolled as in a convenience sampling.

The women were selected through medical records to check age and parity of the potential participants before the medical interview. The cases and controls that met the inclusion criteria were invited to participate and sign the informed consent form before being enrolled. Women with communication difficulties and any other condition that might lead to misunderstanding the questions were also excluded from the study. Then, a 50-minute interview was conducted, in which the women answered objective questions on sociodemographics, reproductive and obstetric history, habits and comorbidities in a data collection form developed specifically for this study. Psychological issues were assessed using the self-esteem scale of Rosenberg, which rates self-esteem as high, medium or low,[11–13] (low, medium or high self-esteem were considered when the punctuation amounted to < 20, 20–30 or > 30 points respectively) and the evaluation of the participants' relationships with their parents and partners, measured by them using a 1 to 10 grading system. For the questions concerning contraception and intention to get pregnant, the "London Measure of Unplanned Pregnancy" questionnaire, tested and validated by Barrett et al (2004),[1] was applied.[4] The questionnaires were filled out with no participant identification. Data were collected during the hospitalization of women 1 to 3 days postpartum in an inpatient unit for mothers and their infants, where a multidisciplinary team operates that prioritizes good mother-child interaction, stimulates breastfeeding and guides care for the newborn.

After data were collected, we compared the groups of adolescents using the Mann-Whitney test for numerical variables, and the Fisher exact test and Chi-squared test were used for categorical variables. For a univariate and multivariate analysis of the RPTeens, we compared this group to the primiparous adolescents using logistic regression, with stepwise selection of variables for the multivariate analysis. The same was done in the comparison with the adult women. The odds ratio was calculated, considering a confidence interval (CI) of 95%.

The Institutional Review Board from the University of Campinas, Brazil, CAAE report 00602612.7.1001.5404, approved this study. All the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement items for a prospective study were followed and checked in this manuscript.[15]

Results

We collected information of ~ 90 women, distributed equally between the 3 groups. The median age among 1stPTeens and RPTeens was 16.8 and 18 years, respectively ($p = 0.003$). Among the adults, the median age was 26.5 years.

►**Table 1** shows the obstetric and sociodemographic characteristics among the participants. Mostly, there were no significant differences between the groups for social characteristics, except for educational achievements and drugs use. Repeat pregnancy during adolescence was associated with lower schooling (36.7% vs 70% of both adults and 1stPTeens; $p = 0.007$ and $p = 0.019$, respectively), higher drop-out rates (80% vs 33.3%) in comparison with 1stPTeens ($p < 0.001$) and with adults ($p = 0.003$). The case group (RPTeens) was more often related to drugs use (43.3% vs 13.3%) in comparison with 1stPTeens ($p = 0.010$) and adults ($p < 0.001$).

Comparing RPTeens with adults, it was also noted that the case group showed lower frequency of paid work (33.3% vs 63.3% of adults; $p = 0.039$) and lower age of first sexual intercourse, showing sexual activity under the age of 15 more frequently (43.3% vs 13.3% of adults; $p < 0.001$).

Some differences among the groups were confirmed when we made a univariate analysis, which showed that RPTeens presented higher risks for drugs use when compared with 1stPTeens (OR 4.97[1.39–17.8]), lower educational level (OR 4.03 [1.37–11.8]) and more school interruption (OR 8.16 [2.36–28.2]). The case group (RPTeens) also seemed to have a higher number of people living in the same home (median of 4.77 vs 3.53; OR 1.39 [1.01–1.90]). These results are shown in ►**Table 2**.

When we compared the case group with adult women, RPTeens referred lower family income (OR 2.98 [1.04–8.53]). They are more prone to use drugs (OR 47.0 [2.63–840.9]) and had the first sexual intercourse at a younger age, before 15 years old (OR 9.04 [2.80–29.1]). Adolescents in the case group also presented higher risk for lower educational level (OR 4.03 [1.37–11.8]), school abandon (OR 7.20 [2.15–24.1]) and first delivery before the age of 15 (OR 19.5[1.06–358.4]) (►**Table 2**).

The multivariate analysis showed that between 1stPTeens and RPTeens, schooling remained as a significantly factor associated with repeat pregnancy (OR 16.3 [3.61–73.6]). In comparison with adults, we found a statistically significant difference for non-white skin color (OR 6.2 [1.15–41.0]), drugs use [OR 17.5 (2.62–116.6)] and first sexual intercourse under 15y (OR 18.0 [2.82–115.0]) as characteristics associated with repeat pregnancy (►**Table 3**).

The evaluation of psychological factors using the self-esteem scale of Rosenberg and the "London Measure of Unplanned Pregnancy" questionnaire showed that RPTeens presented lower self-esteem scores than 1stPTeens and Adults (median of 26.8 ± 4.75 vs 31.1 ± 3.12; $p < 0.001$ and 30.9 ± 3.17; $p < 0.001$ respectively). The RPTeens presented significantly more "medium" self-esteem when compared with 1stPTeens, who had significantly more "high" self-esteem results (80% of RPTeens vs 47.6% of 1stPTeens with self-esteem scores of 20–30 and 16% vs 52.4%, respectively, for scores higher than 30) (►**Table 4**). When we compared RPTeens pregnancy with adults, it was noted that family acceptance of pregnancy was significantly lower among younger women (median score of 9.37 ± 1.33 vs 9.83 ± 0.65; $p = 0.027$). For family relationships, women in the three groups referred relationship with their mothers better than with their fathers and partners however the difference was not significant (data not shown).

Most of participants in the three groups referred to have used contraceptive methods at some point in their lives, with

Table 1 Comparison between obstetric and sociodemographic characteristics among 1st pregnancy teenagers, repeated pregnancy teenagers and adults ($n = 90$)

Variables	1stPTeens n (%)	1stPTeens vs RPTeens *p*-value	RPTeens n (%)	RPTeens vs Adults *p*-value	Adults n (%)
Skin color (white)	17 (56.7)	0.197***	12 (40.0)	0.071***	19 (63.3)
Partner (yes)	20 (66,7)	0.067***	26 (86.7)	1.000***	26 (86.7)
No actual schooling	10 (33.3)	< 0.001**	24 (80.0)	0.003**	12 (40.0)
High school or college	21 (70.0)	0.019**	11 (36.7)	0.007**	16 (70.0)
Family income ≥ 3 MW	13 (43.3)	0.598***	11 (36.7)	0.039***	19 (63.3)
Paid work	14 (46.7)	0.510**	10 (33.3)	0.011**	19 (63.3)
Smoking	4 (13.3)	1.000**	5 (16.7)	0.519**	7 (23.3)
Alcohol	8 (26.7)	0.347***	5 (16.7)	0.707***	3 (10.0)
Drugs use	4 (13.3)	0.010***	13 (43.3)	< 0.001***	0 (0.00)
Menarche < 12 years	7 (23.3)	0.390***	10 (33.3)	0.787***	11 (36.7)
First sexual intercourse < 15yrs	18 (60.0)	0.273**	22 (73.3)	< 0.001***	7 (23.3)
First delivery < 15 years	3 (10.0)	0.166***	7 (23.3)	0.011***	0 (0.00)
Prenatal care < 6 visits	1 (3.70)	0.054*	7 (23.3)	0.146*	2 (6.67)
Vaginal delivery	20 (66.7)	1.000***	20 (66.7)	0.787***	19 (63.3)
Birth weight < 2,500kg	5 (16.1)	1.000**	5 (16.1)	0.275**	2 (6.67)
Preterm birth (< 37 weeks)	4 (13.3)	1.000**	5 (16.7)	0.707**	3 (10.0)
Previous contraception (yes)	23 (76.7)	1.000***	(76.7)	0.317***	26 (86.7)

Abbreviations: 1stPTeens, group of teenagers at first pregnancy ($n = 30$); Adults, group of adult women with more than one pregnancy ($n = 30$); MW, Brazilian minimum wage; RPTeens, group of non-primiparous teenagers ($n = 30$).
*p-value according to Mann-Whitney test.
**p-value according to Fisher exact test.
***p-value according to Chi-squared test.

no significant difference among them. Comparing Adults and RPTeens, the last ones referred use of injectable methods more often (65.2% vs 19.2%; OR 7.13 [1.93–26.3]), but there was no significant difference about other types of contraceptive methods. In contrast, when asked about the use of contraceptives right before getting pregnant, most 1stPTeens and Adults women referred irregular use (82.6% and 73.1%, respectively, vs 27.6% of RPTeens). The RPTeens referred no use of any contraception more frequently than the control groups (51.7% vs 17.3% of 1stPTeens and 26.9% of adults). When asked about their intention to become pregnant, primiparous adolescents were more likely to refer unintended pregnancy when compared with the other groups (75% of primiparous adolescents vs 53.3% of non-primiparous adolescents and 33.3% of adult women) (►**Table 4**).

Between adult women and RPTeens, there were also no difference concerning obstetrical issues, such as quality of prenatal care, mode of delivery, maternal pathological conditions or neonatal outcomes, including Apgar scores and birth weight. Additionally, there was no significant difference about tobacco or alcohol use either.

Discussion

Our study shows some factors associated with repeat pregnancy in adolescents, such as early sexual debut (before 15 years), first delivery before 15 years of age and drugs use. Additionally, having a second delivery significantly increases the risk of educational interruption in comparison with adolescents who had only one delivery.

These results are in concordance with the literature. Many studies confirm the age of first sexual intercourse, whether consented or not, as a risk factor for repeat adolescent pregnancy, as well as for rapid repeat pregnancy (new pregnancy in less than 2 years after the first delivery).[16] In our study, this was more evident when we compared non-primiparous adolescents with adult women, as 73.3% of adolescents referred first sexual intercourse before the age of 15, whereas only 23.3% of adults related early sexual debut (OR 9.04; CI 2.80–29.1). The difference in sexual behavior between these groups may be due to an easier exposition to sexual contents alongside with lack of parental counseling and guidance.

Usually, rates in girls under 15 years are unstable because these data routinely collected from statistics from around the world. In our study, few participants had given birth before 15 years, but most had sexual debut before the age of 15 and ~ 26% of them had sexual relations before 13 years.

Socioeconomic factors, such as low education and low family income, are not so clearly defined as a cause or consequence of early pregnancy. There is evidence that adolescent mothers have lower educational achievements, perhaps because they have never had access to schools, or because they are more likely to interrupt school before or during pregnancy or even after delivery, besides, many may never get the chance

Table 2 Factors associated with repeat adolescent pregnancy comparing 1st pregnancy teenagers to repeated pregnancy teenagers and adults (Univariate logistic regression = 90)

Variables	Categories	1stPTeens n (%)	1stPTeens vs RPTeens OR (95%CI)	RPTeens n (%)	RPTeens vs Adults OR (95%CI)	Adults n (%)
Age	Continuous variable (md ± sd)	16.8 ± 1.58	1.90 (1.22–2.95)	18.0 ± 1.10	———	26.5 ± 3.88
Schooling	High school/college	—	1.00	—	1.00	—
	Less than high school/college	9 (30.0)	4.03 (1.37–11.8)	19 (63.3)	4.03 (1.37–11.8)	9 (30.0)
Actual schooling	Out of school	17 (56.7)	1.00	5 (16.7)	1.00	18 (60.0)
	At school	3 (10.0)	1.13 (0.10–13.4)	1 (3.33)	10.09 (0.36–284.5)	0 (0.00)
	Interrupted school	10 (33.3)	8.16 (2.36–28.2)	24 (80.0)	7.20 (2.15–24.1)	12 (40.0)
Onset of labor	Spontaneous Induced Elective C-section	23 (76.7) 7 (23.3) 0 (00.0)	1.00 1.21 (0.36–4.06) 10.8 (1.01–214.1)	19 (63.3) 7 (23.3) 4 (13.3)	1.00 0.64 (0.20–1.99) 9.00 (0.45–178.7)	19 (63.3) 11 (36.7) 0 (0.00)
N of people at home	Continuous variable (md ± sd)	3.53 ± 1.70	1.39 (1.01–1.90)	4.77 ± 2.43	1.23 (0.89–1.70)	4.13 ± 0.94
Drugs use	No	26 (86.7)	1.00	17 (56.7)	1.00	30 (100)
	Yes	4 (13.3)	4.97 (1.39–17.8)	13 (43.3)	47.0 (2.63–840.9)	0 (0.00)
Family monthly income	≥ 3 salaries	13 (43.3)	1.00	11 (36.7)	1.00	19 (63.3)
	< 3 salaries	17 (56.7)	1.32 (0.47–3.72)	19 (63.3)	2.98 (1.04–8.53)	11 (36.7)
First sexual intercourse	≥15 years	12 (40.0)	1.00	8 (26.7)	1.00	23 (76.7)
	<15 years	18 (60.0)	1.83 (0.62–5.45)	22 (73.3)	9.04 (2.80–29.1)	7 (23.3)
First birth	≥15 years	27 (90.0)	1.00	23 (76.7)	1.00	30 (100)
	<15 years	3 (10.0)	2.74 (0.63–11.8)	7 (23.3)	19.5 (1.06–358.4)	0 (0.00)
Postpartum contraception after second birth	Oral	NE	NE	8 (34.8)	1.00	19 (73.1)
	Injectable			15 (65.2)	7.13 (1.93–26.3)	5 (19.2)
	Others			0 (0,00)	0.46 (0.02–10.6)	2 (7.70)
	No use			7 (23.3)	4.16 (0.95–18.3)	4 (13.3)

Abbreviations: 1stPTeens, group of teenagers at first pregnancy ($n = 30$); Adults, group of adult women with more than one pregnancy ($n = 30$); md, median; NA, not applicable; NE, Not evaluated; OR, odds ratio for repeated pregnancy; RPTeens, group of non-primiparous teenagers ($n = 30$); sd, standard deviation.

to return to it. Investments in health and behavioral education, such as effective interventions to prevent the first and repeated adolescent pregnancies, when combined with community and family participation reinforce the importance of contraceptive counseling for avoiding early pregnancies, thus allowing these women to have the education and economic benefits that schools could offer.[2,17]

In this study, modifiable factors, such as school interruption and poor education, were associated with repeat adolescent pregnancy. This shows the need for care practitioners to undertake efforts to stimulate these girls by explaining the possible consequences of school evasion for them and their babies, while also reinforcing the opportunities they could have by taking control of the decision-making process in their lives.

Adolescent mothers are submitted to several difficulties during transition to motherhood. Their adaptations to this new reality get easier when they have a strong family nucleus that is able to provide the support needed. According to our results, although not significantly different, women tended to have better relationship with their mothers than with their fathers or sexual partners. Other studies[18,19] found an association between strong family support and fewer rates of teen pregnancies, showing that good communication between adolescent girls and their parents (especially their mothers) discouraged early pregnancy and improved the teenage mothers' psychological adjustment.

Self-esteem is a psychological construction defined as an interpretation of self-concept. It comprehends feelings and thoughts about positive and negative values that a woman attributes to herself. Our results showed that adolescents who have repeat unintended pregnancy tend to present lower self-esteem scores more often than their peers. This finding is concordant with a study that appoints low self-esteem as an independent risk for ineffective use of contraceptives and therefore a risk for unwanted pregnancy.[20]

Table 3 Factors associated with repeat adolescent pregnancy comparing (Multivariate logistic regression = 90). 1st pregnancy teenagers to repeated pregnancy teenagers and adults

Variables	Categories	1stPTeens n (%)	1stPTeens vs RPTeens OR (95%CI)	RPTeens n (%)	RPTeens vs Adults OR (95%CI)	Adults n (%)
Age	Continuous variable (md ± sd)	16.8 ± 1.58	**2.34 (1.39–3.94)**	18.0 ± 1.10		
Actual schooling	Out of school	17 (56.7)	1.00	5 (16.7)		
	At school	3 (10.0)	2.70 (0.14–52.8)	1 (3.33)		
	Interrupted school	10 (33.3)	**16.3 (3.61–73.6)**	24 (80.0)		
Skin color	White			12 (40.0)	1.00	63.3
	Non-white			18 (60.0)	**6.20 (1.15–41.0)**	36.7
Drugs use	No			17 (56.7)	1.00	30 (100)
	Yes			13 (43.3)	**17.5 (2.62–116.6)**	0(0.00)
First sexual intercourse	≥15 years			8 (26.7)	1.00	23 (76.7)
	<15 years			22 (73.3)	**18.0 (2.82–115.0)**	7 (23.3)

Abbreviations: 1stPTeens, group of teenagers at first pregnancy ($n = 30$); Adults, group of adult women with more than one pregnancy ($n = 30$); Criterion, stepwise selection of variables; md, median; OR, odds ratio for repeated pregnancy; RPTeens, group of non-primiparous teenagers ($n = 30$); sd, standard deviation; 95%CI, 95% confidence interval.

Table 4 Comparison between 1st pregnancy teenagers, repeated pregnancy teenagers and adults regarding self-esteem scores, intention to become pregnant and contraception before actual pregnancy

Variables	Categories	1stPTeens n (%)[a]	1stPTeens vs RPTeens (*p*-value)	RPTeens n (%)[b]	RPTeens vs Adults (*p*-value)	Adults n (%)[c]
Self-esteem (md ± sd)	< 20 20–30 > 30	0 (0.00) **10 (47.6)** **11 (52.4)**	**0.018****	1 (4.00) **20 (80.0)** **4 (16.0)**	0.053**	0 (0.00) 12 (54.5) 10 (45.4)
Intent to be pregnant	Intended Unintended	7 (25.0) 21 (75.0)	0.086***	14 (46.7) 16 (53.3)	0.118***	20 (66.7) 10 (33.3)
Contraception before pregnancy	No use Irregular use Ideal use	**4 (17.4)** **19 (82.6)** 0 (0.00)	< **0.001****	**15 (51.7)** **12 (41.4)** 2 (6.90)	**0.002****	**7 (26.9)** **19 (73.1)** 0 (0.00)

Abbreviations: 1stPTeens, group of teenagers at first pregnancy ($n = 30$); Adults, group of adult women with more than one pregnancy ($n = 30$). md, median; RPTeens, group of non-primiparous teenagers ($n = 30$); sd, standard deviation.

**p*-value according to Fisher exact test.

***p*-value according to Chi-squared test.

[a]Missing data from 9 women for self-esteem score, 2 women for answer about intention to become pregnant and 7 women for answer about contraception use before pregnancy.

[b]Missing data from 5 women for self-esteem score and 1 woman for answer about contraception use before pregnancy.

[c]Missing data from 8 women for self-esteem score and 4 women for answer about contraception use before pregnancy.

In addition, RPTeens had significantly more drugs use than adults or teens at first pregnancy. About 35% of adolescents smoke during pregnancy and tend to resume smoking habits during the peripartum period, and they are also often more likely to present alcohol and substance abuse.[3]

Despite the high efficacy of long-action reversible contraceptives (LARC), many adolescents chose less effective forms or no postpartum contraception at all. Some studies point that teenagers have the lowest LARC usage rates, ~ 4%, compared with any others age group.[8] In our study, most participants had used contraceptive method at least once in life. However, 65% of non-primiparous adolescents referred to be receiving injectable contraceptives before getting pregnant for the second time, mostly with irregular use. As for LARC usage rate, it was more frequent amongst adult women but still much less often than oral contraceptives (3.8% vs 73%). This should be considered when counseling postpartum contraception, as the literature brings evidence of the safety and effectiveness of LARC insertion in postpartum visit, with lower unintended repeat pregnancy rates (18–20%) and longer interval between pregnancies.[9]

This study had limitations because of the short sample, and the fact that some participants did not answer the self-esteem questionnaires fully, which made it difficult to evaluate the psychological impacts related to adolescent pregnancy. The retrospective nature of the questionnaire may lead to inaccuracy of information, especially about previous use of contraceptives. Another limitation was due to the

scenario in which the interviewing took place, as many girls were with their partners or family members and this may have influenced their answers concerning psychological issues and family relationship.

This study evaluated psychological factors among teenagers with two or more births in comparison to primiparous adolescents and adults. Our findings value the importance of modifiable risk factors, significantly associated with unintended repeat pregnancy among adolescents. According to this, it is possible to assume repeat pregnancy in adolescents is a changeable reality alongside all economic, educational and psychological benefits of its prevention.

Conclusion

An association was established between repeat pregnancy during adolescence and lower education, as these adolescents are more likely to interrupt school and present educational underachievement. Additionally, teenagers with repeat pregnancy are more often likely to present history of drugs use and to initiate early sexual activity (before 15 years). According to this, adolescent repeat pregnancy is more often unintended, probably due to absent or ineffective use of contraceptives. Moreover, these girls tend to present lower self-esteem in comparison with first-time adolescent mothers and adult women.

Contributions

Galvão R. B. F., Figueira C. O., Borovac-Pinheiro A., Paulino D. S. M., Faria-Schützer D. B. and Surita F. G. contributed with project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Maternal Factors Associated with Low Birth Weight in Term Neonates: A Case-controlled Study

Fatores Maternos Associados ao Baixo peso de Nascimento em Neonatos a Termo: um Estudo de Caso-controle

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Abstract

Objective To identify maternal factors associated with the presence of low birth weight in term neonates.

Methods Matched hospital-based case-controlled study performed in a high complexity institution located in the city of Neiva, Colombia. The study included women with term gestation and singleton live fetuses. Patients with prior diseases, coming from other regions, with pregnancy resulting from assisted reproduction, or with a diagnosis of fetal abnormality or aneuploidy were excluded. Low birth weight was the dependent variable, and the independent variables that were analyzed were maternal sociodemographic and clinical characteristics. Adjusted and non-adjusted odds ratios (aOR and OR) together with the 95% confidence intervals (95% CI) were reported.

Results The study included 270 participants (90 cases and 180 controls). Controlling for maternal age, educational level, socioeconomic and civil status, social security and the presence of maternal disease during gestation, it was found that weight gain (aOR 0.77, 95% CI 0.70–0.85) and the absence of prenatal care (aOR 8.20, 95% CI 3.22–20.87) were among the factors associated with low birth weight.

Conclusions The absence of weight gain and of prenatal care are factors associated with the presence of low birth weight in term neonates and should be considered in clinical practice.

Keywords
- case-controlled studies
- developing countries
- low birth weight
- risk factors
- term birth

Resumo

Objetivo Identificar fatores maternos associados à presença de baixo peso ao nascer em neonatos a termo.

Métodos Estudo de caso-controle realizado em uma instituição de alta complexidade localizada na cidade de Neiva, Colômbia. O estudo incluiu mulheres com gestação a termo e fetos vivos únicos. Pacientes com doenças prévias, provenientes de outras regiões, com gravidez resultante de reprodução assistida, ou com diagnóstico de anormalidade fetal ou aneuploidia foram excluídos. O baixo peso ao nascer foi a variável

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dependente, e as variáveis independentes analisadas foram as características sociodemográficas e clínicas maternas. Razões de chance ajustadas e não ajustadas (RCa e RC) juntamente com os intervalos de confiança de 95% (IC 95%) foram relatadas.

Resultados O estudo incluiu 270 participantes (90 casos e 180 controles). Controlando a idade materna, nível escolar, socioeconômico e civil, segurança social e a presença de doença materna durante a gestação, constatou-se que ganho de peso (RCa 0,77, IC 95% 0,70–0,85) e ausência de pré-natal (RCa 8,20, IC 95% 3,22–20,87) estavam entre os fatores associados ao baixo peso ao nascer.

Conclusão As ausências de ganho ponderal e de pré-natal são fatores associados à presença de baixo peso ao nascer em recém-nascidos a termo e devem ser considerados na prática clínica.

Introduction

The World Health Organization (WHO) defines low birth weight as weight at birth lower than 2,500 g.[1] However, birth weight is determined by two critical considerations: gestational age at delivery and the rate of fetal growth.[2] Consequently, low weight determining factors may differ between a preterm and a term neonate because, in the former, low weight is usually explained by prematurity, while in the latter, it is result of intrinsic and/or extrinsic factors that impact on developmental potential.[1,2] Therefore, it comes as no surprise that low birth weight neonates have a worse prognosis in terms of survival and neural development.[3]

According to The United Nations International Children's Emergency Fund (UNICEF), more than 20 million infants are born with low weight in the world, accounting for 15% of all births. Of these, more than 95% are born in middle- and low-income countries, with those in Asia, Africa and Latin America being the most frequently affected.[4] Prevalence in these countries is twice as high as the ones observed in developed countries, reflecting the inequities faced by pregnant women in those regions of the world where adverse conditions, such as malnutrition, poor weight gain, anemia or pregnancy-related disorders, like hypertension, possibly explain the observed frequencies.[1,5]

Preventing low birth weight is a public health priority, and one of the goals for the new millennium.[4] Reducing the frequency of low birth weight pregnancies could have a positive impact on infant mortality in middle- and low-income countries, which are the ones with the largest shortage of resources required for the care of these neonates.[4] Consequently, efforts aimed at identifying risk factors associated with this condition are mandatory.[6] Knowledge of the factors that influence low birth weight will contribute to the timely identification and early intervention in pregnant women at risk.[7] Therefore, the objective of this study was to identify maternal factors associated with the presence of low birth weight in term neonates born in 2015 and 2016 in a high complex institution in the city of Neiva, Colombia.

Methods

This was a retrospective, analytical case-controlled study conducted at Hospital Universitario Hernando Moncaleano Perdomo, a high complexity institution located in the city of Neiva, serving the population of southwestern Colombia.

The subjects included were women with term gestations and singleton live fetuses, who were treated at the participating institution between January 2015 and October 2016. Patients with any existing diseases before pregnancy (such as hypertensive vascular disease, nephropathy, diabetes mellitus, thrombophilia, heart, neurodegenerative, cancer or autoimmune diseases), coming from a different geographic area, with a gestation resulting from assisted reproduction, or with a confirmed diagnosis of major fetal abnormality or aneuploidy were excluded.

Cases were defined as live neonates with a weight at birth under 2,500 g and a gestational age of 37 weeks of gestation or more. Gestational age was estimated based on the last menstrual period or ultrasound. Term neonates weighing 2,500 g or more were considered controls. The cases were identified using entries in the database of the epidemiological surveillance system corresponding to low birth weight, and the information was compared with the newborn vital statistics registry. In Colombia, the birth of a neonate with low weight is a public health event and reporting is mandatory. Controls were selected from the vital statistics database of the participating institution and the quality of the data was verified by means of a clinical record review. The cases and controls were selected by random sampling until the required sample size was completed.

Sample size estimation was based on the approach suggested by Freeman, consisting of the use of the event of interest by variable. In this way, the sample size for a non-conditioned logistic regression was determined to be $10^{*}(k+1)$, in which k is the number of study variables.[8] According to this principle, and given that for this study, *a priori,* research into the potential association between low birth weight and maternal age, weight gain, educational level, socioeconomic and marital status, social security, gestational age at the start of prenatal care, and the presence of maternal disease during gestation had been proposed, at least 90 cases and an equal number of controls

were required ($n = 180$). However, it was decided to select 2 controls for every case to increase the power. Thus, the required sample size for the study was 270 participants.

The data were analyzed using the Stata software package, version 15 (StataCorp. College Station, TX, USA). Descriptive statistics were applied to clinical and sociodemographic variables. The central trend and scatter were estimated for continuous data, and proportions and frequency measurements were used for qualitative data. The frequency and distribution were examined for categorical variables, and a normal distribution and variance homogeneity were analyzed for continuous variables. For the categorical variables, differences between cases and controls were tested using the Fisher exact test or the Pearson Chi-squared test. Continuous variables were compared using the Mann-Whitney test, given the absence of a normal distribution. A univariate logistic regression was applied to assess the association between candidate variables and low birth weight.

A multivariate logistic model was built to incorporate the clinical and sociodemographic variables mentioned above. A non-conditional logistic regression was performed to adjust for the presence of potential confounding factors, the predictive ability of the model was estimated, and the goodness of the adjustment was assessed using McFadden R^2. However, to identify the most parsimonious model, a second analysis was performed using the stepwise backward approach, to which the Bonferroni correction was applied, thus adjusting the significance level.[9] For the second model, the independent variables associated with the outcome of interest were preserved, with a significance level lower than 0.005.[9] Confidence intervals were estimated, and adjusted and non-adjusted odds ratios (aOR and OR) are presented as the association measure. The study protocol was approved by the Ethics Committee of the participating institution (Reference 009–006).

Results

There were 4,882 term deliveries in the participating institution during the study period. Of this total, 3.0% were neonates with low birth weight for gestational age. Once the target population was identified, the cases and controls were selected by random sampling until the required sample size was completed. For each selected case and control, we verify the inclusion and exclusion criteria before their incorporation into study. Finally, the study population was then assembled and consisted of 90 cases and 180 controls.

In terms of the characteristics of the population analyzed, the mean age was 23 years, and there was a predominance of secondary education level, low socioeconomic bracket, free union as marital status, affiliation with the subsidized healthcare regime, and urban place of residence. Regarding clinical characteristics, 54.0% of the women were multiparous and 61.4% had attended 5 or more prenatal care visits; 62.9% were vaginal deliveries, the mean gestational age at the time of delivery was 38.4 weeks, and the mean birth weight was 2,965 g (SD ± 552 g). ►**Table 1** summarizes the baseline characteristics of the population by group (cases or controls).

Table 1 Description of the sociodemographic and clinical characteristics of cases and controls

Variable Mean	Cases ($n = 90$)		Controls ($n = 180$)		*p value*
	Mean	Range	Mean	Range	
Age	22.0	(14–42)	24.1	(13–45)	$p = 0.00$[a]
Variable measured	**n (%)**		**n (%)**		***p value***
Educational level					$p = 0.29$[b]
None	0 (0.00)		1(0.56)		
Primary	20 (22.22)		30 (16.67)		
Secondary	61 (67.78)		138 (76.6)		
Technical/ University	9 (10.00)		11 (6.11)		
Socioeconomic status					$p = 0.00$[b]
Low	58 (64.44)		139 (77.22)		
Medium	27 (30.00)		40 (22.22)		
High	5 (5.56)		1 (0.56)		
Marital status					$p = 0.89$[c]
Single	39 (43.33)		79 (43.89)		
Free union	43 (47.78)		88 (48.89)		
Married	8 (8.89)		13 (7.22)		
Social security					$p = 0.52$[b]
Subsidized	83 (92.22)		154 (85.56)		
Contributive/ Special	6 (6.67)		23 (12.78)		
No payment capability	1 (1.11)		3 (1.67)		
Place of residence					$p = 0.37$[c]
Urban	64 (71.11)		137 (76.11)		
Rural	26 (28.89)		43 (23.89)		
Gestational age at the start of prenatal care					$p = 0.00$[c]
First trimester	30 (33.33)		86 (47.78)		
Second trimester	16 (17.78)		48 (26.67)		
Third trimester	20 (22.22)		39 (21.67)		
No prenatal care	24 (26.67)		7 (3.89)		
Disease during pregnancy					$p = 0.00$[c]
No	58 (64.44)		143 (79.44)		
Yes	32 (35.56)		37 (20.56)		
Sex of the newborn					$p = 0.79$[c]
Female	48 (53.33)		93 (51.67)		
Male	42 (46.67)		87 (48.33)		

[a]Mann-Whitney test for mean differences.
[b]Fisher exact test.
[c]Pearson Chi-squared test.

The two groups were similar, except in terms of socioeconomic status, gestational age at the start of prenatal care, and the presence of disease during pregnancy. ►**Table 2** summarizes the frequency and type of disease by group (cases or controls).

Table 2 Frequency and type of disease during pregnancy by group (cases or controls)

Disease during pregnancy	Cases (n = 90)	Controls (*n* = 180)	*p*-value
	n (%)	n (%)	
No	58 (64.4)	143 (79.4)	$p = 0.00$[a]
Yes	32 (35.5)	37 (20.5)	
By type			
Hypertensive disorder	19 (21.1)	17 (9.4)	
Perinatal infection	6 (6.6)	7 (3.8)	
Endocrine disease	2 (2.2)	5 (2.7)	
Placental-amniotic fluid disease	4 (4.4)	2 (1.1)	
Anemia	0 (0.0)	4 (2.2)	
Neurological condition	1 (1.1)	1 (0.05)	
Pulmonary disease	0 (0.0)	1 (0.05)	

[a]Pearson Chi-squared test.

Maternal age was significantly different between the groups, although the difference observed was not clinically relevant. For the neonates (data not shown), the mean gestational age at the time of birth was 37.9 weeks for the cases and 39.0 weeks for the controls, while the average weight was 2,328 g (SD ± 166 g) for the cases and 3,282 g (SD ± 371 g) for the controls. Of the low-weight neonates, 78.2% were admitted to the kangaroo program and 3.2% to the neonatal intensive care unit.

The univariate logistic regression revealed that maternal age (OR 0.94, 95% CI 0.90–0.98) and weight gain during pregnancy (OR 0.77, 95% CI 0.70–0.84) behaved as protective factors. The risk was also significantly lower depending on the educational level of the mother (technical/university education OR 0.10, 95% CI 0.01–0.83). On the other hand, the absence of prenatal care (OR 9.82, 95% CI 3.84–25.13) and the presence of maternal disease during pregnancy (OR 2.13, 95% CI 1.21–3.74) behaved as risk factors. ►**Table 3** shows the results of the logistic regression, together with their respective aOR and CI.

Table 3 Multivariate analysis of maternal factors associated with low birth weight

Variables	First model[a] aOR (95% CI)[b]	Second model[a] aOR (95% CI)
Maternal age	0.91 (0.86–.96)	3[c]
Weight gain	0.77 (0.69–0.86)	0.77 (0.70–0.85)
Absence of prenatal care	10.67 (3.49–32.64)	8.20 (3.22–20.87)

Abbreviations: aOR, adjusted odds ratio; 95% CI, 95% confidence interval.
[a]Adjusted for variables: level of schooling, socioeconomic bracket, marital status, social security and the presence of maternal disease.
[b]Adjusted odds ratios together with the 95% confidence intervals;
[c]Variable removed from the model: *p* of 0.01 but greater than 0.005.

Following this exploration, a multivariate analysis was performed with the main goal of identifying the clinical or sociodemographic characteristics that could be linked to the presence of low birth weight. An initial model was built, ratifying the role played by maternal age, low weight gain and absence of prenatal care. When the goodness of the adjustment was assessed, the McFadden R^2 was 0.27, with a predictive capacity of 80.3%, reflecting a high percentage of correctness.[10] However, when the second analysis was performed, only the absence of prenatal care and of adequate weight gain continued to be statistically significant. This time, the McFadden R^2 was 0.17, with a predictive capacity of 72.4%, showing an acceptable percentage of correctness.[10]

Discussion

Low birth weight is one of the most important determinants of infant morbidity and mortality because it increases the frequency of adverse perinatal outcomes.[11] Identification of factors that may have an impact on potential fetal growth is an excellent opportunity to have an impact on the health conditions of the population.[12]

There were 4,882 term live births during the observation period, of which 3.0% were low birth weight neonates. The population consisted mainly of young, single mothers with low socioeconomic and education levels, living in urban areas. Only 43% of the women started prenatal care during the first trimester of gestation. In our study, the prevalence of low birth weight was similar to that reported in other Latin American countries, but substantially lower than the one described for countries in Southeast Asia.[13–19] These differences could be explained, at least in part, by the rate of fetal growth, genetic factors and the presence of other extrinsic circumstances not related to pregnancy.[7,20]

On the other hand, regarding the multivariate analysis, it revealed that maternal weight gain (aOR 0.77, 95% CI 0.70–0.85) behaves as a protective factor, while the absence of prenatal care (aOR 8.20, 95% CI 3.22–20.87) increases the probability of an unfavorable outcome. Our findings are similar to those documented in the literature. Observational studies have shown the association between maternal weight gain and neonatal birth weight.[7] For example, it is known that infants born to mothers with poor weight gain are at a higher risk of being small for gestational age, while those born to mothers with substantial weight gain have a higher probability of being large.[21] This association is consistent in low, middle and high-income countries alike.[22]

Regarding poor prenatal care or absence thereof, the observed association emerges in populations from middle and low-income countries, and it is not completely clear in developed countries.[7,23–27] The potential explanation is that early and adequate prenatal care could be of greater benefit in women with less favorable conditions, where the implementation of this intervention could help address harmful behaviors that affect fetal growth (for example, smoking), early detection and treatment of diseases affecting gestation

(such as anemia, malnutrition), and promote healthy lifestyle habits that can have a positive impact on the fetal environment.[20,28]

Finally, although maternal age was eliminated as a variable in the second model, the observed association seems plausible, is clinically relevant, and has been documented in other studies.[29] This association could be explained by the conditions of inequity and disadvantage faced by teen mothers when compared with older women. Therefore, not surprisingly, the risk of low birth weight decreases as a function of older maternal age, given that older women may have better socioeconomic conditions and find themselves less at a social disadvantage.[30] It is no secret that racial segregation and deprivation are associated with low birth weight.[31] Notwithstanding, it needs to be said that this conclusion must be interpreted cautiously, given that the finding could be the result of multiple comparisons.

This study has some strengths, starting with the appropriate and widely accepted definition of the cases, which are considered representative of the study population because all the eligible neonates with the outcome of interest were included. In Colombia, reporting of low birth weight events is mandatory, hence there is a low probability of having missed a case.[32,33] On the other hand, given matched and independent data recording, there is confidence regarding the reliability of the data and a low probability of error in the definition of cases and controls.

Case-controlled comparability was achieved by means of the design and the analysis.[34] In the design, stringent inclusion and exclusion criteria were used in an attempt to arrive at a relatively homogenous population. In the analysis, a mathematical model was used to adjust for the presence of confounding factors. Although it is true that excluding the presence of residual confounding factors is not feasible, given the nature of the design, the importance and number of the variables considered allows, in some way, for acceptable case-controlled comparability.[35] Finally, the other strength of this study is that exposure was proven through entry in the clinical record and in the vital statistics database of the Health Secretariat, reducing the risk of poor classification.[35]

This study also has weaknesses. The subjects used as controls came from the same institution and not from the community, making the study prone to selection bias (Berkson fallacy) because, given the origin of the controls, they could be more prone to having certain factors associated with low birth weight, leading to potential distortions for some exposure-disease associations.[35] Sample size is yet another weakness of the study. Although a design was developed *a priori* for estimating sample size, the critical assessment of the confidence intervals points to some degree of inaccuracy.[36]

Despite its limitations, this study has many practical implications. First, it highlights the need to ensure adequate weight gain during pregnancy. This is important because adequate weight gain during gestation behaves as an indirect indicator of good nutritional status of the pregnant woman. Secondly, the association observed between poor prenatal care and low birth weight should prompt timely and adequate access to medical care during gestation, especially for vulnerable populations. Medical care during the reproductive period is a valuable opportunity to have a positive impact on health conditions by means of education regarding healthy lifestyle and to ensure early detection and treatment of diseases affecting gestation. Finally, the role of an unfavorable socioeconomic environment could play out in the association observed between maternal age and low birth weight. Hence the need for highlighting the relevance of providing timely and equitable access to quality healthcare systems.

Conclusion

Based on the findings of this study, low maternal weight gain and untimely initiation of prenatal care are some of the factors known to be associated with the presence of low birth weight in term neonates. On the other hand, the role of maternal age could also be relevant, considering that this association reflects, at least in part, the conditions of poverty and deprivation of the study population. This study, despite its many strengths, has limitations. Therefore, further studies are required to undertake a more extensive evaluation of the maternal factors associated with the presence of low birth weight among term neonates.

Contributions

Each author participated actively in the planning, execution and conduction of this study. The authors drafted the manuscript, edited, and approved the final, submitted version. None of the authors has a financial or any other conflict of interest.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Gene Polymorphisms in *FAS* (Rs3740286 and Rs4064) Are Involved in Endometriosis Development in Brazilian Women, but not those in *CASP8* (rs13416436 and rs2037815)

Polimorfismos do gene FAS (rs3740286 e rs4064) estão envolvidos no desenvolvimento de endometriose em mulheres brasileiras, mas não os no CASP8 (rs13416436 e rs2037815)

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Abstract

Objective The present study aims to investigate the association between *caspase-8* (*CASP8*) (rs13416436 and rs2037815) and *Fas cell surface death receptor* (*FAS*) (rs3740286 and rs4064) polymorphisms with endometriosis in Brazilian women.

Methods In the present case-control study, 45 women with a diagnosis of endometriosis and 78 normal healthy women as a control group were included. The genotyping was determined by real-time polymerase chain reaction (PCR) with Taqman hydrolysis probes (Thermo Fisher Scientific, Darmstadt, Germany). Genotypic and allelic frequencies were analyzed using Chi-squared (χ^2) test. In order to determine the inheritance models and haplotypes ,SNPStats (Institut Català d'Oncologia, Barcelona, Spain) was used. Levels of 5% ($p = 0.05$) were considered statistically significant.

Results No significant difference was observed in genotypic or allelic frequencies between control and endometriosis groups for rs13416436 and rs2037815 (*CASP8* gene). On the other hand, a significant difference between rs3740286 and rs4064 (*FAS* gene) was found. Regarding polymorphisms in the *FAS* gene, a statistically significant difference was found in co-dominant and dominant models. Only the haplotype containing the rs3740286A and rs4064G alleles in the *FAS* gene were statistically significant.

Conclusion The polymorphisms in the *CASP8* gene were not associated with endometriosis. The results indicate an association between *FAS* gene polymorphisms and the risk of developing endometriosis.

Keywords
- endometriosis
- apoptosis
- genetic polymorphism
- real-time polymerase chain reaction
- genetic predisposition to disease

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Resumo

Objetivo Investigar a associação entre os polimorfismos dos genes *caspase-8* (*CASP8*) (rs13416436 e rs2037815) e *FAS* (rs3740286 e rs4064) em mulheres brasileiras com endometriose.

Métodos Trata-se de um estudo do tipo caso-controle, no qual foram incluídas 45 mulheres com diagnóstico de endometriose e 78 controles. A genotipagem das amostras foi determinada usando a reação em cadeia de polimerase em tempo real com sondas de hidrólise TaqMan (Thermo Fisher Scientific, Darmstadt, Germany). As frequências genotípicas e alélicas foram analisadas usando o teste do qui-quadrado. O SNPStats (Institut Català d'Oncologia, Barcelona, Espanha) foi usado para determinar os modelos de herança e os haplótipos. Os níveis de significância estatística considerados foram de 5% ($p = 0,05$).

Resultados Não foi observada diferença significativa nas frequências genotípicas ou alélicas entre os grupos de controle e de endometriose para os polimorfismos rs13416436 e rs2037815 (gene *CASP8*). Por outro lado, foi encontrada uma diferença significativa entre os polimorfismos rs3740286 e rs4064 (gene *FAS*). Em relação aos polimorfismos do gene *FAS*, foi encontrada uma diferença estatisticamente significativa nos modelos codominante e dominante. Apenas o haplótipo contendo os alelos rs3740286A e rs4064G no gene *FAS* foi estatisticamente significativo.

Conclusão Não há associação entre os polimorfismos do gene *CASP8* e endometriose. Entretanto, há associação entre os polimorfismos do gene *FAS* e o risco de desenvolver endometriose.

Palavras-chave

- endometriose
- apoptose
- polimorfismo genético
- reação em cadeia da polimerase em tempo real
- predisposição genética para doença

Introduction

Endometriosis is a multifactorial disease that is characterized by the presence and growth of endometrial glands and stroma outside the uterus. It affects 10% of women in the reproductive age, and its main clinical manifestations include infertility, chronic pelvic pain, dysmenorrhea, and dyspareunia.[1,2]

Previous studies showed that endometriosis-related symptoms significantly predict a negative impact on the daily life activities, work performance and social and marital life of the patients.[3,4] In addition, the results of a recent systematic literature review indicated that there is a significant economic burden associated with endometriosis, as observed by both direct and indirect costs. The direct costs included inpatient, outpatient, surgery, drug and other healthcare service costs. The indirect costs were related to absenteeism and presenteeism (loss of productivity at work).[5]

Laparoscopic exploration with histopathological examination is the gold standard for the diagnosis of endometriosis.[6] During the surgery, lesion excision enables the histological confirmation of endometriosis based on the criteria of the American Society for Reproductive Medicine,[7] in four stages: I (minimal disease), II (mild disease), III (moderate disease) and IV (severe disease).[7] To prevent unnecessary surgery,[6] the identification of a high-risk patient population for endometriosis with a complete clinical assessment should be performed, supported by a selective use of laboratory and imaging studies followed by surgery only on the high-risk population.

In women with endometriosis, the percentage of endometrial cells undergoing apoptosis is significantly decreased. On the other hand, the number of surviving cells is increased, and they still show physiological activity. The eutopic endometrium in women with endometriosis presents an increased expression of anti-apoptotic factor and a decreased expression of pro-apoptotic factors compared with the endometrium in healthy women. These differences could contribute to the survival of regurgitating endometrial cells into the peritoneal cavity and to the development of endometriosis.[8,9] The data in the literature indicate that apoptosis plays a critical role in the pathogenesis of endometriosis.[8–10] Another study reviewed the role of apoptosis-associated molecules in the treatment of endometriosis with potential clinical applications in the future.[11]

Single nucleotide polymorphisms (SNPs) in apoptotic genes, such as those of the *Fas cell surface death receptor* (*FAS*) and the *caspase-8* (*CASP8*) genes, may be involved with the development of endometriosis.

Caspase-8 is a critical modulator of cell death, which initiates the apoptotic signaling via the extrinsic pathway, and plays a key role in the regulation of apoptosis.[12]

The FAS, also known as *TNFSF6*, *CD95*, or *APO-1*, is a cell surface receptor involved in the apoptotic signal transmission in many cell types that interacts with its natural *Fas ligand* known as FASL to initiate the death signal cascade that leads to apoptotic cell death.[13] Although best characterized in terms of its apoptotic function, previous studies have identified several other cellular responses that include migration, invasion, inflammation, and proliferation.[14] A recent study determined that stage III/IV endometriosis was associated with higher

serum *CD95*/*FAS* and *hypoxia inducible factor 1 subunit alpha* (*HIF-1α*) levels, but not with *TEK receptor tyrosine kinase* (*Tie-2*) levels, compared with stage I/II endometriosis. These biomarkers may be useful for reproductive surgeons to improve the quality of counseling to women about the presence and the severity of endometriosis.[15]

Currently, genome-wide association studies (GWASs) have been very successful in identifying common genetic risk variants for several complex diseases. Genome-wide association studies have reported a significant association of endometriosis with chromosomes 2 and 10, which harbor *CASP8* and *FAS* genes respectively.[16–21]

Therefore, the present study aims to investigate the association between *CASP8* (rs13416436 and rs2037815) and *FAS* (rs3740286 and rs4064) polymorphisms with endometriosis in Brazilian women.

Methods

Sample Characterization

This is a case-control study with 123 women treated in a public hospital in the interior of the state of Minas Gerais, Brazil. The women were divided into a control group ($n = 78$; 63.4%) and a case group ($n = 45$; 36.6%). The case group was characterized by the presence of endometriosis, and the control group, by the absence of it, both verified by laparoscopy or laparotomy. The inclusion factors were the surgical procedure that enabled the confirmation of the presence (patients) or absence (controls) of endometriosis, and a written informed consent form (WICF) for the participation in the present research. Women that have not met the aforementioned criteria were excluded. Among the women of the control group, the main reasons for surgical indication were tubal sterilization (24.4%), followed by chronic pelvic pain (7.7%) and infertility (6.4%). The total mean age was 39.1 (±9.6) years. In the control group, the mean age was 40.7 (±10.3) years, and in the endometriosis group, the mean age was 36.2 (±7.8) years.

Regarding the endometriosis staging, according to the American Society for Reproductive Medicine (ASRM),[7] 6 women (13.4%) presented stage I disease, 1 (2.2%) presented stage II, 7 (15.5%) presented stage III, 1 (2.2%) presented stages III/IV, 12 (26.7%) presented stage IV, and in 18 women (40.0%) it was not possible to obtain this information.

All participants of the present study received an explanation about the present study and signed the WICF. The present research was approved by the Ethics Committee of Universidade Federal do Triângulo Mineiro (UFTM, in the Portuguese acronym) under protocol number 1628, and was conducted according to the principles described in the Declaration of Helsinki and in Resolution 466/2012 of the Brazilian National Health Council (CNS, in the Portuguese acronym). After signing the WICF, 10 mL of peripheral blood was drawn by venipuncture from the women who accepted participating in the present research.

DNA Extraction and Genotyping

Using the salting-out protocol described by Miller et al,[22] DNA was extracted from the peripheral blood samples collected in an ethylenediaminetetraacetic acid (EDTA) tube. The samples were then resuspended in Tris-EDTA (TE) 20:1, and the DNA integrity was verified in 1% agarose gel.

The four polymorphisms were genotyped via real-time polymerase chain reaction (PCR) with Taqman hydrolysis probes (Thermo Fisher Scientific, Darmstadt, Germany). The genotypes were determined by allelic discrimination. The chromosomal localizations of the polymorphisms rs13416436 and rs2037815 in the *CASP8* gene are Chr.2: 202099113 and Chr.2: 202101715 respectively. The chromosomal localizations of the polymorphism rs3740286 and rs4064 in the *FAS* gene are Chr.10: 90751340 and Chr.10: 90751380 respectively.

Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was evaluated by the Chi-squared (χ^2)test, using Haploview 4.2 software (Broad Institute, Cambridge, MA, US), and the case group was in HWE. The statistical power was calculated using the G*Power 3.1.9.2 software (Heinrich-Heine University, Düsseldorf, Germany). A statistical power of 80% was obtained, with an effect size of 0.29 and an α level of significance of 0.05. Genotypic and allelic frequencies were analyzed using the Chi-squared test. Levels of 5% ($p = 0.05$) were considered statistically significant.

SNPStats (Institut Català d'Oncologia, Barcelona, Spain) was used to determine the haplotype and to perform the logistic regressed analysis for inheritance models, using codominant (major homozygotes versus heterozygotes versus minor homozygotes), dominant (major homozygotes versus heterozygotes plus minor homozygotes), and recessive (major homozygotes plus heterozygotes versus minor homozygotes). The risk estimates were expressed as the odds ratio (OR) with a 95% confidence interval (95%CI).

Results

Concerning the polymorphisms studied, it was not possible to obtain the genotype of all of the participants of the present study, due to technical reasons – no amplification of the sample. For polymorphism *FAS* rs3740286 (A G) and *FAS* rs4064 (C G), 116 and 75 of the 123 samples were amplified respectively. For polymorphisms *CASP8* rs13416436 (A T) and *CASP8* rs2037815 (A G), the number of the samples amplified were 119 and 101 respectively.

For polymorphism *FAS* rs3740286 (A G), the association between the genotypes of the polymorphism and the development of endometriosis was observed ($\chi^2 = 8.52$; $p = 0.014$) (►**Table 1**). To verify the association, the AG and GG genotypes were grouped in "G presence", and the genotype AA, in "G absence." It was observed that G presence was more frequent in the control group ($\chi^2 = 8.51$; $p = 0.004$). When the OR was calculated, the value obtained was 0.31 (95%CI = 0.14–0.69), suggesting that women with this allele have no presumed risk of developing endometriosis (►**Table 2**).

Regarding the polymorphism *FAS* rs4064 (C G), there was an association between the genotypes of the polymorphism studied and the development of endometriosis ($\chi^2 = 6.48$; $p = 0.039$) (►**Table 1**). To verify the association, the GC and

Table 1 Frequency distribution of the genotypes of polymorphisms *FAS* rs3740286 (A G), *FAS* rs4064 (C G), *CASP8* rs13416436 (A T) and *CASP8* rs2037815 (A G), in women with endometriosis and in the control group

Diagnosis							
	Control group		Endometriosis		Total		
Polymorphism/genotype	*n*	%	*n*	%	*n*	%	
rs3740286(A G)							
AA	26	51.0	25	49.0	51	100	$p = 0.014$
AG	36	76.6	11	23.4	47	100	
GG	14	77.8	04	22.2	18	100	
Total	76	65.5	40	34.5	116	100	
rs4064 (C G)							
CC	26	76.5	08	23.5	34	100	$p = 0.039$
GC	17	56.7	13	43.3	30	100	
GG	04	36.4	07	63.6	11	100	
Total	47	62.7	28	37.3	75	100	
rs13416436 (A > T)							
AA	02	100	00	0.00	02	100	$p = 0.42$
AT	15	71.4	06	28.6	21	100	
TT	60	62.5	36	37.5	96	100	
Total	77	64.7	42	35.3	119	100	
rs2037815 (A > G)							
AA	21	60.0	14	40.0	35	100	$p = 0.39$
AG	33	64.7	18	35.3	51	100	
GG	12	80.0	03	20.0	15	100	
Total	66	65.3	35	34.7	101	100	

Table 2 Frequency distribution of the presence of the G allele of the polymorphism *FAS* rs3740286 and *FAS* rs4064, presence of an allele of the polymorphism *CASP8* rs13416436 and presence of the G allele of the polymorphism *CASP8* rs2037815, in women with endometriosis and in the control group

Diagnosis							
	Control group		Endometriosis		Total		
G presence rs3740286	*n*	%	*n*	%	*n*	%	
No	26	51.0	25	49.0	51	100	$p = 0.004$
Yes	50	76.9	15	23.1	65	100	OR = 0.31
Total	76	65.5	40	34.5	116	100	
G presence rs4064							
No	26	76.5	08	23.5	34	100	$p = 0.024$
Yes	21	51.2	20	48.8	41	100	OR = 3.09
Total	47	62.7	28	37.3	75	100	
A presence rs13416436							
No	60	62.5	36	37.5	96	100	$p = 0.30$
Yes	17	73.9	06	26.1	23	100	OR = 0.59
Total	77	64.7	42	35.3	119	100	
G presence rs2037815							
No	21	60.0	14	40.0	35	100	$p = 0.41$
Yes	45	68.2	21	31.8	66	100	OR = 0.7
Total	66	65.3	35	34.7	101	100	

Abbreviation: OR, odds ratio.

GG genotypes were grouped in "G presence", and the CC genotype was grouped in "G absence." The absence of the G allele was more frequent in the control group ($\chi^2 = 5.06$; $p = 0.024$). When the OR was calculated, the value obtained was 3.09 (95%CI = 1.14–8.43), suggesting that the absence of the G allele confers a protection 3 times higher against the development of endometriosis in comparison to women who present this allele (►**Table 2**).

However, when the polymorphisms in the *CASP8* gene were assessed, no association between the polymorphisms studied (rs13416436 and rs2037815) and the development of endometriosis was found. For the polymorphism *CASP8* rs13416436 (A T), no association between the genotypes of the polymorphism studied and the development of endometriosis was found ($\chi^2 = 1.71$; $p = 0.42$) (►**Table 1**). The AA and AT genotypes were grouped in "A presence", and the TT genotype was grouped in "A absence" to assess if there was an association between the presence of the A allele and the susceptibility to the development of endometriosis. However, no statistically significant differences were found ($\chi^2 = 1.06$; $p = 0.30$; OR = 0.59; 95%CI = 0.21–1.63) (►**Table 2**).

Regarding the polymorphism *CASP8* rs2037815 (A G), there was no association between the genotypes of the polymorphism studied and the development of endometriosis ($\chi^2 = 1.87$; $p = 0.39$) (►**Table 1**). The AG and GG genotypes were grouped in "G presence", and the AA genotype was grouped in "G absence" to evaluate if there was an association between the presence of the G allele and the susceptibility to develop endometriosis. However, no statistically significant difference was found ($\chi^2 = 0.68$; $p = 0.41$; OR = 0.7; 95%CI = 0.3–1.64) (►**Table 2**).

Regarding the polymorphisms rs13416436 (A > T) and rs2037815 (A G) in the *CASP8* gene, no statistically significant difference was found in any of the genetic models analyzed (codominant: $p = 0.34$ and $p = 0.34$; dominant: $p = 0.26$ and $p = 0.25$; recessive: $p = 0.24$ and $p = 0.23$ respectively). Regarding the polymorphisms rs3740286 (A > G) and rs4064 (G > C) in the *FAS* gene, a statistically significant difference was found in the codominant and dominant models ($p = 0.02$, $p = 0.04$; and $p = 0.006$, $p = 0.01$ respectively) (►**Table 3**).

The prevalence of haplotypes in the polymorphisms rs13416436 (A > T) and rs2037815 (A G) in the *CASP8* gene, and the rs3740286 (A > G) and rs4064 (G > C) in the *FAS* gene is shown in ►**Table 4**. Only the haplotype containing the rs3740286A and rs4064G alleles in the *FAS* gene was statistically significant (OR = 0.33; 95%CI = 0.15–0.72; $p = 0.0062$).

Table 3 *FAS* and *CASP8* gene polymorphism analysis in different genetic models

Gene/SNP	Model	OR (95%CI)	*p*-value
FAS rs3740286	Codominant (AA x AG x GG)	1.00	
		3.03 (1.24–7.41)	0.02
		3.24 (0.92–11.35)	
	Dominant (AA x AG + GG)	1.00	
		3.09 (1.36–6.99)	0.006
	Recessive (AA + AG x GG)	1.00	
		1.99 (0.60–6.59)	0.24
FAS rs4064	Codominant (GG x CG x CC)	1.00	
		0.35 (0.11–1.06)	0.04
		0.20 (0.04–0.88)	
	Dominant (CC x CG + GG)	1.00	
		0.30 (0.10–0.84)	0.01
	Recessive (CC + CG x GG)	1.00	
		0.33 (0.08–1.29)	0.11
CASP8 rs13416436	Codominant (TT x AT x AA)	1.00	
		1.64 (0.56–4.76)	0.34
		–	
	Dominant (TT x AT + AA)	1.00	
		1.80 (0.63–5.16)	0.26
	Recessive (TT + AT x AA)	1.00	
		–	0.24
CASP8 rs2037815	Codominant (AA x AG x GG)	1.00	
		1.49 (0.59–3.77)	0.34
		2.80 (0.64–12.20)	
	Dominant (AA x AG + GG)	1.00	
		1.49 (0.59–3.77)	0.25
	Recessive (AA + AG x GG)	1.00	
		2.21 (0.56–8.66)	0.23

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

Discussion

According to the data in the literature, apoptosis plays an important role in the development of endometriosis.[8–10] A recent review aimed to shed light on the role of the apoptosis pathways in the modulation of the fine-regulated peritoneal microenvironment during endometriosis.[23] Considering the large amount of evidence retrieved from in vitro as well as in vivo models, the reduced apoptosis of endometriotic cells together with the increased apoptosis of peritoneal fluid mononuclear cells may address the peritoneal homeostasis to a permissive environment for the progression of the disease.[23]

Endometriosis is a gynecologic condition characterized by the growth of endometrial tissue outside the uterus. Therefore, genes that regulate the growth and the reproduction of endometrial cells and genes that aid the survival of cells and

Table 4 Haplotype analysis between rs13416436 (A > T) and rs2037815 (A > G) of the *CASP8* gene and rs3740286 (A > G) and rs4064 (G > C) in the *FAS* gene on the risk of developing endometriosis

Gene	Haplotype	ED	Control	OR (95%CI)	*p-value*
CASP8	T-A	0.6494	0.4459	1.00	—
	T-G	0.2824	0.4308	1.74 (0.89 - 3.39)	0.11
	A-A	0	0.1234	2.10 (0.77 - 5.77)	0.15
	A-G	0.0682	0		
FAS	G-C	0.2111	0.4048	1.00	—
	A-G	0.4489	0.2558	0.33 (0.15–0.72)	0.0062
	A-C	0.3139	0.3231	0.66 (0.31–1.39)	0.27
	G-G	0.0262	0.0162	1.17 (0.07–20.52)	0.92

Abbreviations: 95% CI, 95% confidence interval; ED, endometriosis; OR, odds ratio.

eliminate apoptosis are activated.[8,9,11] This is the reason why, in connection with endometriosis, we have focused on the analysis of polymorphisms associated with apoptosis. It is important to search for biomarkers that could be useful to determine the predisposition and/or the prognosis.

In the present study, we have hypothesized that genetic factors are involved in the etiology of endometriosis; therefore, our aim was to evaluate the genetic predisposition to the development of endometriosis regarding the presence of four polymorphisms: rs13416436, rs2037815, rs3740286 and rs4064.

The polymorphisms rs13416436 and rs2037815 are characterized by an A/T and A/G single-nucleotide variation respectively, on human chromosome 2, while SNPs rs3740286 and rs4064 are located on chromosome 10 and correspond to A/G and C/G alterations respectively. The present study was the first to analyze the possible associations of these polymorphisms with endometriosis in a Brazilian sample population.

The present study indicated the absence of association between polymorphisms in the *CASP8* gene and the risk of developing endometriosis. Our results are in line with a previous study conducted by our group.[24] There are no studies on the polymorphisms rs13416436 and rs2037815 of the *CASP8* gene regarding endometriosis. Only two studies analyzed these polymorphisms in preeclampsia and multiple sclerosis (MS).[24,25] Orlando et al[24] showed the absence of association between rs13416436 and rs2037815 with the development of preeclampsia. However, for SNP rs2037815, GG homozygosity was associated with cases of primary progressive MS when compared with cases of relapse-onset MS and controls.[25]

Previous studies using genome-wide association (GWA) analysis have identified susceptibility genes for endometriosis in chromosome 2.[17,18,20,26] Adachi et al[17] showed that four of the top five SNPs were in and around interleukin 1α (IL1A) at 2q13, which might be a functional candidate gene for endometriosis. Another GWA meta-analysis in 4,604 cases of endometriosis and 9,393 controls identified 7 SNPs associated with endometriosis, 2 of them in chromosome 2 (rs13394619–2p25.1 and rs4141819–2p14).[18] Sundqvist et al[20] observed a weak association with endometriosis (all stages) for rs1250248 in the 2q35 locus ($p = 0.049$). A recent meta-analysis showed a remarkable consistency in endometriosis GWA results across studies, with little evidence of population-based heterogeneity.[26] It also recommended functional studies in relevant tissues to understand the effect of the variants on downstream biological pathways.[26] An interesting finding common to these three researches[17,18,20] was the identification of the polymorphisms associated with endometriosis in chromosome 2, in which the *CASP8* gene, investigated in the present study, is located. However, despite the evidence of the participation of this chromosome in the etiology of endometriosis, the present study has not associated the polymorphism of the *CASP8* gene with the disease.

Regarding the two *FAS* SNPs, our results suggest a significant effect on the susceptibility to endometriosis. Only one study evaluated the three polymorphisms located within the *FAS* (-1377 G > A and -670 A > G) and *FASL* (-843 C > T) genes as susceptibility factors for endometriosis.[27] The results indicated that the variants analyzed are not involved in the pathogenesis of the disease in the sample . The authors suggest that a complete genetic analysis of the genes involved in the intricate regulatory system of the apoptosis may lead to the identification of susceptibility factors for the disease and a better understanding of its etiology.[27] In spite of showing an absence of association between *FAS* polymorphisms and endometriosis, Fernández et al[27] reported that this does not allow us to completely exclude these genes as potential candidates for the disease. Our results corroborate this finding.

Although we have identified an association of polymorphisms in chromosome 10 with susceptibility to endometriosis, another study showed that polymorphisms in the *cytochrome P450 family 17 subfamily A member 1* (*CYP17A1*) and *interferon-induced protein with tetratricopeptide repeats 1*(*IFIT1*) genes in chromosome 10 did not contribute to the risk of endometriosis in the Australian population.[28] A systematic literature review conducted in 2008 showed that: 1) there is evidence of genetic linkage to chromosomes 7 and 10; 2) genetic variants in 76 genes were associated with endometriosis; and 3) GWAs are recommended to locate the genetic variants that contribute to a range of common diseases.[29]

The present study is limited due to the small sample size, which decreased our ability to solidify statistic associations. Despite the small sample size, the post hoc statistical power was 80%. Since the endometriosis patients recruited in our study are all Brazilian, the association between these four polymorphisms and other populations should also be investigated. In summary, further studies with different ethnic populations and with a larger sample could help to confirm

the true significance of the association between these polymorphisms and the risk of endometriosis. Another limitation of the present study was the absence or lack of scientific works on these polymorphisms in endometriosis and other biological conditions, which has made the data generalization and comparison difficult.

A strong point of the present study is that all women who participated (cases and controls) were surgically evaluated to test for endometriosis. In addition, the present work is the first study to focus on the possible contribution of apoptosis-related gene polymorphisms to the development of endometriosis.

Conclusion

The polymorphisms in the *CASP8* gene are not associated with endometriosis. The results indicate a positive association between the rs3740286 and rs4064 of the *FAS* gene and the risk of developing endometriosis. Therefore, further studies on the functional relevance of the *CASP8* and *FAS* polymorphisms are required to confirm our observations.

Contributions

Cristina Wide Pissetti: conceptualization; formal analysis; funding acquisition; writing of the original draft; writing of the review and editing. Sarah Cristina Sato Vaz Tanaka: formal analysis; methodology; writing of the original draft. Andrezza Cristina Cancian Hortolani: methodology; writing of the original draft. Alessandra Bernadete Trovó de Marqui: conceptualization; formal analysis; writing of the original draft; writing of the review and editing.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Frozen Section in the Management of Ovarian and Uterine Tumors: The Past 5 Years in a Tertiary Centre

Exame de congelação no tratamento de tumores uterinos e do ovário: experiência de 5 anos em um centro terciário

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Abstract

Objective Intraoperative frozen section (IFS) is a valuable resource, and its use in gynecological pathology has not been sufficiently emphasized. The main goal of the present study is to evaluate the reliability and agreement rates between IFS and the final paraffin section (PS) and determine how reliable IFS is.

Methods A retrospective study of all IFSs performed on uterine tumors and suspicious adnexal masses between January 2012 and December 2016 (excluding metastases) at the department of obstetrics and gynecology of the Centro Hospitalar Tondela Viseu. Frozen versus permanent section diagnosis were compared regarding the histologic type of the tumor, and the depth of myometrial invasion.

Results A total of 286 cases were eligible for the present study, including 102 (35.7%) IFSs of uterine tumors, and 184 (64.3%) IFSs of ovarian tumors. The overall rate of deferred cases was 5.2% (15/286). The accuracy of the diagnosis in cases of endometrial carcinoma was 96.25% (77/80). Among the ovarian tumors, misdiagnoses occurred in 2 cases (1.1%), corresponding to a borderline tumor (serous type) and a clear cell intracystic adenocarcinoma.

Conclusion The IFS analysis plays an important role in selected situations and is associated to a high sensitivity and specificity in cases of ovarian and endometrial tumors. Its high accuracy is almost universally associated with the possibility of obtaining an optimal surgical treatment at the time of the first surgical approach.

Keywords

- intraoperative frozen section
- ovarian tumors
- uterine tumors

Resumo

Objetivo O diagnóstico intraoperatório por congelação é um recurso importante cujo uso em patologia ginecológica não tem sido suficientemente enfatizado. O objetivo do presente estudo foi avaliar as taxas de concordância entre o diagnóstico intraoperatório por congelação e o estudo anatomopatológico definitivo e determinar o quanto o diagnóstico intraoperatório por congelação é um método confiável.

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Métodos Um estudo retrospectivo de todos os diagnósticos intraoperatórios por congelação realizados em tumores uterinos e massas anexiais suspeitas entre janeiro e 2012 e dezembro de 2016 (excluindo metástases) no serviço de ginecologia e obstetrícia do Centro Hospitalar Tondela Viseu. Comparação do diagnóstico intraoperatório por congelação com o resultado do estudo definitivo em relação ao tipo histológico do tumor e profundidade de invasão miometrial.

Resultados Um total de 286 casos foram elegíveis para o estudo, incluindo 102 (35.7%) tumores uterinos e 184 (64.3%) tumores ovarianos. A taxa global de casos deferidos foi de 5.2% (15/286). Entre os tumores uterinos, a acuidade de diagnóstico nos casos de carcinoma endometrial foi de 96.25% (77/80). Entre os tumores ovarianos, não se verificou concordância em 2 casos (1.1%), correspondendo a um tumor borderline do tipo seroso e a um adenocarcinoma de células claras intracístico.

Conclusão O diagnóstico intraoperatório por congelação apresenta-se com um importante papel em situações selecionadas, sendo acompanhado de elevada taxa de sensibilidade e especificidade para tumores endometriais e ovarianos. A sua elevada acuidade diagnóstica encontra-se associada à possibilidade de obter um tratamento cirúrgico adequado na primeira abordagem cirúrgica

Palavras-chave
- diagnóstico intraoperatório por congelação
- tumores do ovário
- tumores uterinos

Introduction

Intraoperative frozen section (IFS) can prove to be a valuable resource, and its use in gynecological pathology has not been emphasized in the literature to the same degree as in other surgical fields. It is important for pathologists and surgeons to understand the role and limitations of IFS in gynecological oncology.[1]

Intraoperative frozen section plays a critical role in guiding gynecological tumor surgical procedures, determining whether the sample tissues are benign or malignant.[2]

The use of IFS is one of the most important steps in the operative management of suspicious adnexal masses. The IFS is usually requested to define the adequate surgical plan either by obtaining histological confirmation of suspected malignant or borderline primary ovarian tumors, or by ruling out malignancy in a suspicious adnexal mass.[3]

Regarding endometrial cancer (EC), IFS can potentially define the grade of the tumor, the depth of myometrial invasion, the histological type, and the existence or absence of cervical extension. Intraoperative frozen section is the only way to identify during surgery the subgroup of patients who are at a higher risk of extrauterine disease and therefore provide adequate guidance toward optimal surgical staging.[4,5]

Relevant clinical information should include not only the previous history of malignancy, pathology reports, imaging studies such as ultrasonography or computed tomography (CT) scan and serum markers, but also the impression of the surgeon during the operation. Ovarian tumors represent the most common request site for intraoperative diagnosis, followed by endometrium, cervix, and vulva tumors.[2]

Intraoperative frozen section requires pathologists to possess excellent gross and microscopic diagnostic skills. The overdiagnosis can lead to unnecessary surgical intervention and increased morbidity and mortality. On the other hand, underdiagnosis is associated with tumor spread and need for additional surgeries.[3]

Surgeons should be aware that IFS diagnosis is based on the assessment of a few sections from the grossly most suspicious or representative portion of the tumor, while the final diagnosis is made after the evaluation of an internationally agreed standard of a minimum of one section per centimeter of maximal tumor diameter.[4]

An ideal IFS would have 100% accuracy for the evaluation of ovarian tumors. Nevertheless, the sensitivity and specificity for IFS in ovarian tumors range from 65 to 97% and from 97 to 100%, respectively.[6] Large diameter, mucinous type and borderline tumors were shown to increase the discrepancy between IFS and the definitive pathological result.[6,7]

Regarding endometrial tumors, the accuracy of IFS has been extensively discussed in the literature and concordance rates between IFS and paraffin section (PS) range from 68 to 95% for tumor grade and from 72 to 95% for depth of myometrial invasion.[4,5]

Several investigators have suggested that IFS is an accurate and useful tool to guide intraoperative decision making for surgical staging in EC.[2,6] In contrast, several others have presented data that question the reliability of IFS.[7,8] Simple total hysterectomy (TH) plus bilateral salpingo-oophorectomy (BSO) remains a cornerstone for the management of EC, whereas the value of systematic lymphadenectomy is a matter of great debate.[9] Many gynecologic oncologists have turned to IFS analysis as a means of determining which women should undergo lymph node sampling.[10]

At our institution, lymphadenectomy in the context of IFS is usually performed on patients with grade 1 or 2 endometrioid adenocarcinoma presenting with cervical involvement and/or more than 50% myometrial invasion in the IFS. Regarding ovarian tumors, the same is true for those with an IFS diagnosis of malignancy.

The aim of the present study is to evaluate the reliability and agreement rates between IFS and the final PS and to determine whether IFS is a reliable method for guiding the intraoperative decision-making or not, namely regarding the need for lymphadenectomy.

Methods

In the present retrospective study, all IFSs performed on uterine and suspected ovarian tumors between January 2012 and December 2016 (excluding metastases) at the department of obstetrics and gynecology of the Centro Hospitalar Tondela Viseu were included. Frozen versus permanent section diagnoses were compared regarding the histologic type of the tumor, and the depth of myometrial invasion. During surgery, the uterus or/and adnexa were given to the pathologist for IFS examination. The pathologist determined the number of sections to be examined; assessed tumor size, grade, histologic subtype and, regarding endometrial tumors, the invasion of the cervix or of the external half of the myometrium. The results were reported to the operating surgeon while the patient was still anesthetized. The surgeon then determined the surgical conduct accordingly. In cases in which no definitive conclusions can be achieved by IFS, the pathology report is deferred. In most of these cases, a strong suspicion or possible exclusion of a particular diagnosis is given orally to the surgeon.

After reporting the results of the frozen section, the specimens were processed routinely for final PS analysis. Regarding ovarian tumors, the results of IFS and PS were divided in benign, borderline, and malignant. Regarding uterine tumors, the results were divided in benign (excluded) and malignant, including invasion of the cervix and of the external half of the myometrium. After that, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined separately for benign, borderline, and malignant cases by considering the final PS diagnosis as the gold standard (►**Table 1**).

A total of 307 patients underwent hysterectomy and/or adnexectomy including IFS, 123 of which had a preoperative diagnosis of endometrioid adenocarcinoma of the uterus, complex atypical hyperplasia (CAH) or suspected cancer in hysteroscopy combined with inconclusive sampling.

Table 1 Characteristics of the patients

	Ovarian tumors ($n = 184$)	Uterine tumors ($n = 102$)
Characteristic		
Age mean	54.7	51
Age range	16–86	31–79
Body mass index mean (kg/m2)	26.2	32
Body mass index range	17–35	20–37
Postmenopausal	47.8%	90.2%

Age in years.

Twenty-one patients were excluded from the study group: six cases of polypoid endometrium, three cases of adenomyosis, three cases of tubal benign tumors, two cases of endometrial hyperplasia without atypia, two cases of uterine fibroids, two cases of ovarian metastasis (one from the colon and another from the appendix), one case of cervical carcinoma, one case of parametrial fibroid and one case of ovarian varicocele.

Hence, 286 patients were eligible for analysis. These patients were analyzed with IFS to determine the need for complete surgical staging, including pelvic and para-aortic lymphadenectomy.

The approval of the institutional review board was obtained for the reviews of the medical records and pathologies of all patients. The ethical approval protocol was based on the World Medical Association's Declaration of Helsinki. No patient consent was required because the data were analyzed anonymously.

Results

There were 102 (35.7%) uterine tumors and 184 (64.3%) ovarian tumors. The overall rate of deferred cases was 5.2% (15/286).

Ovarian Tumors

A total of 184 patients were identified. The mean age was 54.7 ± 15.9 years old (range 16–86 years old). The majority of patients (84.7%) were > 40 years old and 47.8% (88) of them were postmenopausal.

The median serum concentration of the tumor marker CA125 was 20.6 (range 2.4–12548.0) IU/L ($n = 133$). The risk of ovarian malignancy algorithm (ROMA) was calculated in 100 cases with a high-risk result in 57 (57.0%) cases ($n = 100$).

The intraoperative frozen section of the 184 ovarian specimens revealed 75% (138) benign tumors, 1.6% (3) borderline tumors, 16.8% (31) malignant tumors, and 6.5% (12) deferred diagnoses. The final PS diagnoses revealed 77.1% (142) benign tumors, 4.9% (9) borderline tumors, and 17.9% (33) malignant tumors.

Of the 142 benign cases, 62 were non-neoplastic cystic lesions of the ovary, including endometriotic, follicular, and corpus luteal cysts. The most common benign neoplastic tumor was serous cystadenoma (28 cases), followed by mucinous cystadenoma (24 cases), mature cystic teratoma (21 cases), fibromas (6 cases) and Brenner tumor (1 case). Among the borderline neoplasms, 7 cases were of borderline serous and 2 cases of borderline mucinous neoplasms. The most common malignant tumors were serous carcinoma (17 cases) followed by endometrioid carcinoma (6 cases), clear cell carcinoma (5 cases), mucinous carcinoma (2 cases), malignant granulosa cells tumor (1 case), malignant epithelioid mesothelioma tumor (1 case) and Brenner malignant tumor (1 case).

Among the ovarian tumors, misdiagnosis occurred in 2 cases (1.1%), corresponding to a borderline tumor (serous type) and a clear cell intracystic adenocarcinoma, which were underdiagnosed as benign mucinous proliferation and borderline serous tumor, respectively, on the IFS.

Table 2 Comparison between intraoperative frozen section and final histological diagnoses of ovarian masses

Frozen Diagnosis	Final histological diagnosis		
	Malignant	Borderline	Benign
Malignant	31	0	0
Borderline	1	2	0
Benign	0	1	137
Total	32	3	137

Table 3 Sensitivity, specificity, positive predictive value and negative predictive value of the intraoperative frozen section for ovarian neoplasms

	Benign	Borderline	Malignant
Sensitivity	100%	66.7%	96.9%
Specificity	97.1%	99.4%	100%
Positive predictive value	99.3%	66.7%	100%
Negative predictive value	100%	99.4%	100%

Six patients (3.3%) had bilateral disease, and 21 patients (11.4%) had tumor spread beyond the ovaries.
All the patients with malignant intraoperative frozen section diagnosis underwent radical surgery, except four cases in which the tumor was unresectable.

In the 12 cases in which the IFS conclusions were deferred, the final diagnoses were: borderline mucinous tumor in 6 (5 serous and 1 mucinous type) cases, serous cystadenoma in 3 cases, mucinous cystadenoma in 1 case, teratoma in 1 case, and bilateral serous adenocarcinoma in 1 case (►**Table 2**).

The sensitivity and specificity for benign, borderline, and malignant tumors were 100%, 66.7%, 96.9%, and 97.1%, 99.4%, 100%, respectively. The PPV and NPV for benign, borderline, malignant tumors were 99.3%, 66.7%, 100%, and 100%, 99.4% and 100%, respectively (►**Table 3**).

Uterine Tumors

A total of 102 patients were included. The mean age was 51.0 years old (range 31–79 years old). In the study group, 92 (90.2%) women were postmenopausal and 59 (64.1%) presented with postmenopausal bleeding. Ten patients were premenopausal (9.8%) and 6 of them (60%) had complaints of heavy and/or irregular menstrual bleeding.

As shown in ►**Table 2**, there were 64 patients with a preoperative diagnosis of endometrial carcinoma, 31 patients with CAH, 1 patient with complex hyperplasia without atypia, and 6 patients with suspected carcinoma at hysteroscopy with inconclusive biopsy. All of the patients were evaluated initially by IFS, and then by a definitive PS to determine the degree of concordance between IFS and PS.

A total of 26 patients underwent lymphadenectomy in the same operative process (18 bilateral pelvic and para-aortic, 6 bilateral pelvic and 2 unilateral pelvic). In five cases, there was metastatic disease in the pelvic lymph nodes, and in three cases both in the pelvic and para-aortic lymph nodes. One patient presented with metastatic disease in the periganglionar adipose tissue. In five cases, lymphadenectomy was not performed due to technical difficulties, such as lack of access, obesity or other significant comorbidities.

Table 4 Correlation results between intraoperative frozen section and final histological diagnoses in endometrial tumors

	Number	Percentage
Preoperative diagnosis		
Cancer	64	62.7
Complex atypical hyperplasia	31	30.4
Complex hyperplasia without atypia	1	1.0
Suspected carcinoma	6	5.9
IFS		
Cancer	77	75.5
▪ Inner half	50	
▪ Outer half	27	
Without invasion	22	21.6
Deferred	3	2.9
	Number	**Percentage**
Postoperative diagnosis (PS)		
Cancer	80	78.4
▪ Inner half	50	
▪ Outer half	30	
Complex atypical hyperplasia	11	10.8
Benign	11	10.8

Abbreviations: IFS, intraoperative frozen section; PS, paraffin section.

Concerning the tumor staging according to the International Federation of Gynecology and Obstetrics (FIGO, in the French acronym) classification system, 47 patients (58.7%) were included in stage IA, 19 patients (23.75%) in IB, 6 patients (7.5%) in IIA, 2 patients (2.5%) in IIIA and 6 patients (7.5%) in IIIC. From the study group, 75 (93.75%) women had type I and the remaining patients had type II endometrial carcinomas, including 2 with mixed adenocarcinoma (clear cell and serous); 1 with carcinosarcoma with cervical invasion; 1 with a mixed adenocarcinoma with neuroendocrine elements and 1 with a large cells neuroendocrine carcinoma (►**Table 4**). The Accuracy of the Diagnosis of Endometrial Carcinoma was 96.25% (77/80).

The IFS correctly diagnosed the histologic type in 75 of 80 patients (93.75%). The depth of myometrial invasion was accurately diagnosed in 94.8% of the patients (73/77).

In the final PS, 75/80 tumors remained endometrioid adenocarcinomas, whereas 5 that were originally diagnosed as endometrioid adenocarcinoma in the IFS were changed to mixed histology in the PS. One was read as a grade 3 carcinosarcoma with cervical invasion, 1 as a grade 3 mixed papillary

Table 5 Comparison between intraoperative frozen section and final histological diagnoses in terms of the presence or absence of endometrial cancer

IFS diagnosis	Final pathology result			Total
	No EC	EC Inner half	EC Outer half	
No EC	18	3	–	21
Deferred	3	–	–	3
EC				
▪ inner half myometrium	1	46	3	50
▪ outer half myometrium	–	1	27	28
Total	22	50	30	102

Abbreviations: EC, endometrial cancer; IFS, intraoperative frozen section.

serous adenocarcinoma, 1 as a grade 3 mixed adenocarcinoma with neuroendocrine elements, 1 as large cells neuroendocrine tumor carcinoma, and 1 as a grade 3 mixed adenocarcinoma (clear cells and serous). Our correlation rate between IFS and PS for histological subtype was 93.75% (75/80). It is important to note that the intraoperative management was not affected in any of the five cases mentioned above (►**Table 5**).

Complex Atypical Hyperplasia

A total of 31 patients had a preoperative diagnosis of CAH. In the IFS study, 11 cases were read as malignant, 17 as negative for malignant lesions and 3 with deferred diagnosis. In the postoperative PS, 11 cases were read as CAH, 7 cases were read as no residual disease, and 13 as endometrial cancer. It is important to note that 2 cases thought to be non-cancerous in the IFS were later determined to be cancerous in the final PS. These two cases had received a diagnosis of "no residual disease" in the IFS diagnosis. They were non-invasive grade 1 cancers, in which the discrepancy was not relevant to the surgical management, and they were staged according to the FIGO classification system as IA.

Discussion

Intraoperative Frozen Section in Ovarian Tumors

Ovarian cancer is the third more common malignant tumor, and its incidence has increased, especially in younger women.[11]

The clinical diagnosis of ovarian malignancy is challenging due the difficulty in obtaining a histological diagnosis before the definitive treatment.[12]

The optimal surgical management of ovarian tumors depends very much on their correct categorization as benign, borderline or malignant. The need for an additional surgical procedure may arise from an incomplete preoperative evaluation of a complex adnexal mass, followed by an inadequate surgery. It is to avoid this unwanted sequence that the IFS represents a potentially powerful tool for the gynecologic oncology surgeons in the right setting.

The IFS analysis of ovarian masses allows gynecological oncologists to perform the optimal surgery to a given patient, therefore preventing the unnecessary morbidity of excessive surgical staging in benign cases and the need for restaging procedures in early-stage malignant tumors.[12] The IFS analysis is only valuable if it may alter the procedure that the surgeon performs at the time of the operation, which is the case of ovarian cancer surgery.

The use of IFS offers a very good diagnostic accuracy in distinguishing women with malignant and benign ovarian tumors. In contrast, for borderline ovarian tumors, IFS results in more diagnostic discrepancies.

In a study of 274 patients, the sensitivity and specificity of IFS for benign, borderline and malignant tumors were 97% and 81%, 62% and 96% and 88% and 99%, respectively. The histologic type (mucinous), tumor size ($<$ 10 cm), the borderline component ($<$ 10%) and the pathologist experience predicted the misdiagnosis of borderline tumors.[13] In another study, the IFS diagnosis agreed with the PS diagnosis in 94% of all cases (98.5% for malignant tumors, 94% for benign tumors, and 78.6% for borderline tumors). The sensitivity and specificity values for malignant tumors were 93 and 99%; for borderline tumors, 61 and 99%; and for benign tumors, 98 and 93%, respectively.[14]

In a majority of studies, the sensitivity, specificity and predictive values of IFS diagnoses for benign and malignant tumors were found to be relatively high.[5–7,15,16] On the other hand, the sensitivity of IFS for borderline ovarian tumors was $\sim$ 60% in previous reports.[14,17]

In our experience, the sensitivity and specificity for benign, borderline, and malignant tumors were 100%, 66.7%, 96.9%, and 97.1%, 99.4%, 100%, respectively.

Out of the 184 IFSs reported in the present study, 98.9% of the women were submitted to the correct operative procedure at the initial surgical operation, only 0.54% of the women were under-staged at the first surgery, and 0.54% of the women were over-staged based on the IFS report.

The present study shows that IFS can contribute significantly to determine the malignant or benign nature of epithelial ovarian tumors, whereas for borderline tumors, its accuracy appears to be more dependent on the experience of the pathologist and on the characteristics of the tumor.

The main limitation of the IFS is the difficulty to obtain an accurate diagnosis of borderline ovarian tumors, mainly of the mucinous type.

Various reasons have been proposed for the relative inaccuracy of IFS in the diagnosis of borderline tumors. In a large borderline tumor, there may be only occasional foci of atypia amounting to the borderline category. On the other hand, severe atypia and/or invasion may be focal, but amounting to frank malignancy in the final reporting. Ovarian mucinous borderline tumors may contain benign, borderline and malignant areas in the same tumor. Therefore, the final reporting may require a large number of sections to be processed, an option not usually available during IFS, as it is very labor-intensive and time-consuming. It has also been suggested that it may be more difficult to diagnose borderline mucinous tumors compared with borderline serous tumors because of their larger average size.[18]

In a univariate analysis, underdiagnosis was shown to be more likely in non-serous epithelial tumors.[15] Another study showed a 9% inaccuracy rate in serous tumors compared with 36.6% in mucinous tumors.[19] Most false negatives occur in mucinous neoplasms and borderline tumors of various types.[12]

In summary, IFS can be of clinical use and the surgeons may feel confident enough to base appropriate surgical action upon a given result in experienced centers. Proximity between surgeons and pathologists seems advisable.

Intraoperative Frozen Section in Uterine Tumors

Endometrial cancer is the most common malignant tumor of the genital tract worldwide.[7]

In endometrial carcinoma, the incidence of pelvic/para-aortic lymph node metastasis is related to the grade of the tumor, the depth of myometrial invasion and the presence of cervical involvement. These factors determine the type of initial surgery and the extent of the surgical staging.[20] The IFS analysis has been used for this purpose to identify patients requiring pelvic/para-aortic lymphadenectomy.

The key finding from the study was that, in experienced hands, the IFS analysis is accurate in identifying the subgroup of patients with high-risk EC who will benefit from full surgical staging at the time of their primary surgery.

In the present study, IFS for both histologic grade and depth of myometrial invasion correlated strongly with the final pathology analysis, supporting the use of IFS as a means to guide intraoperative decisions regarding lymphadenectomy.

The depth of myometrial invasion was accurately diagnosed in 94.8% (73/77) of the cases. The inaccuracy resulted in sub-optimal intraoperative surgical care in only 3.9% (3/77) of the patients, with 2.6% and 1.3% being under and over-treated, respectively, at the time of the primary surgery.

The correlation between IFS and paraffin histology in patients with endometrial carcinoma was 96.25% (77/80). However, the three cases not detected in IFS were not surgically undertreated in the end.

Lymphadenectomy was performed in 32.5% (26/80) of the patients with malignant disease. In 5 cases (6.25%), lymphadenectomy was not performed due to technical difficulties, while 61.25% (49/80) were considered low-risk and were spared of being submitted to lymphadenectomy. Two patients (2.5%) were incorrectly diagnosed as low-risk and were not submitted to lymphadenectomy.

There is controversy about the use of IFS in the evaluation of endometrial tumors. In some studies, IFS accurately identified 90% of the patients requiring pelvic/para-aortic lymphadenectomy. Histologic grade on IFS correlated with the final diagnosis in 91.4 to 94% of the cases.[6,16] The depth of myometrial invasion was accurately reported in 80 to 95% of the cases.[2,5,7,16] However, other studies showed that IFS for histological grade and depth of myometrial invasion in EC correlates poorly (58%) with the final pathology analysis.[7] In some studies, the evaluation of the depth of myometrial invasion with IFS has a sensitivity and a specificity of 74 and 95%, respectively, and this is not significantly higher than the radiological assessment.[21,22]

It is important to say that, in IFS, we cannot expect a high accuracy concerning the histopathological classification of the tumor and its grade because both depend on:

1. Sampling criteria (for example, is it necessary to count the percentage of solid areas in microscopy); 2. evaluation with complementary techniques (for example, diverse histological types, mixed tumors, heterologous elements, etc.); 3. we can rarely make a diagnosis of a neuroendocrine tumor in the IFS; it may be suspected in extreme cases of very good differentiation or extremely small differentiation, but only with paraffin processing and immunophenotype study can we make the final diagnosis.

Criteria 1 and 2 are not subject to definitive observation in IFS; they imply total tumor inclusion. Neither is it allowed to freeze tissue more than necessary, because freezing alters the processing and complementary immune techniques, such as irreversibly preventing a correct histopathological diagnosis.

There are several reasons for inaccuracies related to all IFS samplings, including inadequate sampling and potential artifacts. If the tumor is macroscopically confined to the endometrium, it is difficult to reveal myometrial invasion in IFS, even with multiple cuts, leading to a sampling error.

For the group of patients with a preoperative diagnosis of CAH, endometrial carcinoma was diagnosed at the IFS study in 35.5% (11/31) of the cases, and all of them were confirmed in the final PS. However, the IFS failed to identify 2 cases of endometrial carcinoma. According to several studies, a considerable number of patients with EC can be missed on IFS. In one study, the diagnosis of EC was missed in 7/20 patients with perioperative CAH.[23] In another study, the diagnosis was missed in 14/125 patients.[24] It is important to reinforce that in the present study, as well as in other reports, these cases were early stage ECs without myometrial invasion, which can provide an explanation for the discrepancies in these cases, findings which, again, were not relevant to the surgical management.

Conclusion

The IFS diagnosis has important implications regarding the type and extent of the surgery performed at the initial surgical approach. The IFS analysis plays a critical role in providing an appropriate surgical treatment and in avoiding under or over-treatment. We have found a high sensitivity and specificity in IFS in the diagnosis of ovarian tumors and in the determination of their malignant potential. Therefore, IFS should always be used when the preoperative diagnosis is not conclusive, in order to determine the extent of surgical resection. However, underdiagnosis can occur in tumors of the borderline category, especially those with a mucinous histology, which can be minimized by increased sampling on the frozen section. Our results demonstrate the reliability of IFS in identifying patients who should undergo lymphadenectomy. At our institution, high rates of agreement between IFS and PS were found for histological subtype and myometrial invasion. These are histopathological risk factors that are routinely used to guide the management of clinical, early-stage EC. Uterine type-II carcinomas and ovarian borderline tumors are the most challenging diagnoses and accounted for the majority of IFS misdiagnoses.

The limitations of the present study are inherent to its retrospective nature, as well as to the relatively limited sample. Regular audits, including specific analysis of cases in which IFS and PS are different, should be conducted by both surgeons and pathologists as part of a quality assurance process for the intraoperative management of patients with suspected or proven ovarian or uterine cancer.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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A Simple, Reproducible and Low-cost Simulator for Teaching Surgical Techniques to Repair Obstetric Anal Sphincter Injuries

Um Simulador simples, reproduzível e de baixo custo para o ensino de técnicas cirúrgicas para reparar lesões obstétricas do esfíncter anal

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Abstract

Objective To describe and evaluate the use of a simple, low-cost, and reproducible simulator for teaching the repair of obstetric anal sphincter injuries (OASIS).

Methods Twenty resident doctors in obstetrics and gynecology and four obstetricians participated in the simulation. A fourth-degree tear model was created using low-cost materials (condom simulating the rectal mucosa, cotton tissue simulating the internal anal sphincter, and bovine meat simulating the external anal sphincter). The simulator was initially assembled with the aid of anatomical photos to study the anatomy and meaning of each component of the model. The laceration was created and repaired, using end-to-end or overlapping application techniques.

Results The model cost less than R$ 10.00 and was assembled without difficulty, which improved the knowledge of the participants of anatomy and physiology. The sutures of the layers (rectal mucosa, internal sphincter, and external sphincter) were performed in keeping with the surgical technique. All participants were satisfied with the simulation and felt it improved their knowledge and skills. Between 3 and 6 months after the training, 7 participants witnessed severe lacerations in their practice and reported that the simulation was useful for surgical correction.

Conclusion The use of a simulator for repair training in OASIS is affordable (low-cost and easy to perform). The simulation seems to improve the knowledge and surgical skills necessary to repair severe lacerations. Further systematized studies should be performed for evaluation.

Keywords

- natural childbirth
- suture techniques
- anal sphincter/ injuries
- simulation training

Resumo

Objetivo Descrever e avaliar a utilização de um simulador simples, de baixo custo e reprodutível para o ensino de sutura de lacerações perineais de 4° grau.

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Métodos Participaram da simulação 20 residentes de ginecologia e obstetrícia e quatro profissionais especialistas. Um modelo de laceração de 4° grau foi criado com materiais de baixo custo (preservativo simulando a mucosa retal, tecido de algodão simulando o esfíncter anal interno e carne bovina simulando o esfíncter anal externo). O simulador foi inicialmente montado com ajuda de fotos anatômicas, para estudar a anatomia e o significado de cada componente do modelo. A laceração foi criada e suturada, utilizando técnicas de borda a borda e de sobreposição do esfíncter anal.

Resultados O modelo custou menos de R$ 10,00 e foi montado sem dificuldade, aprimorando os conhecimentos dos participantes sobre anatomia e fisiologia. As suturas das camadas (mucosa retal, esfíncter interno e esfíncter externo) foram realizadas seguindo a técnica cirúrgica. Todos os participantes ficaram satisfeitos com a simulação e consideraram que esta melhorou seus conhecimentos e habilidades. Entre 3 a 6 meses após o treinamento, 7 participantes presenciaram em sua prática lacerações graves e relataram que a simulação foi útil para a correção cirúrgica.

Conclusão A utilização de um simulador para treinamento de sutura de lacerações obstétricas graves é acessível (baixo custo e fácil execução). A simulação parece aprimorar conhecimentos e habilidades cirúrgicas para sutura de lacerações graves. Mais estudos sistematizados devem ser realizados para avaliação.

Palavras-chave
- parto natural
- técnicas de sutura
- esfíncter anal/ lesões
- treinamento de simulação

Introduction

Severe perineal laceration involving the anal sphincter is an important complication of vaginal delivery. Its incidence is used as a safety marker in childbirth, and it can be used to evaluate an institution or region.[1–3] The reported incidence varies according to hospital, country, obstetric practice, and diagnosis, ranging from 1.2 to 6% of births.[3–5]

An obstetrician should be able to diagnosis and adequately correct obstetric anal sphincter injuries (OASIS).[6,7] However, there are few training opportunities for resident doctors to practice surgical skills in vivo, and there is a lack of knowledge regarding the recognition and repair of OASIS.[8] Considering that the procedure has a learning curve,[9] and lacerations corrected by experienced obstetricians or specialized surgeons are more likely to have a proper result,[7] the importance of training in this repair stands out.

The use of simulators and simulation environments for teaching health professionals is well established.[9–12] They replicate a clinical scenario, with a controlled situation, allowing a detailed observation of the students in action, with feedback and the possibility of several repetitions without any harm to patients.[9,10]

Overall, the quality of the evidence about simulation-based learning (SBL) is low, but it suggests that the method is effective and leads to better and longer-lasting results compared with traditional teaching.[11,13] In surgical training, for instance, it may reduce costs and improve clinical outcomes.[9,14]

While simulated environments and high-fidelity simulators have proved to be useful, there are barriers to their use in teaching, mainly concerning their cost.[9,10,15] There is no evidence that a hyper-reality simulator improves the learning of participants.[16] Therefore, low-cost simulators can be effective in the teaching and learning process,[9,14] with characteristics demonstrated even in obstetric situations.[9,15,17] Several simulators aimed to improve surgical skills in the repair of vaginal lacerations and OASIS were described, all with positive results.[9,18–22]

The objective of the present study was to describe and evaluate a simple, low-cost and reproducible simulator, adapted to the Brazilian reality, for teaching OASIS repair.

Methods

This is an observational qualitative-quantitative research. The research is part of the project "handmade simulators for teaching in obstetrics", which was developed by the authors and seeks to create, discover, compile, and disseminate the possibilities of using simulators and accessible simulations (http://saudesimuladores.paginas.ufsc.br/).

The simulations took place in classrooms of two public hospitals with medical residents, both located in the southern region of Brazil. They lasted approximately 2 hours each and were done through classes and clinical discussions with residents during the year of 2017. Participants included gynecology and obstetrics residents and experts in the area. There were $\sim$ 12 participants per simulation, and some respondents did the simulation twice. The criteria for participating in the study were: being a gynecologist and obstetrician resident or expert, participating in the simulation and agreeing to complete the questionnaire, and signing the informed consent form.

The simulation model was created based on existing models.[9,22] To assemble the simulator, anatomical photos were used to determine the anatomical structures and the function of each component of the model. The material needed for the assembly included: chocolate bar or similar; condom (preferably without lubricant); 15 cm $\times$ 10 cm

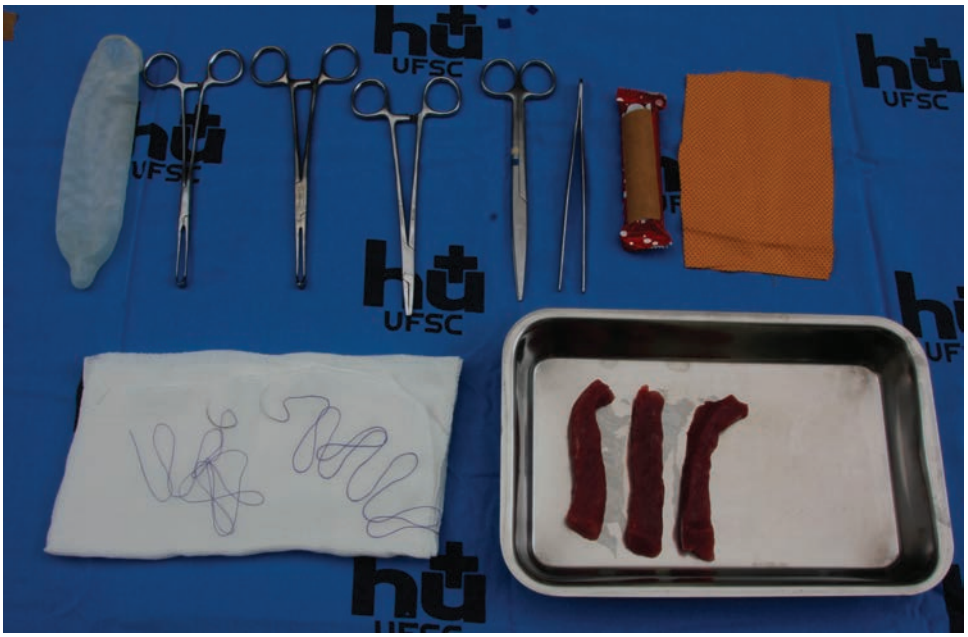

Fig. 1 Material used for simulator assembly and simulated laceration repair - Chocolate bar, condom, 15 cm × 10 cm cotton cloth flap, beef strips ~ 1 cm × 1 cm × 8 cm, surgical material (tweezers, needle holder, scissors, Allis clamp) and suture.

cotton cloth flap; beef strips of ~ 1 cm × 1 cm × 8 cm; surgical material (tweezers, needle holder, scissors, Allis clamp) and suture (►**Fig. 1**). The beef was fat-free and had the longest fibers running longitudinally to simulate the sphincter fibers.

A condom with a chocolate bar inserted in it represented the rectal mucosa and the intestinal contents (necessary to give volume to the model). The internal anal sphincter is a bright, fibrous structure that, when completely torn, generally retracts laterally. Suturing this structure separately from the external anal sphincter improves the posterior results,[5,23] so it was decided to include it in the simulation, represented by a flap of cotton cloth. The beef strip represented the external anal sphincter. After assembling the model, a laceration was created (►**Fig. 2**).

The practical aspects of diagnosing and suturing severe lacerations include the need to evaluate the sphincter and the rectal mucosa after the delivery, adequate anesthesia, positioning of the patient, illumination, a good surgical field, and antisepsis.[23–25] The most appropriate wires for each anatomical layer were presented. The torn anal mucosa is repaired using a continuous (nonlocking) 3-0 or 4-0 braided polyglactin on a tapered needle; a monofilament suture such as poliglecaprone 25 is also acceptable. The internal anal sphincter should be properly identified and repaired as a separate layer (►**Fig. 3**) using a continuous 3-0 polyglactin suture or a 3-0 monofilament synthetic suture (for example, poliglecaprone 25) on a tapered needle.[24,25] The external anal sphincter was sutured with end-to-end techniques or overlapping plication (►**Fig. 4**) using interrupted or figure-of-eight sutures; 2-0 or 3-0 polydioxanone or 2-0 polyglactin suture on a tapered needle.[24,25] In the simulation, to reduce costs, yarns that were past due or cheaper, such as catgut, were used.

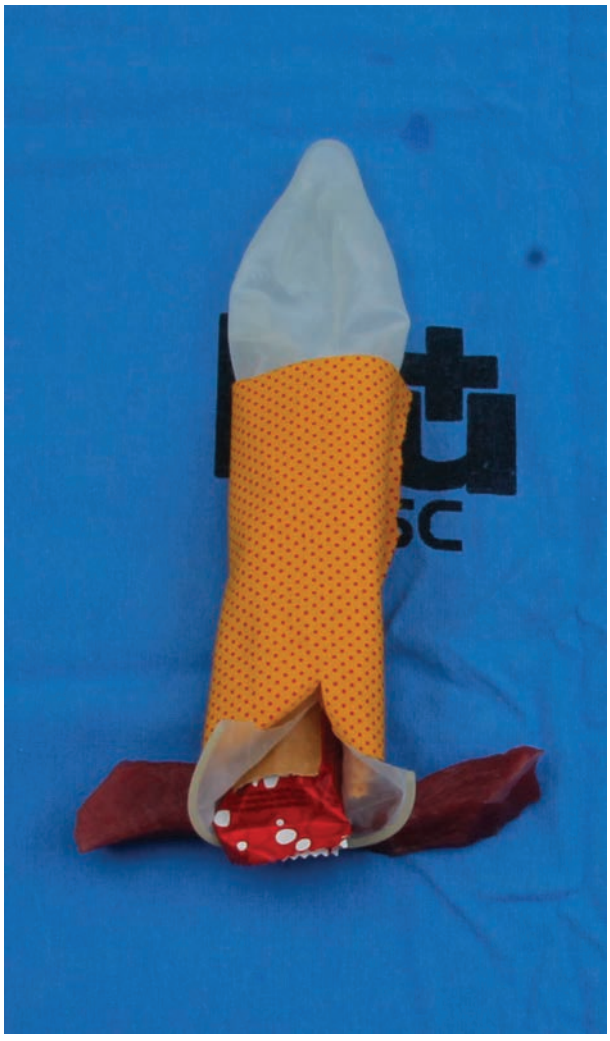

Fig. 2 Representation of the severe perineal laceration in the simulator.

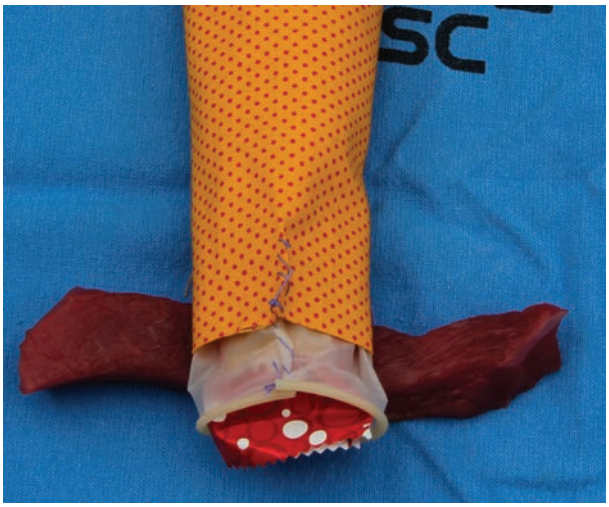

Fig. 3 Representation of the rectal mucosa and the internal anal sphincter sutured with a simple continuous suture.

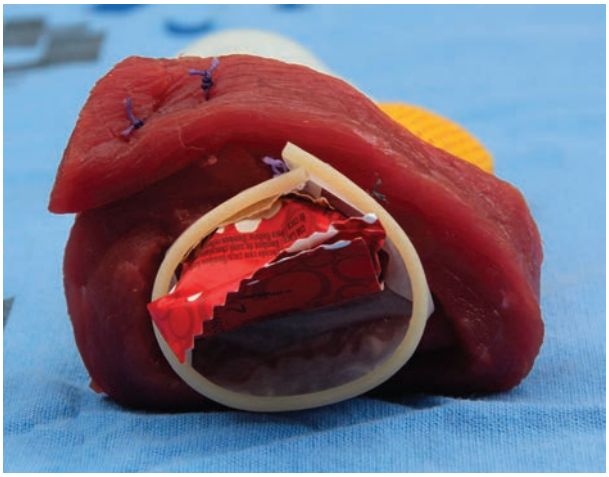

Fig. 4 Representation of the external anal sphincter repair: overlapping plication.

All the participants answered a questionnaire three to six months after the simulation. The questionnaire sought to evaluate the experience, satisfaction, and learning with the simulator and to determine if the participants had encountered any cases of severe perineal laceration after the simulation and whether they had noticed changes in their surgical performance.

The quantitative variables were analyzed with descriptive statistics, and the qualitative variables were categorized according to their content. The local ethics committee approved the research project.

Results

The simulator was created at a cost of approximately R $10.00. Twenty resident doctors and four expert obstetricians participated in the simulations. Only one resident who participated did not respond to the questionnaire. The mean age of the participants was 30.83 years old (standard deviation [SD] = 6.99), and the time since graduation in medicine was 4.5 years (SD = 5.64). Among the participants, five were in the first year of residence; seven were in the second; and eight were in the third. The time of experience of the experts varied between 10 and 20 years at the time of the simulation.

All the participants were satisfied with the training and considered that the simulation improved their knowledge and skills for correction of severe perineal lacerations. In the open questions, greater security and confidence in the case of necessity to perform the suture were the most cited categories.

The majority (78%) of the participants considered that the simulator was effective in replicating the anatomical structures, with inherent limitations to the model.

- "The thickness of the layers is very reliable and simulates the technical difficulties of the actual tear." (Expert 3)
- "It allows visualizing the anatomy, mainly the texture/thickness of the external anal sphincter." (Resident 14)
- "I have done training with 100% synthetic material, and this is closer to reality." (Resident 8)
- "It is very difficult to simulate the anatomy; the model is very simplified." (Resident 4)
- The majority (69%) of the participants also considered that they were not immersed in the experience (as if it were a real service).
- "The class was relaxed; we played, made mistakes, and we did it again. In practice, nervousness and responsibility weigh heavily on the procedure." (Resident 18)
- "Remember step-by-step in case of necessity, but far from being a real situation." (Resident 3).

►**Table 1** shows the self-evaluation of the participants regarding their preparedness to repair OASIS before and after the simulation.

Four resident doctors attended cases of severe perineal rupture after participating in the simulation and considered that the training helped them remain calm and know how to proceed, in addition to having improved their surgical skills. Of the four experts, three attended serious lacerations after participating in the simulation and also considered that they were more confident and calmer when performing the procedure.

- "I felt more confident; I was able to better identify the structures involved." (Resident 5)
- "... the suture becomes more automatic." (Expert 1).

Table 1 Self-evaluation of the participants of the simulation regarding their preparedness to suture a severe laceration

Do you feel ready to repair OASIS?	Before simulation	After simulation
	n (%)	n (%)
No	14 (60.87)	1 (4.35)
Partially	5 (21.74)	7 (30.43)
Yes	4 (17.39)	15 (65.22)

$p < 0.05$.
Abbreviation: OASIS, obstetric anal sphincter injuries.

Discussion

There are several models for training the repair of severe perineal lacerations, the most described being synthetic,[8,26] or pigs' or goats' anal sphincter.[8,18] In addition, some authors describe the use of a set with cattle' or pork' tongue with other meats or coupled with synthetic material.[19,21] The simulation of the internal anal sphincter is not performed in most models of this type.[9,22] In the model used in the present study, the anal sphincter was simulated using a flap of cotton cloth.

There is no need for the simulation to be ultra-realistic; a more simplified scenario can achieve the same objectives and is more accessible and reproducible at low cost.[10,21] In the present case, the model is simple, affordable, and achieves the objectives (to improve the knowledge and skills for suturing severe perineal laceration). However, it was not possible to accurately reproduce the anatomy, which other models do more effectively (such as the use of goat or pig anal sphincter).[8,18] Regardless, no model reproduces the human anatomy perfectly.[18]

The format of the simulation (limited time in a classroom, several people training at the same time) did not allow an immersion in the experience; the students did not feel the simulation as real. Although the immersion in the simulation is important in some contexts (emergencies, teamwork),[9,10] other studies on suture of severe lacerations do not mention immersion as a variable, probably because the focus is a specific surgical skill. Other formats that simulate the surgical environment or have separate stations can help to improve the experience in this regard.

The improvement in surgical skills was achieved and assessed only by the self-evaluation of the participants, a method also used in other researches.[19,21] In other studies, there was an improvement of skills, and the evaluation was done objectively with tests and/or objective structured assessment of technical skills (OSATS).[8,19,21,26]

A simple, accessible, and easily reproducible simulator for suture training for severe perineal laceration repair was created and used. All the participants enjoyed the simulation and assessed that their knowledge and skills improved. At least seven of the participants had to attend serious lacerations after participating in the simulation and reported feeling more confident and secure. Improved self-confidence to care for a case is described in other studies.[8,19,21,26] It is believed that, because of the simplicity of the simulator, it can be widely replicated. The training can be done by more obstetricians and resident doctors, improving the results of corrections of severe perineal lacerations.

The simulation was done in class time, with no need for a specific environment, which on the one hand is a disadvantage, since it did not allow students to immerse in the simulation. On the other hand, it can be seen as an advantage, since it can be done in all institutions, without the need of more a complex preparation.

The present study has some limitations. Only the apprentices themselves evaluated the knowledge and skills acquired in a single moment. The teachers who guided the simulation belong to the institution and are known to the resident doctors. Although the questionnaires are anonymous, there may be a courtesy bias in the answers. For future investigations, a pre- and postsimulation evaluation is suggested, either with a theoretical test or with an OSATS and evaluation sometime later, to evaluate the retention of knowledge. It was possible, however, to notice changes in the behavior of the learners (level 3 on the Kirkpartick scale, defined as behavioral changes in the work environment attributed to the learning opportunity).[27]

Conclusion

The use of a simulator for OASIS repair is affordable (low-cost and easy to perform) and can be an alternative for resident doctors and expert training. The simulation seems to improve the knowledge and surgical skills to suture severe lacerations. Further systematized studies should be performed for evaluation.

Contributions

Roxana Knobel: Dr. Knobel worked on the conceptualization and design of the study, data collection, data analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript, and approved the final manuscript as submitted. Lia Karina Volpato: Dr. Volpato worked on the conceptualization and design of the study, data analysis, critically reviewed the manuscript, and approved the final manuscript as submitted. Liliam Cristini Gervasi: Dr. Gervasi worked on data collection, critically reviewed the manuscript, and approved the final manuscript as submitted. Raquel de Almeida Viergutz: worked on the design of the study, data collection, data analysis, approved the final manuscript as submitted. Alberto Trapani Jr: Dr. Trapani revised the manuscript, and approved the final manuscript as submitted. All authors have made substantive contributions to this manuscript, and all have reviewed the final paper prior to its submission.

Conflicts of Interest

None to declare.

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Prenatal Care and Hypertensive Gestational Syndromes: A Systematic Review

Atenção pré-natal e síndromes gestacionais hipertensivas: uma revisão sistemática

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Abstract

Objective Evaluate the influence of prenatal care on the occurrence of gestational hypertension.

Methods The Web of Science, Scopus, Pubmed, Cochrane and ClinicalTrials electronic databases were searched for articles published between January 1st, 2012 and December 31st, 2016. No language restrictions were imposed. The following keywords were used: prenatal care, medical assistance, prenatal education, pregnancy-induced hypertension. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist was employed. Two hundred and forty articles were identified during the initial search, but only seven met the inclusion criteria. This systematic review is registered with the international prospective register of systematic reviews (PROSPERO; #CRD42017064103).

Results The seven studies had a low risk of bias, with methodological quality scores ranging from six to eight points. Five studies found a positive relationship between prenatal care and pregnancy-induced hypertension, whereas two studies found no significant association between the two variables. The divergence among the studies may have been due to the type of healthcare service at which the study was conducted and the sample size.

Conclusion Although the studies analyzed differed with regard to methodological aspects, the findings demonstrate the importance of prenatal care during the gestational period as a prevention and health promotion measure.

Keywords

- prenatal care
- medical assistance
- prenatal education
- hypertension pregnancy-induced
- gestation

Resumo

Objetivo Avaliar a influência da assistência pré-natal no acometimento de síndromes hipertensivas gestacionais.

Métodos A revisão buscou artigos publicados nas plataformas eletrônicas de pesquisa Web of Science, Scopus, Pubmed, Cochrane e Clinical Trials, sem restrições de

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linguagem e com os artigos publicados entre 01/01/2012 e 31/12/2016. Os descritores utilizados foram: assistência pré-natal, assistência médica, educação pré-natal, hipertensão induzida pela gravidez, gestação. Foi utilizado o checklist *preferred reporting items for systematic reviews and meta-analyses* PRISMA. A busca na literatura, de acordo com a estratégia adotada, identificou 240 artigos. Contudo, somente 7 artigos foram selecionados de acordo com os critérios de inclusão. A revisão sistemática foi incluída no registro prospectivo internacional de revisões sistemáticas (PROSPERO, na sigla em inglês; #CRD42017064103).

Resultados Cinco estudos encontraram relação positiva entre a assistência pré-Natal e síndromes hipertensivas gestacionais. Dois estudos não encontraram uma associação estatística significativa entre estas duas variáveis. Os sete estudos apresentam um baixo risco de viés, com as pontuações na análise de qualidade variando entre seis e oito. As possíveis diferenças entre os achados podem ser devidas ao momento do diagnóstico das síndromes hipertensiva gestacionais, tipo de serviço onde foi realizada a pesquisa e o tamanho amostral.

Conclusão Embora os estudos apresentem diferentes aspectos metodológicos, observou-se a importância da implementação da Assistência Pré-Natal durante o período gestacional, o que atuará como medida de promoção e prevenção em saúde.

Palavras-chave
- assistência pré-natal
- assistência médica
- educação pré-natal
- hipertensão induzida pela gravidez
- gestação

Introduction

Most women experience pregnancy with no complications. Some, however, have characteristics or conditions that can place their health and the health of the fetus at risk. One such condition is pregnancy-induced hypertension (PIH), which is considered a public health problem due to its frequency as well as maternal and perinatal morbidity and mortality, affecting $\sim$ 10% of pregnancies throughout the world.[1–3]

The periodic measurement of blood pressure in pregnant women is essential to the precise diagnosis of hypertension, which can cause serious problems, such as stroke, premature birth or low birth weight.[4] Pregnancy-induced hypertension occurs when the increase in blood pressure reaches or surpasses 140 $\times$ 90 mm Hg. The following classification is used: gestational hypertension, chronic arterial hypertension, chronic hypertension in conjunction with preeclampsia, preeclampsia and eclampsia. The prevalence and incidence of these conditions are quite high in Brazil and vary depending on age group, race, obesity and the presence of associated diseases, such as diabetes and kidney disease.[5]

Despite the vast accumulation of scientific knowledge in recent years, PIH continues to have serious repercussions. Therefore, individualized care is fundamental for early diagnosis and the establishment of interventions to minimize risks to the mother and fetus.[6] The occurrence of avoidable deaths among pregnant women is associated with insufficient economic, cultural and technological conditions in a given society, making this a serious health problem throughout the world. Such deaths could be avoided if pregnant women had access to quality prenatal care.[7]

Perinatal outcomes are the result of a complex network of biological, socioeconomic and healthcare determinants. Prenatal care can contribute to more favorable situations by enabling the timely detection and treatment of adverse health conditions and the control of risk factors related to complications for the health of the mother and infant.[8]

The aim of the present study was to perform a systematic review of the literature to evaluate the influence of prenatal care on the occurrence of PIH. The following was the research question: Does greater prenatal care diminish the occurrence of PIH?

Methods

Selection of Articles

The present systematic review of the literature included cross-sectional, case-control and cohort studies involving patients with PIH. In December 2016, 2 independent reviewers searched 5 electronic databases (Web of Science, Scopus, Pubmed, Cochrane and ClinicalTrials) for articles published between January 1st, 2012 and December 31st, 2016. No language restrictions were imposed. The following was the search strategy ([Prenatal care OR Medical Assistance OR Prenatal Education] AND [Pregnancy-Induced Hypertension]). The present systematic review is registered with the international prospective register of systematic reviews PROSPERO (#CRD42017064103). The initial online research led to the retrieval of 240 references: 103 in PubMed, 22 in Web of Science, 28 in Cochrane, 84 in Scopus and 3 in ClinicalTrials. Duplicates were removed with the aid of the Reference Manager software, version 12.0.3 (Thomson Reuters, Toronto, ON, Canada), leading to a total of 175 articles, which were analyzed using the eligibility criteria based on readings of the titles and abstracts. Two reviewers underwent a calibration exercise for the application of the eligibility criteria. Following a detailed discussion of the criteria, the reviewers performed independent analyses of a sample of 10% of the abstracts. Interexaminer agreement was determined using the Kappa statistic (K = 0.875).

The inclusion criteria were cross-sectional studies, case-control studies, cohort studies and clinical trials involving prenatal care and PIH, with no restrictions imposed regarding age or language. The exclusion criteria were reviews, clinical cases, editorials, books, abstracts, questionnaire validation studies, studies not addressing PIH, studies published more than 5 years earlier and studies for which data extraction was not possible.

The application of the eligibility criteria led to the exclusion of 159 articles based on the analysis of the titles and abstracts. Among the 16 articles submitted to full-text analysis, 9 were excluded due to the absence of statistical analysis on the association between prenatal care and PIH or for associating prenatal care or PIH with a variable of no interest to the present systematic review (►**Fig. 1**).

Data Extraction

Seven studies performed a statistical analysis of the association between PIH and prenatal care and were included in the present systematic review.

Appraisal of Methodological Quality

Two independent reviewers performed the appraisal of the methodological quality of the studies included in the review using the Newcastle-Ottawa quality assessment scale for case-control and cohort studies.[6,9] For each article, points were awarded for the presence of each item of the different categories (selection, comparability and exposure/outcome).

Data Synthesis

The data were grouped based on study design, characteristics of the population and unit of analysis. A narrative synthesis of the data was also performed.

Results

Type of Study, Setting and Population Characteristics

The articles selected were three case-control studies, two prospective cohort studies, one retrospective cohort study and a cross-sectional study conducted in Central America, South America, Europe, Asia and Africa. Three studies involved the use of a comparative group classified as a control group. Four studies recruited individuals from hospitals, two recruited individuals from maternity clinics and one study was based on data from a national department of statistics. Patient age ranged from 15 to 72.6 years.

Three studies involved convenience sampling but employed eligibility criteria for the determination of the final sample.[9–12]

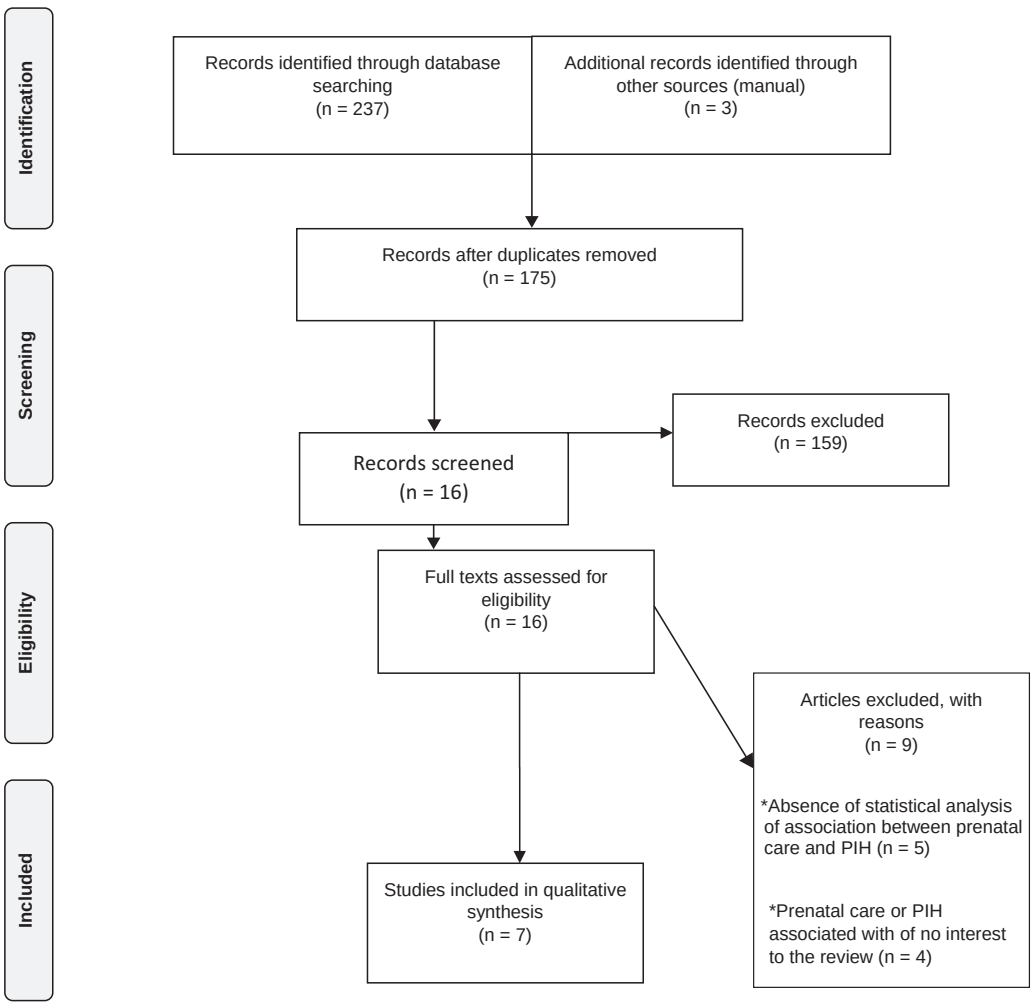

Fig. 1 Flowchart of the article selection process.

Other studies had population-based samples for the investigation of the proposed factors.[13–15] One study failed to describe how many participants were in the sample.[16] However, direct contact with the author enabled the determination that the study in question also employed a population-based sample (►**Table1**).

Categorization of Prenatal Care

Two studies[11,14] classified prenatal care as present or absent, without specifying the number of appointments. Others[12,13,15] categorized prenatal care based on the number of appointments. One study[10] expressed appointment data using mean and standard deviation values for the case and control groups. Another study[17] used the implantation of a broad prenatal care program based on the biopsychosocial model (BPSM), addressing psychosocial and obstetric factors that promote a reduction in morbidity and mortality rates among pregnant women.[17,18]

3.3 Categorization of PIH

Two studies[11,12] addressed preeclampsia and eclampsia. Another[9] used these same categories and included the complication of hemorrhage. Two[10,16] classified PIH as preeclampsia. One study[14] specified the conditions as chronic hypertension, preeclampsia and eclampsia. Another study[15] denominated the conditions as gestational hypertensive disorders, listing gestational hypertension, preeclampsia and eclampsia. Another investigation[15] used the following categorization: isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), isolated systolic or diastolic hypertension with proteinuria (DHP), gestational hypertension (GH), preeclampsia/eclampsia and chronic hypertension (CH).

Statistical Analysis

The studies used prenatal care information as the unit of analysis to investigate the association between prenatal care and PIH. The seven studies[10–16] performed univariate, bivariate and multivariate analyses.

Relationship between Prenatal Care and Pregnancy-induced Hypertension

The studies reported the following associations: prenatal care with fewer appointments was associated with PIH ($p < 0.001$; OR = 2.04);[10] a lack of prenatal care increased the risk of PIH (odds ratio [OR] = 2.3 [95% confidence interval [CI]: 1.19 to 4.38][14] and OR = 3.97 [95% CI: [1.42 to 11.09][11]); BPSM reduced the incidence of preeclampsia (OR = 0.78; 95% CI: 0.67 to 0.88);[16] hypertensive women had a greater number of prenatal care appointments than normotensive women, with significant associations found between ≥ 5 appointments and ISH, IDH, DHP ($p < 0.0001$), GH ($p < 0.05$.) and CH ($p < 0.001$).[13] ►**Table 1** displays the results of the studies that found no association between PIH and prenatal care. Differences were found in the presentation of effect measures, ORs, *p*-values and CIs.

3.6 Appraisal of Methodological Quality

The methodological quality of the studies analyzed ranged from 6 to 8 points on a 10-point scale (►**Table 1**). The cross-sectional study received a score of 6 points. A total of 4 studies received 7 points, and 1 study received 8 points.

Discussion

The present systematic review involved a search of multiple databases with no restrictions with regard to language or year of publication. Sixteen articles were preselected for the full-text analysis. A total of 7 met the inclusion criteria and were submitted to an appraisal of methodological quality, receiving scores of 6 to 8 on a 10-point scale.

The researchers described how the cohort and case-control studies occurred, although the eligibility criteria and participant selection methods were not adequately reported. The variables analyzed in the studies, including risk factors and outcome, were well defined. However, none of the studies reported a calibration exercise for the evaluation of the variables.

A case-control study[12] conducted at a rural maternity clinic in Haiti involving a sample of 689 women (67 in the case group and 622 in the control group) found a 7% prevalence rate of PIH (preeclampsia and eclampsia) among individuals aged 15 to 46 years. The analysis of prenatal care considered the following categories: 0 appointments; 1 to 3 appointments; and 4 or more appointments. Prenatal care was not associated with a reduction in the risk of preeclampsia (1 to 3 appointments: $p = 0.71$, OR = 1.10; 4 or more appointments: $p = 0.50$, OR = 1.20). Thus, the presence or absence of prenatal care exerted no influence on the occurrence of preeclampsia.

Another case-control study[10] conducted at a reference hospital involved a sample of 1,233 individuals: 650 in the case group (mean age: $>$ 30 years) and 583 in the control group (mean age: 28 years). The prevalence of preeclampsia was not reported, but the condition was associated with fewer appointments ($p < 0.001$, OR = 2.04), which is in disagreement with the findings of another study in the present review.[12]

A prospective cohort study[16] conducted at the National Department of Statistics analyzed 387,000 women over a 10-year period. Prenatal care was based on the implantation of a program aimed at controlling obstetric and psychosocial risk factors. The prevalence of preeclampsia ranged from 0.4 to 1.4% among women monitored at a private healthcare service (mean age: 24.2 $\pm$ 6.5 years) and 1.4 to 3.2% among women with no access to a private healthcare service (mean age: 25.1 $\pm$ 6.9 years). The effect of prenatal care involving the biopsychosocial model reduced the incidence of preeclampsia by 22% (OR = 0.78, 95% CI: 0.67–0.88), which is in agreement with the findings of another study,[10] suggesting that an increase in prenatal care reduces the risk of PIH.

A retrospective study[14] conducted at university hospitals involved a sample of 1,015 individuals: 612 (60.3%) with preeclampsia, 346 (34.1%) with eclampsia and 57 (5.6%) with another type of PIH. The mean age was 25.8 years. A lack of prenatal care increased the risk of the emergence of PIH (OR 2.3; 95% CI: 1.19–4.38), which is in agreement with the finding of 2 other studies.[10,16]

A case-control study[11] conducted at 3 reference hospitals involved 299 women: 80 in the case group (prevalence of chronic hypertension: 52%) and 219 in the control group (prevalence of

Table 1 Studies included in the present review of the association between prenatal care and pregnancy-induced hypertension

Authors, year, country	Type of study	Setting	Sample size	Prevalence; age (years)	Categorization of prenatal care	Categorization of PIH	Statistical analysis	Results	Quality
Sekkarie et al. (2016),[12] Haiti	Case-control	Rural maternity	689 subjects (67 cases and 622 controls	7.0%; 15–46	No appointments; 1–3 appointments; 4 or more appointments	Preclampsia and eclampsia	Univariate and multivariate	Prenatal care not associated with reduction in risk of PIH: 1–3 appointments ($p = 0.71$; OR = 1.10) and 4 or more appointments ($p = 0.50$; OR = 1.20)	7 (10)
Luo and Ma (2013),[10] China	Case-control	Tertiary reference hospital	1233 subjects (650 cases and 583 controls)	Prevalence not reported; mean case: 30 + ; control: 28)	Case - mean: M 2.68 ± 6.18 appointments; control - mean: 9.19 ± 4.49 appointments	Preeclampsia	Univariate and multivariate	Preeclampsia associated with fewer prenatal care appointments ($p < 0.001$; OR = 2.04)	7 (10)
Herrera et al. (2014),[16] Colombia	Prospective cohort	National Department of Statistics	387,000	Private service (pre-eclampsia = 0.4%- 1.4%); Without private service (preeclampsia = 1.4% - 32%); mean: 24.2 ± 6.5 and 25.1 ± 6.9	Implantation of BPSM program	Preeclampsia	Univariate and multivariate	Implantation of BPSM program reduced incidence of pre-eclampsia by 22% (OR = 0.78, 95% CI: 0.67–0.88)	6 (10)
Berhan and Endeshaw (2015),[14] Ethiopia	Retrospective cohort	University teaching hospitals	1015	612 (60.3%) preeclampsia, 346 (34.1%) eclampsia and 57 (5.6%) other type of PIH; mean: 2.8; range: 15–46.	Prenatal care: yes or no	Chronic hypertension, preeclampsia and eclampsia	Univariate and multivariate	Lack of prenatal care increased risk of PIH (OR 2.3; 95% CI: 1.19 - 4.38).	7 (10)
Assarag et al. (2015),[11] Morocco	Case-control	Three reference hospitals	299 subjects (80 cases and 219 controls)	Chronic hypertension: 52% of case group and 47% of control group; mean: 29.2 in case group and 28.4 in control group; range: 18–49	Prenatal care: yes or no	Preeclampsia, eclampsia, preeclampsia and eclampsia complicated by hemorrhage	Univariate and multivariate	Lack of prenatal care associated with PIH [OR = 3.97; 95% CI: (1.42–11.09)].	8 (10)
Correia et al. (2015),[15] Portugal	Transversal	Five public maternities	7,325	3.19%; 55.4% 25–34; 29.7% ≤24; 14.9% ≥ 35	Does not know; 1–2 appointments, 3–6 appointments, 7–9 appointments, ≥10 appointments	Gestational hypertensive disorders (gestational hypertension, preeclampsia and eclampsia)	Univariate and multivariate	Larger or smaller number of appointments in public or private sector did not affect occurrence of PIH (low-risk pregnancy: OR = 1.12; high-risk pregnancy: OR = 0.53)	6 (10)
Männistö et al. (2013),[13] Finland	Prospective cohort	Community maternity care clinics	10314	17%; mean: 66.7 (62.6 to 72.6)	Prenatal care: ≥ 5 appointments	ISH, IDH, DHP, GH, Preeclampsia / Eclampsia, CH	Univariate and multivariate	Prenatal care associated with ISH, IDH, DHP ($p < 0.0001$); GH ($p < 0.05$); and CH ($p < 0.001$)	7 (10)

Abbreviations: BPSM, biopsychosocial model; CH, chronic hypertension; CI, confidence interval; GH, gestational hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; OR, odd ratio; PIH, pregnancy-induced hypertension; DHP, isolated systolic or diastolic hypertension with proteinuria.

chronic hypertension: 47%). The ages ranged from 15 to 49 years, with a mean of 29.2 years in the case group and 28.4 in the control group. A lack of prenatal care increased the risk of PIH (preeclampsia and eclampsia as well as preeclampsia and eclampsia complicated by hemorrhage) (OR = 3.97; 95% CI: 1.42–11.09). Therefore, the absence of prenatal care was related to the occurrence of different types of PIH, placing patients at risk.

In a cross-sectional study[15] conducted at 5 public maternity hospitals involving a sample of 7,325 women (55.4% aged 25–34 years, 29.7% aged 24 years or younger and 14.9% aged 35 years or older), the prevalence of PIH (gestational hypertension, preeclampsia and eclampsia) was 3.19%. Prenatal care was not associated with PIH, as a larger or smaller number of appointments at public or private services did not exert an influence on the emergence of PIH (low-risk pregnancy: OR = 1.12; high-risk pregnancy: OR = 0.53), which is in agreement with the findings of another study in the present review.[12]

In a prospective cohort study[13] conducted at maternity care clinics involving a sample of 10,314 women with a mean age of 66.7 years, the prevalence of PIH was 17%. Prenatal care was associated with the outcome, as women with ISH, IDH, DHP, GH and CH had a larger number of prenatal appointments than normotensive women, which is in agreement with findings reported in two other studies,[12,15] suggesting that prenatal care does not exert an influence on the reduction in or emergence of PIH.

Studies with a sufficient follow-up period involving women of different ages and with the control of possible confounding factors are needed to confirm the effect of prenatal care on the occurrence of PIH. The present review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.[19]

Conclusion

The present findings demonstrate the importance of greater prenatal care as a measure for health promotion and a reduction in the occurrence of pregnancy-induced hypertension. Standardized methods are needed to strengthen the statistical power of the studies and prospective investigations are needed to gain a better understanding of the association between these two variables.

Conflicts of Interest

None to declare.

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Surgical Treatment for Stress Urinary Incontinence in Women: A Systematic Review and Meta-analysis

Tratamento cirúrgico da incontinência urinária de esforço em mulheres: revisão sistemática e metanálise

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Abstract

Objective To compare surgical treatments for stress urinary incontinence in terms of efficiency and complications.

Data Sources We searched the MEDLINE and COCHRANE databases using the terms *stress urinary incontinence*, *surgical treatment for stress urinary incontinence* and *sling*.

Selection of Studies Forty-eight studies were selected, which amounted to a total of 6,881 patients with scores equal to or higher than 3 in the Jadad scale.

Data Collection Each study was read by one of the authors, added to a standardized table and checked by a second author. We extracted data on intervention details, follow-up time, the results of treatment and adverse events.

Data Synthesis Comparing retropubic versus transobturator slings, the former was superior for both objective (odds ratio [OR], 1.27; 95% confidence interval [CI], 1.05–1.54) and subjective (OR, 1.23; 95% CI, 1.02–1.48) cures. Between minislings versus other slings, there was a difference favoring other slings for subjective cure (OR, 0.58; 95% CI, 0.39–0.86). Between pubovaginal sling versus Burch surgery, there was a difference for both objective (OR, 2.04; 95% CI, 1.50–2.77) and subjective (OR, 1.64; 95% CI, 1.10–2.44) cures, favoring pubovaginal sling. There was no difference in the groups: midurethral slings versus Burch, pubovaginal sling versus midurethral slings, transobturator slings, minislings versus other slings (objective cure). Retropubic and pubovaginal slings are more retentionist. Retropubic slings have more bladder perforation, and transobturator slings, more leg and groin pain, neurological lesion and vaginal perforation.

Conclusion Pubovaginal slings are superior to Burch colposuspension surgery but exhibit more retention. Retropubic slings are superior to transobturator slings, with more adverse events. Other slings are superior to minislings in the subjective aspect. There was no difference in the comparisons between midurethral slings versus Burch colposuspension surgery, pubovaginal versus midurethral slings, and inside-out versus outside-in transobturator slings.

Keywords
- stress urinary incontinence
- Burch surgery
- midurethral sling
- pubovaginal sling
- meta-analysis

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Resumo

Objetivo comparar tratamentos cirúrgicos para incontinência urinária de esforço (IUE), quanto à eficiência e complicações, por meio de revisão sistemática seguida de metanálise.

Fonte dos dados Fizemos busca nas bases de dados MEDLINE e COCHRANE, utilizando os termos *stress urinary incontinence*, *surgical treatment for stress urinary incontinence* e *sling*.

Seleção dos estudos Selecionamos 48 estudos, totalizando 6.881 pacientes com pontuação igual ou maior do que 3 na escala de Jadad.

Coleta de dados Cada estudo foi lido por um autor, colocado em tabela, e checado por outro autor. Extraímos dados como detalhes das intervenções, tempo de seguimento, resultados do tratamento e eventos adversos.

Síntese dos dados Não houve diferença nas comparações: *sling* de uretra média versus cirurgia de Burch, quanto às curas objetiva (razão de chances [RC]: 1,29; intervalo de confiança de 95% [IC95%]: 0,76–2,20) e subjetiva (RC: 1,16; IC95%: 0,67–2,00); *sling* de uretra média transobturatório *outside-in* versus *inside-out* quanto às curas objetiva (RC: 0,78; IC95%: 0,45–1,35) e subjetiva (RC: 0,83; IC95%: 0,58–1,18); *sling* pubovaginal e de uretra média quanto à cura objetiva (RC: 1,64; IC 95%: 0,52–5,15). Comparando *sling* retropúbico com transobturatório, o retropúbico foi superior quanto às curas objetiva (RC: 1,27; IC95%: 1,05–1,54) e subjetiva (RC: 1,23; IC95%: 1,02–1,48). Entre *minislings* e outros *slings*, houve diferença favorável a outros *slings* quanto à cura subjetiva (RC: 0,58; IC95%: 0,39–0,86) mas não quanto à cura objetiva (RC: 0,72; IC95%: 0,47–1,10). No grupo *sling* pubovaginal e Burch, houve diferença quanto à cura objetiva (RC: 2,04; IC95%: 1,50–2,77) e subjetiva (RC: 1,64; IC95%: 1,10–2,44). *Slings* de uretra média apresentam mais erosão, enquanto a cirurgia de Burch tem mais complicações na ferida operatória e infecção do trato urinário. *Slings* retropúbicos e pubovaginais são mais retencionistas. *Slings* retropúbicos estão mais associados a lesão vascular, hematomas e perfuração vesical, e transobturatórios, à dor na perna e virilha, lesão neurológica e perfuração vaginal.

Conclusão *Slings* pubovaginais são superiores à cirurgia de Burch, porém mais retencionistas. *Slings* retropúbicos são superiores aos transobturatórios, embora tenham mais eventos adversos. Outros *slings* são superiores aos minislings em relação ao aspecto subjetivo. Não houve diferença nas comparações entre *slings* de uretra média e cirurgia de Burch, *slings* pubovaginais, transobturatórios *inside-out* e *inside-in*.

Palavras-chave

- incontinência urinária de esforço
- cirurgia de Burch
- *sling* de uretra média
- *sling* pubovaginal
- metanálise

Introduction

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as the involuntary loss of urine during physical exertion, such as while coughing, sneezing, laughing or running.[1] This condition affects 13 to 46% of women at a young age, reaching even higher rates if we consider postmenopausal women,[2–4] with severe repercussions for quality of life as it affects physical, sexual, emotional and social aspects.[3]

Several clinical and surgical options have been used for the treatment of SUI. Our review does not take into account clinical treatments. For surgical treatments, several techniques are described, including the more commonly known: Burch colposuspension, either abdominal or laparoscopic, pubovaginal slings, retropubic and transobturator midurethral slings, and single-incision slings (minislings).

Burch colposuspension and pubovaginal slings are considered the "gold standard" for surgical treatment of SUI. Since described in 1996 by Ulmsten et al,[5] the synthetic tension-free vaginal tape (TVT) sling has been used in a growing and widespread manner throughout the world. Even though this technique has achieved high cure rates in the mid and long term,[6,7] important complications, such as bladder perforation, retropubic hematomas and voiding dysfunction have also been reported.[8,9] In an attempt to minimize these complications, in 2001, Delorme[10] described a new technique involving the placement of a synthetic mesh under the middle urethra through the transobturator route from the thigh to the vagina (transobturator tape outside-in [TOT]). In 2003, de Leval[11] introduced a modification to the technique, proposing insertion of the mesh toward the opposite direction, from the vagina to the thigh (transobturator tape inside-out [TVT-O]). Both slings placed by transobturator approach have shown

high rates of cure.[10,11] However, several researchers describe thigh pain as a main complication.[12] Thus, to further reduce complication rates, single-incision slings, or minislings, were introduced with objective and subjective cure rates very close to those obtained with TVT and TOT at mid-term follow-up, according to a meta-analysis published in 2014.[13]

The literature is vast regarding surgical procedure success rates for treating female SUI, but the quality of many studies is questionable. In an attempt to clarify the best technique for each case, we proposed this systematic review followed by meta-analysis, based on good quality randomized trials, comparing objective and subjective results, and complications.

Study Search

We searched the MEDLINE and Cochrane Central Register for Controlled Trials databases from January 1990 to December 2016. We used the following keywords to search for studies: *stress urinary incontinence*, *surgical treatment for stress urinary incontinence*, *sling*, *pubovaginal sling*, *retropubic sling*, *transobturator sling*, *minisling*, *Burch colposuspension*. The search was limited to comparative and randomized studies. We included only human studies written in English, French and Spanish. We found some few articles in other languages that did not fill the Jadad criteria. The articles listed in the search results were only used when the full text was available. The authors of the studies were not contacted.

Three of the authors (LMO, MMD, SBM) in our meta-analysis did the initial research of all studies independently. After reading the titles and abstracts, we read the full text of the studies considered potentially eligible, which were later included in a standardized table for data extraction if the eligibility criteria were met.

Study Selection

We selected the relevant studies by applying the three-point questionnaire that form the basis he Jadad scale. Each question was to be answered with either a *yes* or a *no*. Each *yes* would score a single point, each *no* zero points The questions were as follows: *Was the study described as randomized?*; *Was the study described as double blind?* and *Was there a description of withdrawals and dropouts?* To receive the corresponding point, an article should describe the number of withdrawals and dropouts, in each of the study groups, and the underlying reasons. Additional points were given if: *The method of randomization was described in the paper, and that method was appropriate* or *The method of blinding was described, and it was appropriate.* Points would be deducted if: *The method of randomization was described but was inappropriate.* or *The method of blinding was described, but was inappropriate.* A clinical trial could therefore receive a Jadad score between zero and five.[14] Studies with a score lower than three points on this scale were excluded.

To evaluate the results, we included randomized, comparative studies with a minimum of 12 months of follow-up, comparing 2 or more sling procedures or a sling procedure with Burch colposuspension surgery, performed on women over 18 years of age with SUI diagnosed by clinical history, stress test and/or urodynamic evaluation or *pad test.* Studies that included mixed urinary incontinence (MUI), predominantly SUI, and intrinsic sphincteric deficiency (ISD) were also admitted.

Whenever there were three arms in the study, we compared two arms at a time. For the analysis of side effects, we used only the studies that were selected for the meta-analysis.

The types of slings included were midurethral slings (retropubic and transobturator), pubovaginal slings (synthetic and autologous) and minislings.

Studies comparing the Burch technique with any other non-sling surgical modality to treat SUI were not included.

Studies using materials that were withdrawn from the market were excluded from our review, as were studies comparing different products by equal routes.

The results of interest in the studies analyzed were divided into six categories: objective or subjective cure, perioperative results, quality of life and satisfaction questionnaires, sexual function and adverse events (►**Table 1**). However, only meta-analytic studies were performed for objective or subjective cure and adverse events.

Data Extraction and Assessment

Each of the included studies was read by one of the authors, and the data were extracted and inserted in a previously standardized table. Then, each study was checked by a second author. Discrepancies were resolved by consensus among three of the authors. We extracted data on study characteristics, details of interventions, follow-up time, results of treatment and adverse events.

Data Synthesis and Analysis

We compared midurethral sling versus Burch surgery, pubovaginal sling versus Burch surgery, pubovaginal sling versus midurethral sling, retropubic versus transobturator midurethral sling, transobturator outside-in midurethral sling versus transobturator inside-out and minisling versus other slings.

Whenever we found two or more randomized studies comparing the same surgical techniques in relation to the same outcomes and adverse events, we resorted to a meta-analysis, which is the most adequate statistical technique to combine results from different studies.[58,59]

It is natural to think of using the fixed-effect model, which assumes that the effect of interest is the same in all included studies. However, the studies are not identical regarding effect of interest and are therefore considered heterogeneous. Thus, to verify the existence of heterogeneity, we used the Cochran Q test and the I^2 statistic by Higgins and Thompson.[60]

The null hypothesis of the Cochran Q test asserts that the studies are homogeneous. A high Q value indicates that there is great heterogeneity. However, the *p*-value associated with the test indicates whether the heterogeneity is

Table 1 Randomized controlled trials included in the systematic review

Study	Intervention (1)	Comparator (2)	N (1)	N (2)	Follow-up	OC	SC	PO	AE	QoL	SF
MUS versus Burch											
Bai et al. (2005)[15]	Retropubic (TVT)	Burch	31	33	1 year	X			X		
Jelovsek et al. (2008)[16]	Retropubic (TVT)	Burch L	25	28	65 months		X			X	
Liapis et al. (2002)[17]	Retropubic (TVT)	Burch	35	36	2 years	X		X	X		
Paraiso et al. (2004)[18]	Retropubic (TVT)	Burch lap	31	32	21 months	X		X	X	X	
Persson et al. (2002)[19]	Retropubic (TVT)	Burch lap	37	31	1 year	X	X	X	X		
Ward et al. (2008)[20]	Retropubic (TVT)	Burch	72	49	5 years	X		X	X	X	X
Valpas et al. (2015)[21]	Retropubic (TVT)	Burch lap	51	40	5 years	X	X	X	X	X	
PVS versus Burch											
Albo et al. (2007)[22]	PVS (autologous fascia)	Burch	326	329	2 years	X	X	X	X	X	
Bai et al. (2005)[15]	PVS (autologous fascia)	Burch	28	33	1 year	X			X		
Culligan et al. (2003)[23]	PVS (Gore-Tex)	Burch	13	15	73 months	X	X	X	X		
PVS versus MUS											
Bai et al. (2005)[15]	PVS (autologous fascia)	Retropubic (TVT)	28	31	1 year	X			X		
Guerrero et al. (2010)[24]	PVS (autologous fascia)	Retropubic (TVT)	67	69	1 year		X	X	X	X	
Sharifiaghdas and Mortazavi (2008)[25]	PVS (autologous fascia)	Retropubic (TVT)	25	36	40 months	X	X	X	X	X	
TVT versus TOT											
Angioli et al. (2010)[26]	TVT	TVT-O	35	37	5 years	X	X	X	X	X	X
Araco et al. (2008)[27]	TVT	TVT-O	108	109	1 year	X		X	X	X	
Barber et al. (2008)[28]	TVT	Monarc	79	71	1 year	X	X	X	X	X	X
Costantini et al. (2016)[29]	TVT	Obtape	40	47	5 years	X	X	X	X	X	
Deffieux et al. (2010)[30]	TVT	TVT-O	67	65	2 years	X	X	X	X	X	X
Freeman et al. (2011)[31]	TVT	Monarc	85	95	1 year		X	X	X	X	X
Karateke et al. (2009)[32]	TVT	TVT-O	81	83	14 months	X	X	X	X		
Krofta et al. (2010)[33]	TVT	TVT-O	141	147	1 year	X	X	X	X	X	X
Laurikainen et al. (2014)[34]	TVT	TVT-O	131	123	5 years	X	X	X	X		
Lee et al. (2007)[35]	TVT	TVT-O	60	60	13 months	X	X	X	X	X	
Richter et al. (2010)[36]	TVT	TVT-O/Monarc	291	292	1 year	X	X	X	X	X	X
Rinne et al. (2008)[37]	TVT	TVT-O	134	131	1 year		X	X	X	X	
Ross et al. (2009)[38]	Advantage	Obtrix	95	86	1 year	X	X	X	X	X	X
Ross et al. (2016)[39]	Advantage	Obtrix	74	66	5 years	X			X	X	X
Scheiner et al. (2012)[40]	TVT	Monarc	65	34	1 year	X	X	X	X	X	X
Scheiner et al. (2012)[40]	TVT	TVT-O	65	37	1 year	X	X	X	X	X	X
Schierlitz et al. (2012)[41]	TVT	TVT-O	72	75	3 years	X	X	X	X	X	
Teo et al. (2011)[42]	TVT	TVT-O	41	29	1 year	X	X	X	X	X	
Wadie and El-Hefnawy (2013)[43]	TVT	TOT (Aris)	36	35	2 years	X	X	X	X	X	
Wang et al. (2010)[44]	TVT	TOT	70	70	1 year	X	X	X	X	X	
Wang et al. (2009)[45]	TVT	TVT-O	35	30	3 years	X		X	X		
Zhang et al. (2016)[46]	TVT	TVT-O	58	62	95 months	X	X	X	X	X	
TOT versus TVT-O											
Abdel-Fattah et al. (2010)[47]	TOT (Aris)	TVT-O	152	147	1 year	X	X		X	X	X
Houvert et al. (2009)[48]	TOT (Monarco)	TVT-O	86	75	38 months		X	X	X	X	X
Liapis et al. (2008)[49]	TOT (Monarc)	TVT-O	53	61	1 year	X	X	X	X		
Park and Kim (2012)[50]	Monarc	TVT-O	35	39	3 years	X	X	X	X		
Scheiner et al. (2012)[40]	Monarc	TVT-O	34	37	1 year	X	X	X	X	X	X
Minisling versus any sling											
Basu and Duckett (2013)[51]	Miniarc	Retropubic (Advantage)	38	33	3 years		X	X	X	X	

Table 1 (*Continued*)

Study	Intervention (1)	Comparator (2)	N (1)	N (2)	Follow-up	OC	SC	PO	AE	QoL	SF
MUS versus Burch											
Djehdian et al. (2014)[52]	Ophira	TOT (Unitape)	69	61	1 year	X	X	X	X	X	
Gaber et al. (2016)[53]	Contasure-Needleless	TVT-O	70	70	1 year	X	X	X	X	X	
Gaber et al. (2016)[53]	EFA	TVT-O	69	70	1 year	X	X	X	X	X	
Jurakova et al. (2016)[54]	Ophira	TVT-O	44	46	1 year	X	X	X	X	X	
Lee et al. (2015)[55]	Miniarc	TOT (Monarc)	103	103	1 year	X	X	X	X		
Schellart et al. (2016)[56]	Miniarc	TOT (Monarc)	73	72	2 years	X	X	X	X	X	
Sivaslioglu et al. (2012)[57]	TFS	TOT (I-STOP)	36	36	5 years	X	X	X	X		

Abbreviations: EFA, endopelvic free anchor; MUS, midurethral sling; PVS, pubovaginal sling; TFS, tissue fixation system; TOT, transobturator tape; TVT, tension-free vaginal tape; TVT-O, tension-free vaginal tape obturator.

significant or not, if different from zero. A deficiency of this test is its low power when the meta-analysis is made up of a small number of studies. The I^2 statistic by Higgins and Thompson[60] derives from Cochran Q test and the number of studies involved in the meta-analysis. The I^2 statistic can range from minus zero to 100%. Negative values are considered zero. The *p*-value of I^2 is equivalent to the *p*-value of Cochran Q test.[60]

Higgins and Thompson[60] suggest a scale where a value of I^2 close to zero indicates that there is no heterogeneity between studies, while a value close to 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, and more than 75% indicates high heterogeneity.[60]

Just as in the option of effect measure, we used odds ratio (OR). We used the Mantel-Haenszel method because most of the studies included had small sample sizes. However, for certain effects, some studies presented zero events in at least one of the comparison groups, and in these cases, we used the Peto method.[61]

We used the Cochrane Collaboration's Review Manager software (RevMan, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), version 5.3, to conduct our meta-analysis.

Results

The searches performed on MEDLINE and Cochrane resulted in 2,942 abstracts. After reading the titles and abstracts, 2,707 results were excluded and there were 235 remaining, whose texts were read in full. The study search flow is detailed in ►**Fig. 1**. Next, we found 48 articles that met the inclusion criteria in the meta-analysis, totaling 6,881 patients, ►**Table 1**.

Midurethral Sling versus Burch

For this comparison, we found 7 studies that analyzed 531 patients (282 in the midurethral sling group and 249 in the Burch surgery group). All studies used the Gynecare TVT retropubic sling (Ethicon Inc., Somerville, New Jersey, USA), compared with laparotomy[17] or laparoscopic[16,21] Burch surgery. Of the studies included in this group, six yielded objective cure results,[15,17–21] while three presented data on subjective cure,[16,19,21] and six presented data on adverse events, with the exception of Jelovsek et al (2008).[16]

The following tests were used to assess objective cure: pad test,[17,19,20] stress test[15,21] and urodynamic evaluation.[17–20]

For subjective cure, the authors used: satisfaction questionnaire,[19] visual analog scale(VAS),[18,21] Urinary Incontinence Severity Score (UISS),[21] Patients Global Impression of Improvement (PGII),[16,21] Incontinence Severity Index (ISI),[16] Urogenital Distress Inventory 6 (UDI-6),[16,18] Incontinence Impact Questionnaire 7 (IIQ-7),[16,18] Bristol Female Lower Urinary Tract Symptoms (BFLUTS)[20] and Short Form-36 (SF-36).[20]

The meta-analysis showed no significant difference regarding objective cure in the comparison between midurethral sling and Burch surgery (OR, 1.29; 95% confidence interval [CI], 0.76–2.20) ►**Fig. 2**. Moreover, no significant difference was found for subjective cure (OR, 1.16; 95% CI, 0.67–2.00) ►**Fig. 3**.

Regarding adverse events, we observed that the midurethral slings had higher rates of erosion (OR, 5.98; 95% CI, 1.16–30.67) and bladder perforation (OR, 2.74; 95% CI, 1.24–6.03), while Burch surgery had higher rates of surgical wound complications (OR, 0.30; 95% CI, 0.10–0.90) and urinary tract infection (UTI) (OR, 0.30; 95% CI, 0.14–0.63). There was no significant difference between these procedures in relation to the following adverse events: postoperative pain, hematoma, need for further surgery due to erosion or urinary retention, urinary retention for less than 6 weeks and overactive bladder. Adverse events such as blood loss, retention lasting for longer than 6 weeks, transfusion, de novo urgency and vaginal perforation were described in a single study, and therefore did not justify a meta-analysis.

Pubovaginal Sling versus Burch Surgery

For this comparison, we found 3 studies with high-quality evidence including 744 patients; 367 in the pubovaginal sling group and 377 in the Burch group. Two studies used autologous rectus fascia[15,22] and one study used a synthetic sling.[23] The three were compared with laparotomy Burch colposuspension. All the studies in this group presented results for objective cure and adverse events, while only two showed data on subjective cure.[22,23] To assess objective cure, the following tests were used: pad test[22,23] and stress test.[15,22,23] To assess subjective cure, the authors used: UDI and IIQ.[22]

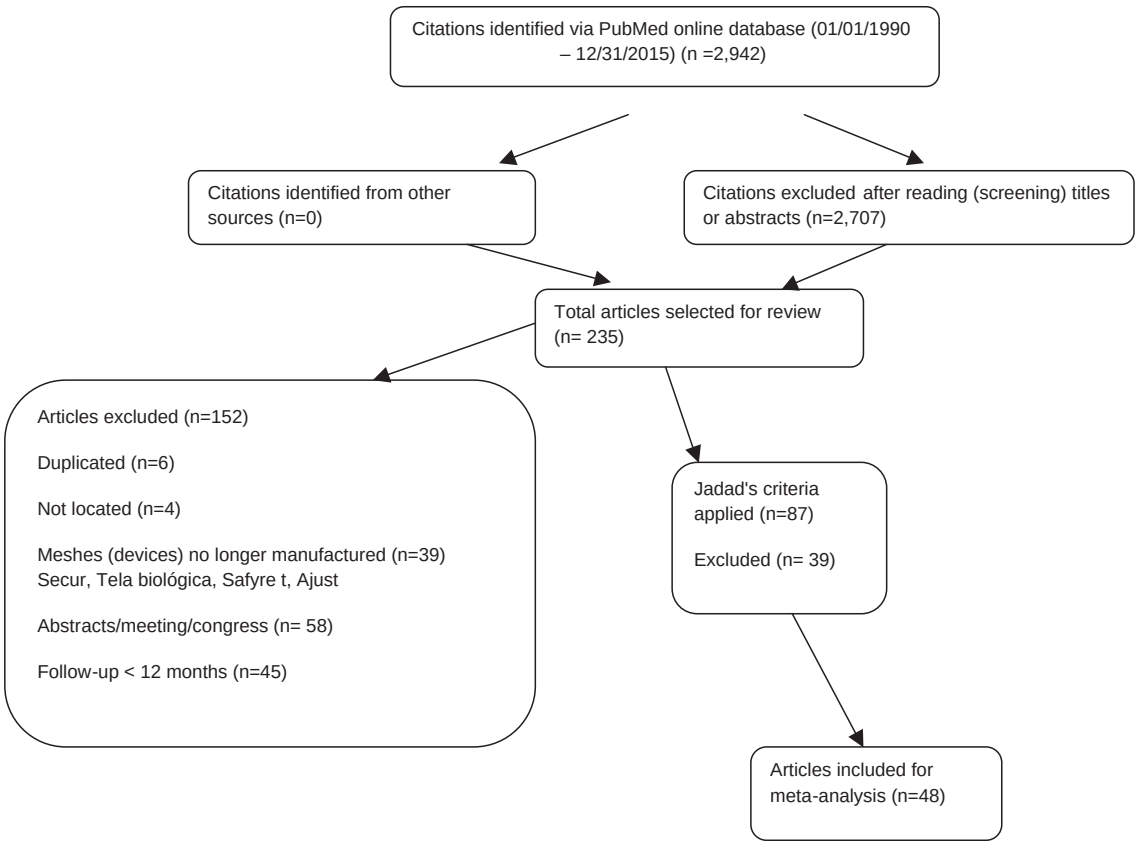

Fig. 1 Flowchart.

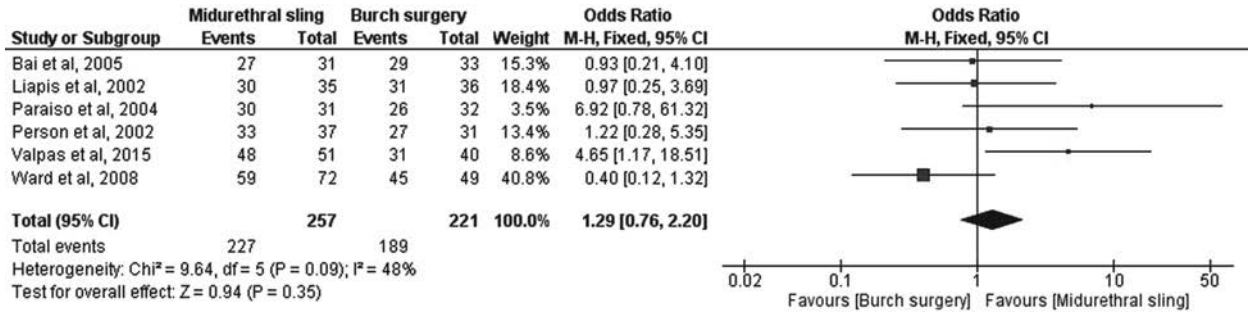

Fig. 2 Objective cure: midurethral slings versus Burch surgery.

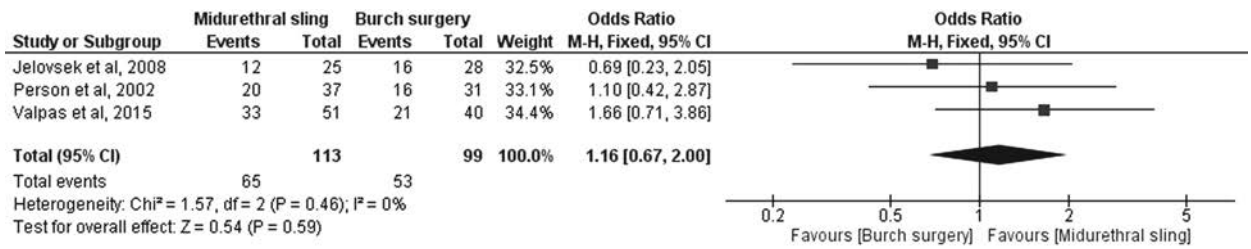

Fig. 3 Subjective cure: midurethral slings versus Burch surgery.

The meta-analysis showed no statistically significant difference regarding objective cure in the comparison between pubovaginal slings and Burch colposuspension (OR, 2.04; 95% CI, 1.50–2.77) (►**Fig. 4**).

Regarding subjective cure, the meta-analysis results showed a significant difference favoring pubovaginal slings over Burch colposuspension (OR, 1.64; 95% CI, 1.10–2.44) (►**Fig. 5**).

Regarding adverse events, we observed that, according to the analysis, the patients returned to the operating room more often due to retention in the group of pubovaginal slings, showing statistical significance (OR, 7.95; 95% CI, 3.34–18.94). Other complications were included in a single study, which precludes a meta-analytical comparison.

Pubovaginal Sling versus Midurethral Sling

For this comparison, we selected 3 studies including 256 patients, 120 in the pubovaginal sling group and 136 in the midurethral sling group. In all studies, autologous rectus fascia was used to construct a pubovaginal sling. For midurethral sling, all studies used retropubic TVT. Of the studies found in this group of analysis, two presented results on objective cure[15] and only one showed subjective cure.[24] To assess objective cure, the authors used: the pad test,[25] stress test[15,25] and urodynamic evaluation.[25] To analyze subjective cure, the authors used: the satisfaction test,[24] BFLUTS[24] and IIQ.[25] Regarding objective cure, the meta-analysis showed that there was no significant between-group difference (OR 1.64, 95% CI: 0.52–5.15) (►**Fig. 6**). For subjective cure, there was no possibility of meta-analysis, since this variable was analyzed in one study only.

In this group, we observed that some adverse events were reported, such as bladder perforation, urinary retention for less than 6 weeks and return to the operating room due to urinary retention, although these were not significant between groups. Other complications, such as blood loss, transfusion, and de novo urgency were described in a single study, and therefore did not justify a meta-analysis.

Retropubic Sling versus Transobturator Sling

In this comparison group, we found 22 studies including 3,638 patients, 1,863 in the group treated with retropubic sling and 1,775 in the transobturator group. In most of them, the Gynecare TVT and TVT-O (Ethicon Inc., Somerville, New Jersey, USA) were compared.[26,27,30,32–35,37,40–42,46,47] In the other studies, TVT and Monarc (American Medical Systems, Minnetonka, MN, USA) were compared.[28,31,40,44] One study, by Richter et al (2010),[36] compared TVT with TVT-O or Monarc. Ross et al (2009, 2016)[38,39] used Advantage (retropubic) and Obtrix (transobturator) (both products made by Boston Scientific, Natick, MA, USA), and Wadie and El-Hefnawy (2013)[43] compared TVT and Aris TOT (Coloplast, Minneapolis, MN, USA). Tension-free vaginal tape and Obtape (Mentor-Porgés, Le Plessis-Robinson, France) were compared by Costantini et al (2016).[29]

Of the studies found in this comparison group, only one[31] did not present results for objective cure. Six studies did not

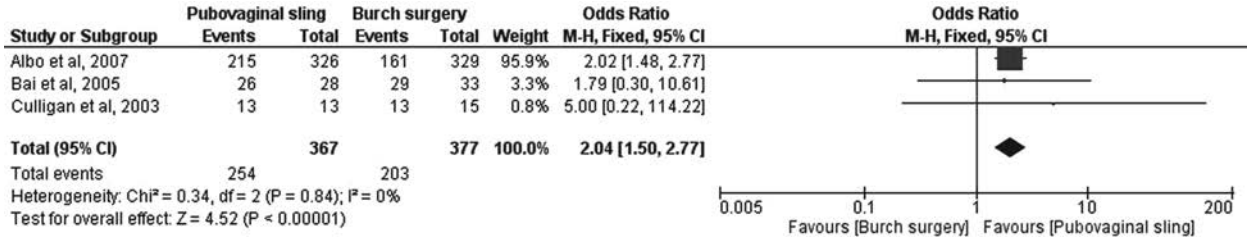

Fig. 4 Objective cure: Pubovaginal sling versus Burch surgery.

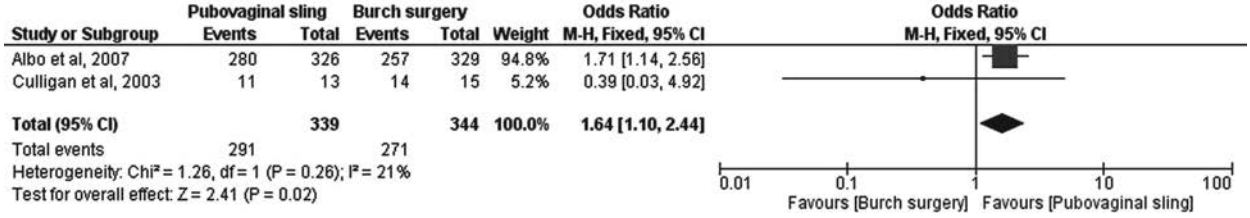

Fig. 5 Subjective cure: Pubovaginal sling versus Burch surgery.

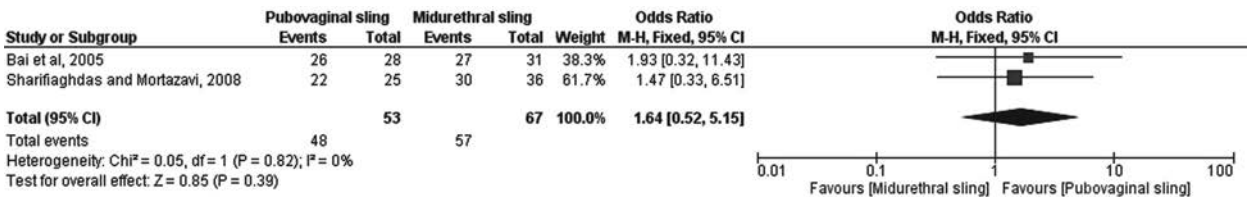

Fig. 6 Objective cure: Pubovaginal sling versus midurethral sling.

assess subjective cure.[27,32,37,39,41,46] All authors reported data on complications.

To assess objective cure, the authors used: the pad test,[29,33,34,36–40,42,43,45,47] stress test[26–30,32–37,40,42–45] and urodynamic evaluation.[26,27,32,41]

To evaluate subjective cure, the authors used the following tools: satisfaction test,[30,32,33,36–38] VAS,[26,30,33,34,37,40] and quality of life questionnaires, including the Incontinence Quality of Life questionnaire (I-QOL),[27,35] ISI,[28] Pelvic Floor Distress Inventory, Short Form-20 (PFDI-20),[28] Pelvic Floor Impact Questionnaire Short Form-7 (PFIQ-7),[28,47] PGII,[28,43,47] Short Form 12 (SF-12),[28] Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short Form (PISQ-12),[28,39,47] Quality Of Life Assessment Questionnaire Concerning Urinary Incontinence (CONTILIFE),[30,33] International Consultation Incontinence Modular Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS),[31] IIQ-7,[29,32,34,37–39,41–43] UDI-6,[29,32,34,37–39,41–43] UISS,[34,37] Detrusor Instability Score (DIS),[34,37] Medical Epidemiological and Social Aspects of Aging (MESA)[36] and King's Health Questionnaire (KHQ).[40]

After the meta-analysis of objective cure data, the conclusion was that there was a statistically significant difference between the surgical treatments with retropubic and transobturator sling favoring the retropubic device (OR, 1.27; 95% CI, 1.05–1.54) ►**Fig. 7**. The same conclusions were drawn regarding subjective cure (OR, 1.23; 95% CI, 1.02–1.48) ►**Fig. 8**.

Regarding complications, the retropubic slings significantly caused a greater number of vascular lesions (OR, 2.96, 95% CI, 1.41–6.24), hematoma (OR, 3.02, 95% CI, 1.34–6.82), bladder perforation (OR, 5.45, 95% CI, 3.33–8.90), urinary retention for less than 6 weeks (OR, 2.00, 95% CI, 1.45–2.77) and return to the operating room due to urinary retention (OR, 3.78, 95% CI, 2.00–7.13). Surgical treatment of SUI using the transobturator sling, in turn, produced significantly more cases of all of the following: leg pain (OR, 0.18, 95% CI, 0.11–0.30), groin pain (OR, 0.17, 95% CI, 0.08–0.35), neurological injury (OR, 0.48, 95% CI, 0.27–0.87) and vaginal perforation (OR, 0.24, 95% CI, 0.14–0.40). There was no significant difference between these procedures related to the following adverse events: blood loss, overactive bladder, surgical wound complications, unspecified pain, erosion, return to the operating room due to

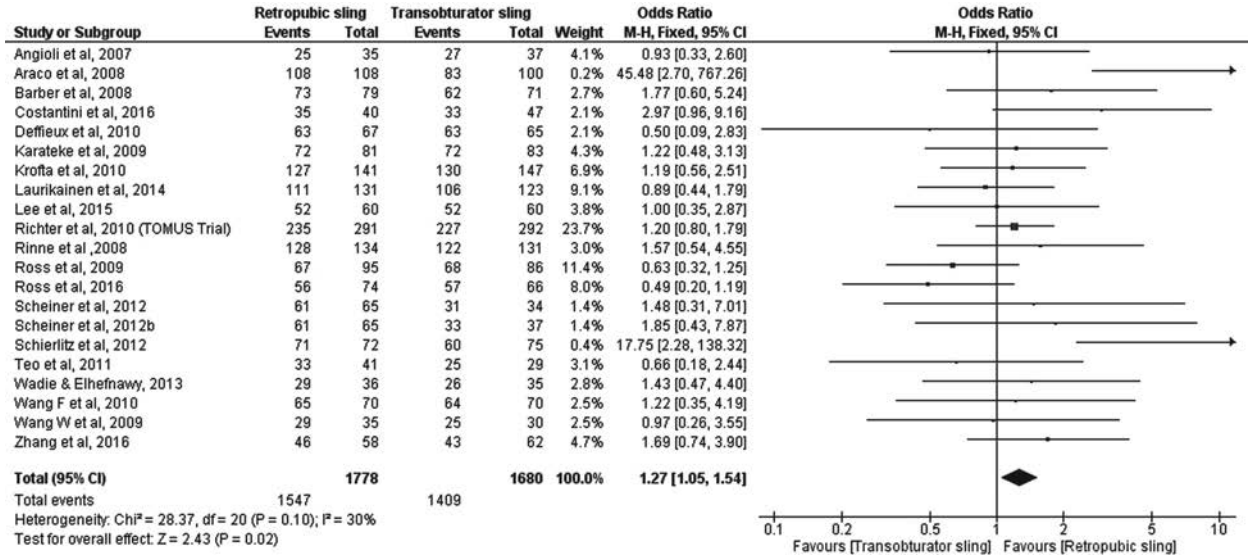

Fig. 7 Objective cure: Retropubic sling versus transobturator sling.

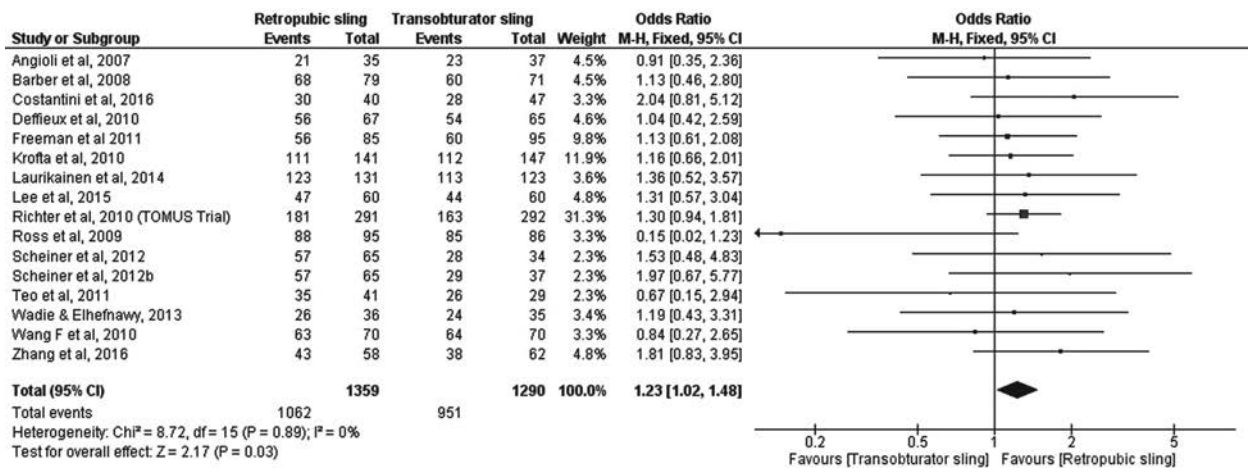

Fig. 8 Subjective cure: Retropubic sling versus transobturator sling.

erosion, urinary tract infection, blood transfusion, urethral perforation, urinary retention lasting for longer than 6 weeks and de novo urgency.

Outside-in Midurethral Transobturator Sling versus Inside-out Midurethral Transobturator Sling

For this comparison, we found 5 studies totaling 719 patients, 360 in the TOT group and 359 in the TVT-O group. In one of the studies, the authors used an Aris TOT sling;[48] TOT Monarc slings[40,48–50] were used in the other studies. These slings were compared with TVT-O slings.

Of the studies found in this group of analysis, four showed results on objective cure.[40,47,49,50] All of the studies presented data on subjective cure and adverse events.

To assess objective cure, the authors used: pad test,[40,47,49] stress test[40,50] and urodynamic evaluation.[49,50]

To assess subjective cure, the authors used: satisfaction test,[47] VAS,[40] and questionnaires on quality of life, including KHQ,[40,47] International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF),[47] PGII,[47] UDI-6[48] and IIQ-7.[48]

The meta-analysis showed no significant difference regarding objective cure in the comparison between TOT and TVT-O slings (OR, 0.78, 95% CI, 0.45–1.35) ►**Fig. 9**. For subjective cure, no significant difference was found in the meta-analysis either (OR, 0.83; 95% CI, 0.58–1.18) ►**Fig. 10**.

Regarding adverse events, we observed that TOT slings presented higher rates of vaginal perforation (OR, 3.31, 95% CI, 1.44–7.61) and erosion (OR, 4.83, 95% CI, 1.28–18.27). There was no significant difference between these procedures in terms of postoperative pain, urinary retention for more or less than 6 weeks, return to the operating room due to urinary retention, de novo urgency and leg pain. Overactive bladder, UTI and urethral perforation were reported in a single study, thus precluding a meta-analysis.

Minisling versus Any Other Sling

For this comparison, we found 8 studies totaling 993 patients, 502 in the minislings group and 491 in the comparison group. In three studies, the authors used the Miniarc minisling (American Medical Systems, Minnetonka, MN, USA),[51,55,56] which was compared with the Advantage retropubic sling[51] and the Monarc transobturator sling.[55,56] One of the studies compared the Ophira minisling and the TOT Unitape (both made by Promedon, Cordoba, Argentina),[52] while others compared the Contasure-Needleless (New Medical Technologies, Barcelona, Spain) minisling and endopelvic free anchor (EFA),[53] and the Ophira minisling[54] with the TVT-O. One study compared the TFS minisling (TFS Surgical, Adelaide, Australia) with the TOT I-STOP (CL Medical, Sainte Foys Les Lyon, France).[57]

Only one study[51] failed to report objective cure. All studies showed results for subjective cure and adverse events.

To assess objective cure, the authors used the pad test[52,57] and stress test.[52–56]

For subjective cure, the authors used the satisfaction test[52] and quality of life questionnaires, including the KHQ,[51] I-QOL,[52] UDI,[52] International Consultation on Incontinence Questionnaire/ Urinary Incontinence Short Form (ICIQ-UIFS),[53–55] International Consultation on Incontinence Questionnaire/ Overactive Bladder (ICIQ OAB),[55] IIQ-7,[55] PGII,[53–56] UDI-6,[56] Patient Global Impression Severity (PGI-S),[56] and Patient Perception of Intensity of Urgency Scale (PPIUS).[54]

The meta-analysis showed no significant difference between minislings and other slings for objective cure (OR, 0.72; 95% CI, 0.47–1.10) ►**Fig. 11**. For subjective cure, we found a significant difference favoring other slings (OR, 0.58, 95% CI, 0.39–0.86) ►**Fig. 12**.

Regarding the adverse events, the group that included other types of slings had a higher rate of groin pain (OR, 0.11 95% CI, 0.04–0.28) and unspecified pain (OR, 0.20, 95% CI, 0.07–0.61), noting that transobturator slings were used in

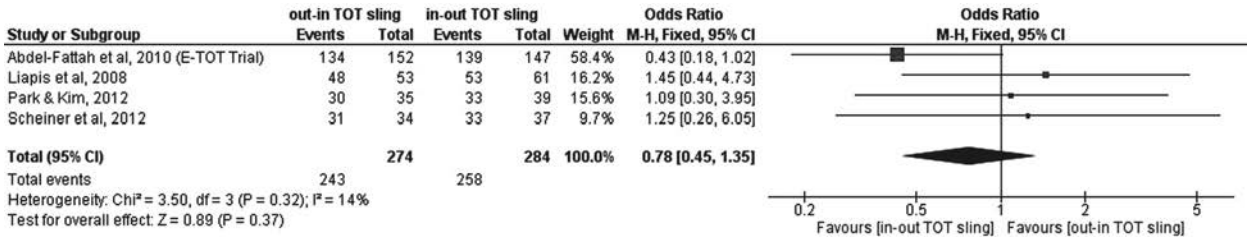

Fig. 9 Objective cure: outside-in transobturator sling versus inside-out transobturator sling.

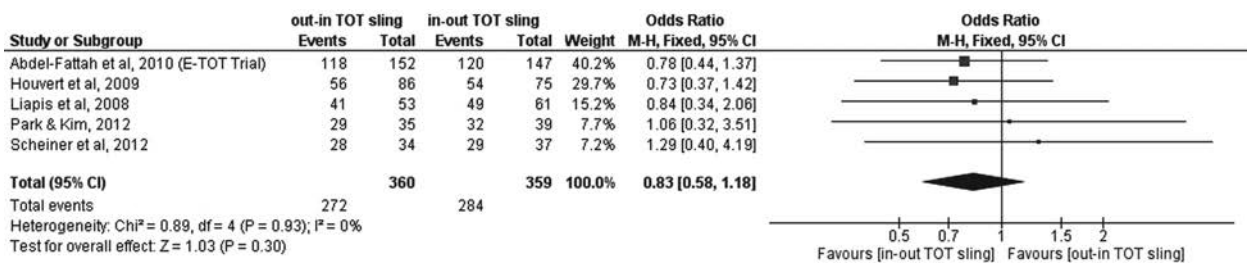

Fig. 10 Subjective cure: outside-in transobturator sling versus inside-out transobturator sling.

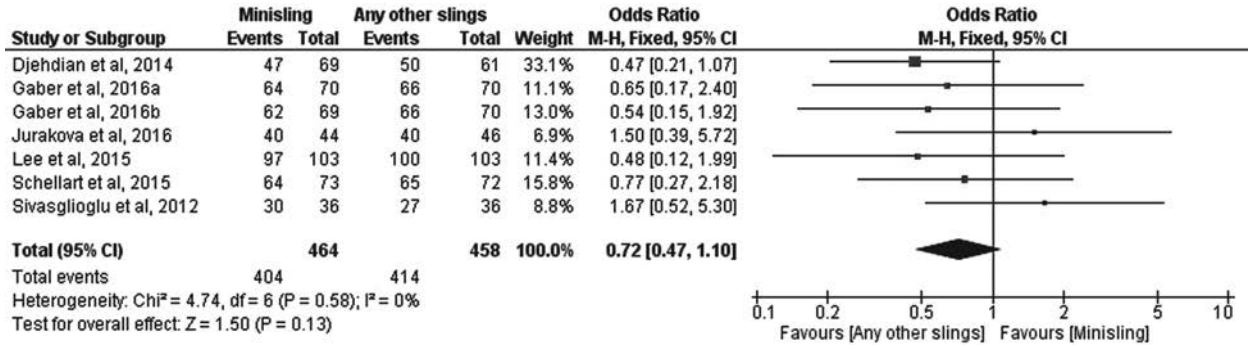

Fig. 11 Objective cure: Minisling versus any other sling.

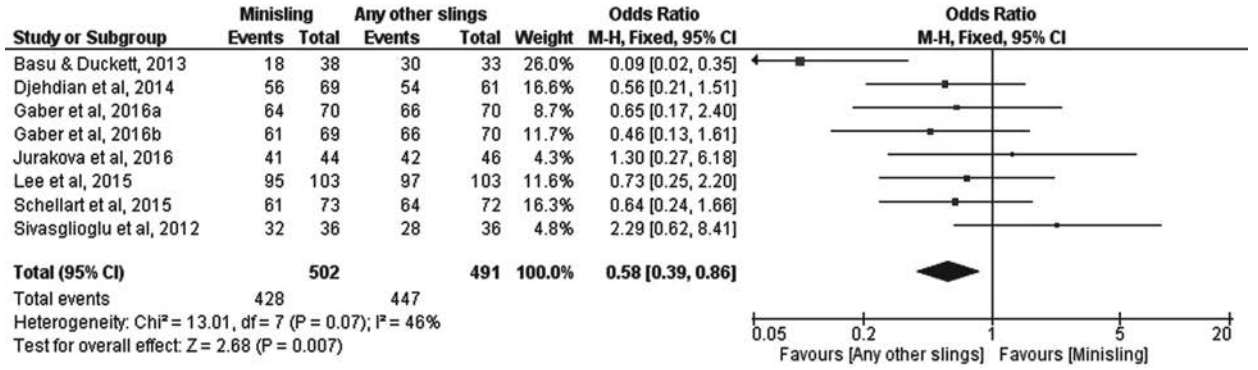

Fig. 12 Subjective cure: Minisling versus any other sling.

the studies that we analyzed for these variables.[55–57] There was no significant difference between the groups for rates of overactive bladder, erosion, UTI, return to the operating room due to urinary retention, urinary retention for more or less than 6 weeks and de novo urgency.

The data on adverse events, leg pain, hematoma, return to the operating room due to erosion, blood loss, urethral perforation and vaginal perforation were all described in a single study, thus precluding a meta-analysis.

Discussion

Several techniques have been described for the surgical treatment of SUI. Burch retropubic colposuspension surgery, considered the gold standard in the treatment of this condition for decades, gave way to the pubovaginal sling, and later, to the retropubic synthetic midurethral sling, described in 1996 by Ulmsten et al,[5] showing a very satisfactory success rate. Next, transobturator slings were introduced using both outside-in and inside-out techniques as described by Delorme, in 2001,[10] and de Leval, in 2003,[11] respectively, in an attempt to reduce adverse events, especially bladder perforation and visceral and vascular lesions. In 2006, a single incision sling was developed following a trend toward minimally invasive procedures to reduce the amount of synthetic material used and reduce the blind needle path, thus minimizing tissue damage and infections.

Due to the large number of articles found in the literature, we decided to select studies of high-scientific quality to perform our meta-analysis.

In our work, we selected articles comparing midurethral sling versus Burch colposuspension, pubovaginal sling versus Burch colposuspension, pubovaginal sling versus midurethral sling, retropubic midurethral sling versus transobturator midurethral sling, outside-in transobturator midurethral sling versus inside-out transobturator midurethral sling, and minisling versus any other slings. The group with the highest number of articles was the one that compared the retropubic midurethral sling versus transobturator, with 22 studies selected.

Our view is that some bias should be considered while analyzing the results of this meta-analysis. Several studies do not distinguish between patients with and without intrinsic sphincteric deficiency, patients with recurrent or untreated SUI, which hinders a more detailed analysis. Another important bias was surgery performed concomitantly with surgical treatment for SUI (vaginal and abdominal hysterectomy, correction of anterior and posterior wall prolapses, and correction of vaginal vault prolapse). Moreover, we do not always find data on the individual conditions of the patients (lung disease, diabetes, neuropathy, etc.). The various criteria used for objective cure are also a bias factor. In the studies selected for our meta-analysis, the cure was defined based on urodynamic evaluation, a stress test and/or pad test. This lack of uniformity can significantly affect results. The same can be said regarding subjective cure, since some studies used quality of life questionnaires, while others only applied satisfaction surveys to define this outcome. Many of the studies analyzed are multicentric, with patients being operated on by different surgeons with varying experience degrees. It is known that surgeon

experience is a determining factor for the success of a surgical procedure, as well as the occurrence of complications.[62,63]

One of the factors that could be considered when choosing the treatment is the cost-benefit ratio. However, very few studies analyzed this variable. Among the studies selected for our meta-analysis, only one[19] included such an evaluation.

As for the comparison of techniques in the analyzed studies, we verified that there was no significant difference regarding objective and subjective cure between midurethral sling and Burch colposuspension, although the latter presented more complications in terms of surgical wounds and UTI. With respect to midurethral slings, there were higher rates of bladder perforation and vaginal erosion, noting that comparisons were made with retropubic slings.

However, when comparing the pubovaginal sling and Burch surgery, the former was superior, in relation to objective and subjective cure, but presented a higher rate of return to the operating room due to urinary retention, which corroborates the literature results that pubovaginal slings are more retentionist.[64,65] We must point out that whenever the patient has indication for gynecological surgery using the abdominal route combined with stress urinary incontinence, Burch colposuspension is an adequate option.

In the comparison of pubovaginal sling versus midurethral sling, both presented high rates of objective cure but no significant difference between the two.

Comparing retropubic and transobturator slings, we observed that the retropubic devices were significantly superior, in relation to objective and subjective cure, despite the small difference. One possible explanation for this result is the more vertical positioning of the tape from the urethral axis in the retropubic route, unlike the horizontal position used via the transobturator route.[66] This hypothesis would also explain the greater effectiveness of the retropubic technique over the transobturator in cases of SUI with IDS[67] as well as the better long-term results favorable to retropubic sling.[29] With regard to adverse events, we found a greater number of cases of bladder perforation, urinary retention, return to the operating room due to urinary retention, vascular injury and hematoma with retropubic slings. These last complications occur due to the blind passage of the needle through the Retzius space, which can lead to injury of veins and arteries, and ultimately bleeding and hematoma, as found in an ultrasound investigation immediately after surgery.[68] The higher rate of urinary retention in retropubic slings is probably due to the more vertical position of the tape compared with the transobturator sling,[28,69,70] as previously mentioned.

The transobturator sling, on the other hand, presented significantly more cases of leg pain, groin pain, neurological lesions and vaginal perforations.

Although the retropubic sling had significantly higher cure rates compared with the transobturator, the difference was small. The choice should therefore be based on the patient's history and individual characteristics, leaving the surgeon to decide the best route based on the possibility of complications, and his or her experience and preference, sharing the decision with the patient.

The TOT, when compared with TVT-O, did not show significant differences regarding objective and subjective cure. However, there was more vaginal perforation and erosion in the TOT group, which probably occurs because the needle passes closer to the vaginal sulcus in this technique.[40]

Compared with other slings, minislings did not show significant difference regarding objective cure; however, there was a significant difference regarding subjective cure, favorable to other slings. For adverse events, the group of other slings had a higher rate of groin pain and unspecified pain, which was only seen in transobturator slings.

In several comparisons, our meta-analysis failed to demonstrate significant differences regarding objective cure, subjective cure, and adverse effects among the various techniques, a result also obtained in a Cochrane meta-analysis published in 2015.[71] Novara et al (2010),[72] in turn, found superiority of retropubic slings compared with transobturator slings with respect to objective cure, and no difference between techniques related to subjective cure.

Our meta-analysis does not offer final conclusions about the effectiveness of the various techniques for intrinsic sphincteric deficiency, since most of the included studies failed to analyze this condition alone.

Conclusion

Our systematic review, followed by the meta-analysis, included studies of high methodological quality aiming at comparing the various techniques available for surgical correction of SUI. According to our results, pubovaginal slings demonstrated better objective and subjective results when compared with Burch colposuspension surgery, but pubovaginal slings exhibited more retention, often resulting in a return to the operating room. When we compared the retropubic and transobturator slings, we observed the superiority of the retropubic sling objectively and subjectively but a greater number of adverse events. In the comparative analysis between minislings and other slings, superiority was noted for the latter in the subjective aspect. When comparing the midurethral slings with Burch colposuspension surgery, t no statistically significant difference in relation to objective or subjective cure was found. When comparing pubovaginal and midurethral slings, there was also no significant difference in relation to the objective cure. Likewise, no statistically significant difference was observed between inside-out and outside-in transobturator slings for both objective and subjective cure. Based on the above, we believe that the choice of technique should be aligned with several factors, such as abdominal or vaginal surgeries performed concomitantly, the surgeon's experience, the patient's prior surgeries, adverse events and availability of materials.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Fine-needle Aspiration Cytology to Identify a Rare Mimicker of Breast Cancer: Plasma Cell Mastitis

Citologia de aspiração com agulha fina para identificar um simulador raro de câncer de mama: mastite celular plasmática

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Abstract

There are rare benign diseases that can mimic malignant breast neoplasms in the clinical exam and in mammography. We evaluated the contribution of an accessible procedure to most clinicians, the fine-needle aspiration cytology, to identify a rare mimicker of malignant breast neoplasms. A type 2 diabetic 85-year-old female presented with a 6-month history of a left breast lump. The physical exam and mammography were compatible with breast cancer. Nevertheless, after fine-needle aspiration cytology, the diagnosis was plasma cell mastitis. Once this rare diagnosis was established, the tumor was extirpated, and the final histologic diagnosis corroborated chronic plasma cell mastitis. The patient's postoperative evolution was uneventful, and no other treatment was needed. Fine-needle aspiration cytology could be a valuable tool to identify rare mimickers of malignant breast neoplasms.

Keywords

- cancer
- breast
- breast cancer
- fine needle aspiration biopsy
- granuloma
- mammography
- mastitis

Resumo

Existem doenças benignas raras que podem mimetizar neoplasias malignas de mama no exame clínico e na mamografia. Avaliamos o valor de um procedimento acessível para a maioria dos clínicos, a citologia por aspiração com agulha fina, para identificar um imitador raro de neoplasias malignas de mama. Uma mulher de 85 anos com diabetes tipo 2 apresentou histórico de 6 meses de um nódulo no seio esquerdo. O exame físico e a mamografia foram compatíveis com câncer de mama. No entanto, após realizar uma citologia por aspiração com agulha fina, o diagnóstico foi mastite celular plasmática. Uma vez que este diagnóstico raro foi estabelecido, o tumor foi extraído e o diagnóstico histológico final corroborou a mastite crônica das células plasmáticas. A paciente teve uma boa evolução pós-operatória, e nenhum outro tratamento foi necessário. A citologia por aspiração com agulha fina pode ser uma ferramenta valiosa para identificar os raros mimetizadores de neoplasias malignas da mama.

Palavras-chave

- câncer
- mama
- câncer de mama
- biopsia por aspiração com agulha fina
- granuloma
- mamografia
- mastite

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Introduction

Breast cancer is a major health problem worldwide and its number is growing.[1] Rarely, there are benign diseases than can mimic malignant invasive breast tumors in clinical exam and mammography.[2] Thus, different forms of biopsy are needed to confirm this diagnosis; this is called the triple test score.

Fine-needle aspiration cytology (FNAC) is an office procedure, involving low-cost and usual medical supplies; this method is accessible to most clinicians. With appropriate training and experience of clinicians and pathologist, its rate of diagnostic accuracy is high: sensitivity (92.7%) and specificity (94.8%).[3] The value of FNAC in recognizing a rare mimicker of breast cancer in clinical and mammographic backgrounds is herein assessed.

Case Description

An 85-year-old woman with type 2 diabetes presented with a 6-month history of a left breast lump. Practicing of self-breast exam and mammography was denied by the patient. At physical exam, the right breast and both axillae were normal; however, the left breast had a hard and painless 3 cm lump in the external upper quadrant. A mammography showed a left breast tumor with irregular margins, distorting the regional breast architecture; the result of the mammography led to the diagnosis of a category V lesion, according to the breast imaging reporting and data system (BI-RADS) (►**Fig. 1b** and **d**). With these findings, a left breast cancer (T2 N0) was suspected. To confirm the clinical and radiological impression, a FNAC was performed; unexpectedly, the cytological diagnosis was plasma cell mastitis (►**Fig. 1e**). To support this extremely rare cytological diagnosis, a wide tumor resection was arranged. The final histopathological diagnosis of the surgical specimen was chronic plasma cell mastitis (►**Fig. 1f**). The patient had an uneventful postoperative course and did not need any other treatment.

Discussion

In this case, the FNAC was an appropriate tool to identify a rare mimicker of breast cancer: the plasma cell mastitis. Fortunately, the FNAC is an accessible diagnostic method to most clinicians. After performing a search in different repositories (PubMed, Lilacs, Scopus, and Google scholar), we found that the potential usefulness of FNAC to identify granulomatous mastitis, as shown in our case, was in accordance with the study of Akcan et al.[4] However, two different groups found opposite results about the FNAC's utility, and they emphasize the great difficulty to differentiate a carcinoma from a granulomatous mastitis with this kind of biopsy.[5,6] A combination of the lack of adequate training and experience in FNAC, technique execution and interpretation is probably the answer to these contradictory findings.[3]

The presented patient was an 85-year-old female. There is inconsistent information concerning the age-group most affected by granulomatous plasma cell mastitis. We agree with Bhaskaran et al[7] about plasma cell mastitis occurring in older women; nonetheless, there are two reports indicating that this kind of mastitis occurs more frequently in young females.[6,8] To increase the complexity of this issue, plasma cell mastitis is a rare form of mastitis, and its pathogenesis is not yet fully understood.[7–9]

Plasma cell mastitis belongs to a rare group of granulomatous breast diseases.[8] Common opinion between experts of this field indicates that all forms of granulomatous mastitis can mimic breast cancer in clinical and radiological backgrounds.[2,4–8] This is why the triple test score is essential for clinicians when evaluating palpable breast tumors: physical exam, radiologic evaluation (mammography and/or echography), and a biopsy.[3] As we can see in this case, the result of the biopsy changed the

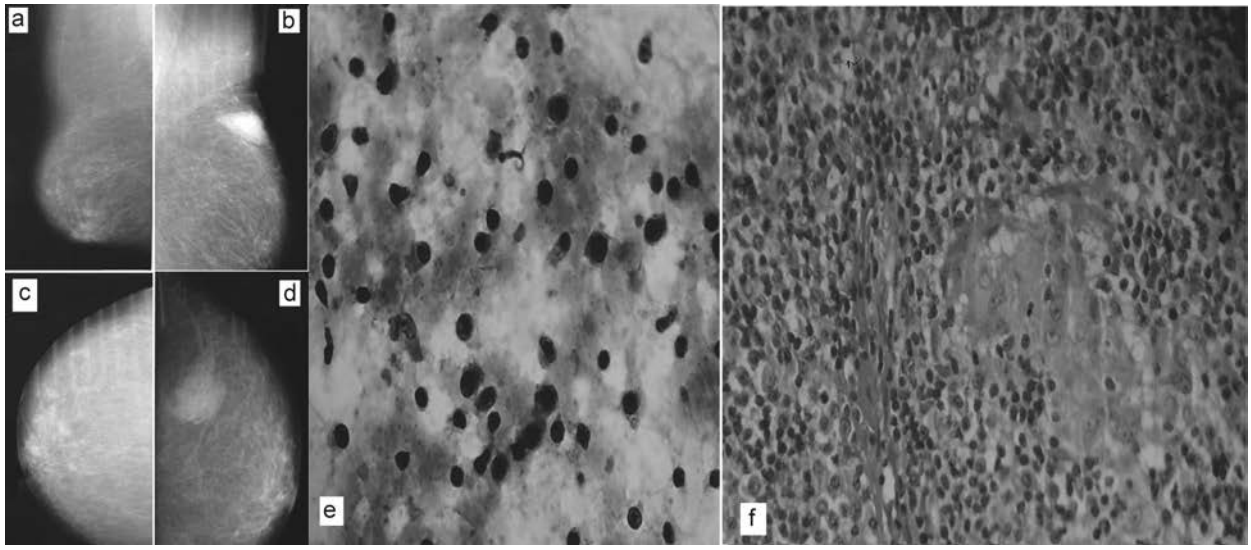

Fig. 1 (**a**) Mammography: Mediolateral oblique view of the right breast. (**b**) Mediolateral oblique view of the left breast. (**c**) Craniocaudal view of the right breast. (**d**) Craniocaudal view of the left breast. (**e**) Fine-needle aspiration cytology specimen of the tumor (Papanicolaou stain) showing many plasma cells. (**f**) Microphotography of the surgical specimen (hematoxylin and eosin [H and E] stain, 100x) showing several plasma cells and giant cells.

diagnosis dramatically. A careful history and a diligent physical exam are the first steps in identifying any disease; however, as with at all medical diagnostic tools, they have their own limitations and exactness.

Conclusion

Fine-needle aspiration cytology is a valuable diagnostic tool. It can detect rare mimickers of malignant breast tumors classified as BI-RADS category V, thus, radically changing the course of treatment.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Conservative Surgical Treatment of a Case of Placenta Accreta

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Abstract

Placenta accreta syndromes are associated with increased maternal mortality and morbidity. Cesarean hysterectomy is usually performed in cases of placenta accreta syndrome. Fertility sparing methods can be applied. In the present study, we report a successful segmental uterine resection method for placenta accreta in the anterior uterine wall in a cesarean section case. A 39-year-old woman underwent an elective cesarean section at 38 + 2 weeks. A placental tissue with an area of 10 cm was observed extending from the anterior uterine wall to the serosa, 2 cm above the uterine incision line. The placental tissue was removed with the help of monopolar electrocautery. The uterine incision was continuously sutured. The patient was discharged on the second postoperative day. The placental pathology was reported as placenta accreta. The American College of Obstetricians and Gynecologists (ACOG) generally recommends cesarean section hysterectomy in cases of placenta accreta because removal of placenta associated with significant hemorrhage. Conservative and fertility sparing methods include placenta left in situ, cervical inversion technique and triple-P procedure. There are several studies reporting that segmental uterine resection is performed with and without balloon placement or artery ligation. Segmental uterine resection may be an alternative to cesarean hysterectomy to preserve fertility or to protect the uterus in cases of placenta accreta when there is no placenta previa.

Keywords
- placenta accreta
- cesarean delivery
- hysterectomy prevention

Introduction

Normal placentation occurs as a result of the placement of the placenta in the decidua. The result of placenta adherence to the myometrium instead of to the decidua results in placenta accreta. Abnormal adhesion is named according to the extent of myometrium and uterine serosal involvement. All of these abnormalities are called placenta accreta syndrome. The most common type of placenta invasion anomaly is placenta accreta, and the most serious is placenta percreta, which is related with the increase in cesarean delivery rates. The incidence of placenta invasion anomalies is up to 1/533 pregnancies.[1] Placenta accreta syndromes are associated with increased maternal mortality and morbidity.[2] Cesarean hysterectomy is usually performed in cases of placenta accreta syndrome. Nowadays, fertility sparing and conservative methods can be applied. These methods include placenta left in situ, cervical inversion technique and triple-P procedure.[3,4] Placenta left in situ and methotrexate use have serious risks, such as late postpartum hemorrhage, infection, and pulmonary embolism. In the cervical inversion technique, the cervix is inverted using ring forceps or straight Allis forceps, after which the placental

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bed is sutured to control bleeding.[4] In the triple-P procedure, a balloon is placed preoperatively in the hypogastric arteries and the balloon is inflated after the baby is born. Recently, a limited number of cases of segmental uterine resection have been reported. We reported a successful segmental uterine resection method for placenta accreta in the anterior uterine wall in a cesarean section case.

Case Report

A 39-year-old, gravida 4, para 3 pregnant woman underwent an elective cesarean section at 38 + 2 weeks. The patient had a history of two previous cesarean sections. Under regional anesthesia, the cesarean section was performed with Pfannenstiel incision and transverse uterine incision. The patient had no placenta accreta diagnosis preoperatively. A healthy 3,100 g male newborn was delivered. Twenty IU of oxytocin (Synptian Fort, Deva, Turkey) was intravenously administered after the delivery of the fetus and the removal of the involved area. The placental tissue was observed extending from the anterior uterine wall to the serosa ~ 2 cm above the uterine incision line (►**Fig. 1**). Placenta percreta was thought with intraoperative. The placenta was not removed due to the possibility of bleeding. The area of 10 cm, which is considered to be a placenta percreta, was removed with the help of monopolar electrocautery. The remaining placenta fragments were removed with gentle traction. The uterine incision was continuously sutured with no.1 vicryl (Polyglactin 910 suture, Doğsan, Trabzon, Turkey) (►**Fig. 2**). Hypogastric or uterine artery ligation was not performed because there was no intensive bleeding. Due to the preoperative approval, tubal ligation was performed with the Pomeroy method. The estimated amount of bleeding was not calculated. A total of 3,000 mL of crystalloids and 500 mL of colloid fluid were administered intraoperatively, assuming that the amount of bleeding was of 1,000 mL. Immediately, 3 units of erythrocyte suspension were prepared for transfusion. The operation was completed in 60 minutes. Hemoglobin 10.3 g/dL, hematocrit value of 31.4% in the preoperative period; hemoglobin 8.5 g/dL and hematocrit value of 31.4% after the transfusion of 1 unit of erythrocyte suspension in the postoperative period. Intraoperative and postoperative complications did not develop. The patient was discharged on the second postoperative day. The placental pathology was reported as a placenta accreta.

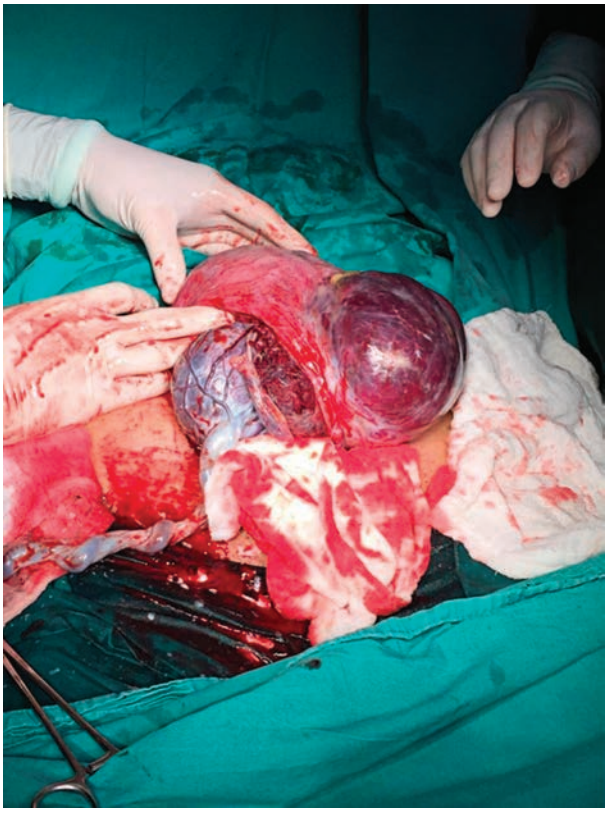

Fig. 1 Placental tissue was observed ~ 2 cm above the uterine incision line.

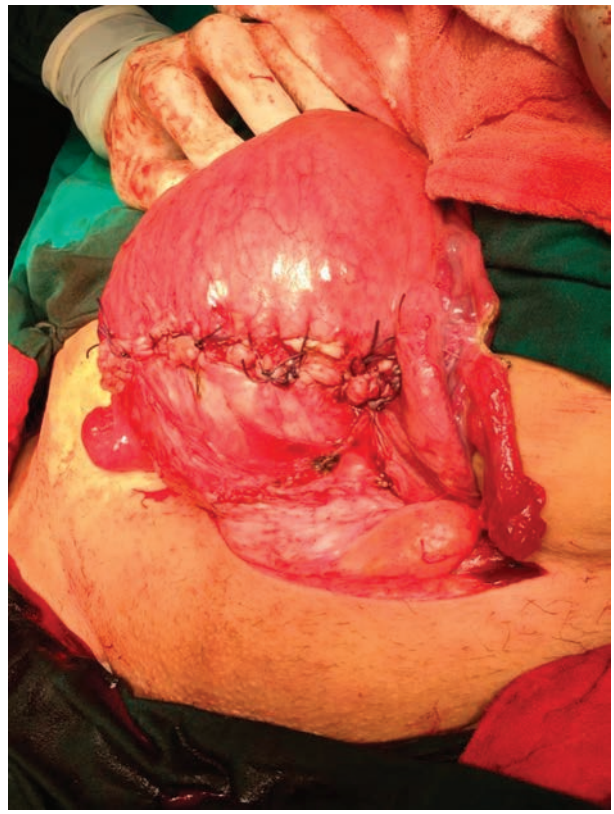

Fig. 2 Reconstruction of the uterine wall.

Discussion

Obstetric hemorrhage due to placenta accreta syndrome is one of the important reasons of maternal mortality and morbidity. The American College of Obstetricano and Gynecologists (ACOG) generally recommends cesarean section hysterectomy in cases of placenta accreta because removal of placenta associated with significant hemorrhage.[5] However, conservative and fertility sparing methods can be applied in selected cases.[6] Subsequently, the uterine wall containing the placenta accreta is removed.[3] Another method is to perform bilateral hypogastric artery ligation intraoperatively, after the removal of the baby, and to perform segmental uterine resection of the placenta percreta area.[7,8] There are some studies reporting that segmental uterine resection is performed without balloon

placement or artery ligation.[9] The duration of the operation is increased in cases of placenta previa with uterine artery ligation.[7] The duration of the operation is shortened when arterial ligation and balloon placement are not performed.[9] Due to the absence of placenta previa and the absence of arterial ligation in our case, the operation was completed within 60 minutes. The amount of bleeding due to the absence of placenta previa was lower than that reported in other studies. For this reason, 1 unit of erythrocyte suspension was sufficient.

Conclusion

Cesarean hysterectomy is usually performed in cases of placenta accreta syndrome. Segmental uterine resection may be an alternative to cesarean hysterectomy, to preserve fertility or to protect the uterus, in cases in which there is no placenta previa

Conflicts of Interest
None to declare.

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Abortion and Zika Virus Congenital Infection

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Rev Bras Ginecol Obstet 2018;40:497.

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Dear Editor,

We read the publication on "Abortion in Cases of Zika Virus Congenital Infection."[1] Mota et al[1] noted that "*it is necessary to have available tests that could diagnose, in the first trimester of pregnancy, that the fetus has been affected by the virus, and that it may have important limitations, in order to subsidize the qualified discussion about abortion in these cases.*" In fact, there is still no evidence that the Zika virus infection in pregnant women is the cause of abortion, and there is still no recommendation for therapeutic abortion in infected pregnant women. The important issue is the relationship between infection during pregnancy and the induction of an abnormal infant. In many regions, especially in tropical Asian countries,[2,3] microcephalic infants are not the common finding in cases with a history of infection during pregnancy. Hence, the recommendation for abortion is not set. In the area where asymptomatic infection is very common, the early diagnosis might be useful for some purposes, such as epidemiological monitoring, but it should not be the presumptive data for decision on abortion for the pregnant woman infected with Zika virus.

Conflicts of interest
None to declare.

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Answer – Abortion and Zika Virus Congenital Infection

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We would like to thank for the comments of the letter to the editor about our article "Abortion in Cases of Zika Virus Congenital Infection."[1] Intrauterine consequences have become a focus of concern when it comes to Zika virus infection.[2] As for the first statement: "There is still no evidence that Zika virus infection in pregnant women is the cause of abortion," in fact, there are records in the scientific literature that strongly suggest this association and report intrauterine fetal death and spontaneous abortion,[3,4] both precocious[4] and late,[2] caused by the Zika virus and confirmed by serological tests on the fetus and the placenta.

We agree with our colleagues about the statement that not all cases of maternal infection by the Zika virus have as a result a fetus with microcephaly. This was initially demonstrated by a series of cases of babies born with normal cephalic perimeter, despite the confirmation of infection of the mother.[5] In view of these findings, there is no doubt that the maternal infection by the Zika virus is not a reliable evidence of fetal infection. However, in our article,[1] we present data that indicate that pregnant women throughout the world, due to the psychological distress and the epidemiology of fetal infection, may be deciding whether to undergo an induced abortion after being infected by the Zika virus Thus, we reinforce the statement that: "Early diagnosis may be useful for some purposes such as epidemiological monitoring, but should not be the presumptive data for the decision on abortion for the pregnant woman infected with zika virus."

We believe that an early diagnosis provides the woman with a better understanding of the fetal situation, which empowers and enables her to decide what would be the best for her and the fetus, according to the law of each country.

Conflicts of Interest
None to declare.

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Preterm Preeclampsia and Timing of Delivery: A Systematic Literature Review

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Rev Bras Ginecol Obstet 2018;40:499.

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Dear Editor,

Hypertensive disorder is the major cause of maternal mortality and morbidity in Brazil and Latin America.[1] Immediate delivery improves maternal and perinatal outcomes in preeclampsia cases over 37 weeks of gestation.[2,3] However, there is no consensus in the literature regarding preeclampsia cases between 34 and 37 weeks of gestation. Guida et al (2017) [4] conducted a systematic review to determine the best timing of delivery for women diagnosed with preeclampsia before 37 weeks of gestation, providing an update on the available evidence. This is an important issue. However, some limitations of this review should be discussed.

The most critical issue regards the search strategy. First, the authors used only one database (Medline). According to the Cochrane Handbook for Systematic Reviews, three databases should be considered when searching for trials: Medline, Embase and CENTRAL.[5] In Brazil, the Ministry of Health recommends that a systematic review should include at least five databases; four essential databases (Medline, Embase, CENTRAL and Lilacs) and one area-specific database.[6] This is an important issue because this procedure ensures that all evidence can be found. Secondly, the search strategy was limited to a 3-year period. This approach ignores all evidence produced before and is not recommended, especially in an update paper.[5] Lastly, the authors reported that the search in the Medline was performed using Medical Subject Headings (MeSh) (*preeclampsia*, *parturition* and *timing of delivery*). However, these search terms are not sufficient, and MeSh such as "*Labor*, *Obstetric*," "*Delivery*, *Obstetric*" and "*labor*, *Induced*" should also be included. All these limitations combined would result in missing articles, influencing the results of this review.

Another important limitation is the lack of risk of bias assessments (qualitative assessment). This tool evaluates the risk of overestimating or underestimating the true effect of the intervention. This is the only available strategy to evaluate internal validity—an important criterion in epidemiologic studies. Therefore, according to the Cochrane Handbook for Systematic Reviews, a qualitative assessment is part of the systematic review method.[5]

In addition, Guide et al (2017)[4] pointed out several recommendations based on the results of this review. However, these recommendations were not classified according to the grading of recommendations assessment, development and evaluation (GRADE) system, taking into account the level of evidence and grading of recommendations.[7]

In summary, this review analyzed an important question; however, the authors should have performed an exhaustive search of the literature and used an appropriate methodological approach. Due to these limitations, any conclusion or recommendation concerning the results of this review should be interpreted with caution.

Conflicts of Interest
None to declare.

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Answer to: Preterm Preeclampsia and Timing of Delivery: A Systematic Literature Review

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Rev Bras Ginecol Obstet 2018;40:500.

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Dear Editor,

We thank Leite T. and Paravidino V. B. for the interest and thoughtful comments, and we agree that the topic of this article is of great clinical relevance.[1] We acknowledge the concern about methodological issues, such as time period and search strategy; and we hope to further clarify the approach used. The review was supported by the National Brazilian Specialized Committee on Preeclampsia of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO, in the Portuguese acronym), aiming to enable national awareness regarding the most important cause of maternal mortality and morbidity in our scenario. This group of specialists revised the presented results and sought to ensure a simple and clear text and method, mostly for an audience of clinicians.

The decision of considering the restricted period (between 2014 and 2017) was mainly due to two reasons. The first one was to reflect the new recommendations adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP), which has broadened the definition of preeclampsia after 2013.[2] Since then, preeclampsia is diagnosed not only if there is a new onset of hypertension and proteinuria, but also if hypertension and significant end-organ dysfunction without proteinuria occur after 20 weeks of gestation. The second reason was to consider a period after which there was a similar Cochrane review.[3] A systematic review is a method to synthesize the available evidence using an explicit, transparent approach, and this was indeed performed.

The present review aimed to update the available evidence on the best timing of delivery for preterm preeclampsia. We do understand all the requirements on the Cochrane Handbook for Systematic Reviews and also acknowledge previous published reviews on the topic by the Cochrane initiative.[3,4] However, the 2013 Cochrane review[3] considered preeclampsia cases between 24 and 34 weeks of gestation, and the 2017 Cochrane review considered cases between 34 weeks of gestation and term pregnancy.[4] We have decided to consider both, before and after 34 weeks of gestation, and to present results in a comprehensive way, to guide counseling. This is why we even included a box that presented "How to talk with pregnant mothers and their families about the risks, benefits and uncertainties of immediate delivery versus expectant management when preterm preeclampsia is diagnosed."

The other key concern about the search strategy is also very relevant. We did initially use many other Medical Subject Headings (MeSh) terms, but chose the simplest combination of terms, with no loss of retrieved articles. To make sure this was true, we have now performed again the same search using the suggested terms and have retrieved the exact same final papers. The same happened with the databases. We should have stated that Lilacs and Embase were searched, but we again chose to present the most straightforward approach.

It is clear from the thoughtful comments presented that there are still unanswered questions on this topic, and we hope to stimulate future studies to guarantee adequate patient care and counseling in cases of preterm preeclampsia. We invite the comment authors to join forces in future researches and reviews on the topic.

Conflicts of Interest
None to declare.

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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.

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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:

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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.

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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

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

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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?

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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.

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

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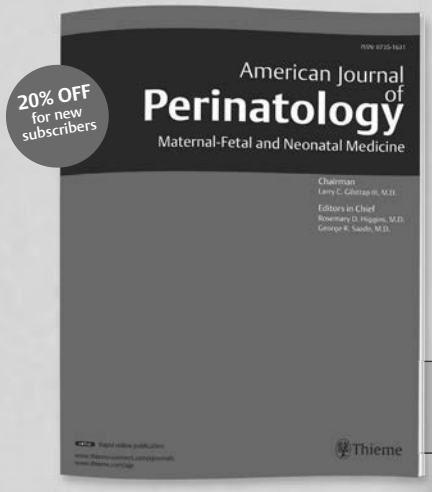

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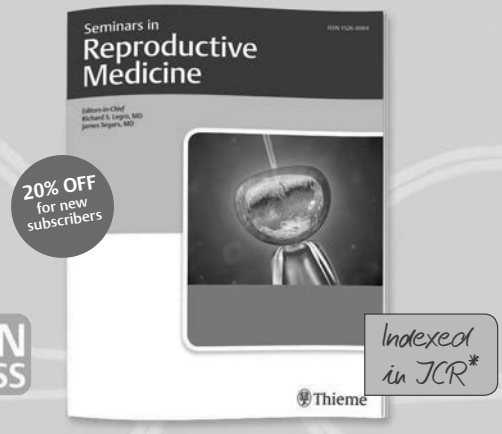

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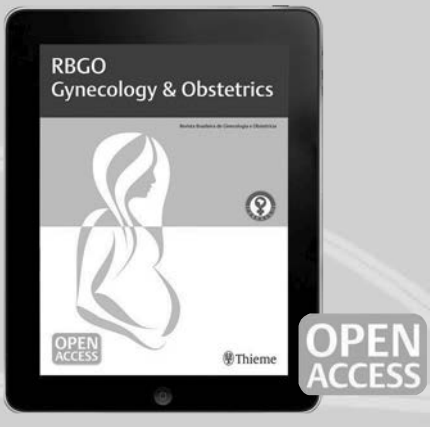

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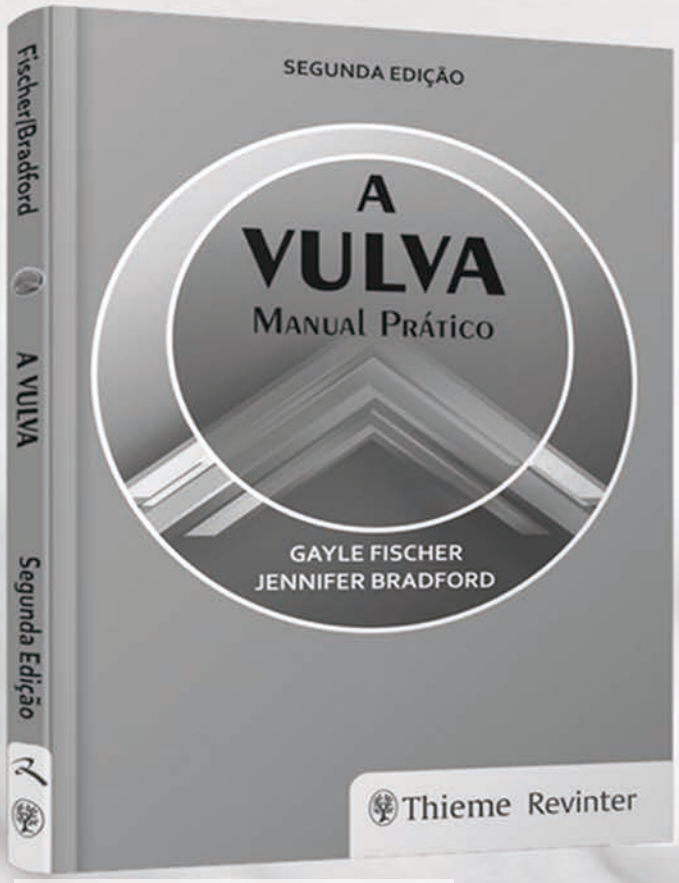

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