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Peripartum Hysterectomy: Is There Any Difference Between Emergency and Planned Surgeries?

Histerectomia periparto: Existe alguma diferença entre as cirurgias de emergência e planejada?

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Abstract

Objective To compare the outcomes of emergency and planned peripartum hysterectomies.

Methods The present retrospective cross-sectional study was conducted in two hospitals. Maternal and neonatal outcomes were compared according to emergency and planned peripartum hysterectomies.

Results A total of 34,020 deliveries were evaluated retrospectively, and 66 cases of peripartum hysterectomy were analyzed. Of these, 31 were cases of planned surgery, and 35 were cases of emergency surgery. The patients who underwent planned peripartum hysterectomy had a lower rate of blood transfusion (83.9% versus 100%; $p = 0.014$), and higher postoperative hemoglobin levels (9.9 ± 1.3 versus 8.3 ± 1.3; $p < 0.001$) compared with the emergency hysterectomy group. The birth weight was lower, although the appearance, pulse, grimace, activity, and respiration (Apgar) scores were higher in the planned surgery group compared with the emergency cases.

Conclusion Planned peripartum hysterectomy with an experienced team results in less need for transfusion and improved neonatal outcomes compared with emergency peripartum hysterectomy.

Keywords

- abnormal placentation
- emergency
- peripartum hysterectomy
- planned
- uterine atony

Resumo

Objetivo Comparar os resultados das histerectomias periparto de emergência e planejada.

Métodos Este estudo transversal retrospectivo foi realizado em dois hospitais. Os resultados maternos e neonatais foram comparados de acordo com as histerectomias periparto de emergência e planejada.

Resultados Um total de 34.020 partos foram avaliados retrospectivamente, e 66 casos de histerectomia periparto foram analisados. Destes, 31 eram casos de cirurgias planejadas, e 35, cirurgias de emergência. As pacientes que foram submetidas à

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histerectomia periparto planejada tiveram uma taxa menor de transfusão de sangue (83,9% *versus* 100%; $p = 0{,}014$), e níveis mais elevados de hemoglobina pós-operatória ($9{,}9 \pm 1{,}3$ *versus* $8{,}3 \pm 1{,}3$; $p < 0{,}001$) em comparação com o grupo de histerectomia de emergência. O peso ao nascer foi menor, embora as pontuações na escala de aparência, frequência cardíaca, irritabilidade reflexa, tônus muscular, e respiração (*appearance*, *pulse*, *grimace*, *activity*, *and respiration*, Apgar, em inglês) fossem maiores no grupo da cirurgia planejada em comparação com os casos de emergência.

Conclusão A histerectomia periparto planejada com uma equipe experiente resulta em menos necessidade de transfusão e melhora os resultados neonatais em relação à histerectomia periparto de emergência.

Palavras-chave
- placentação anormal
- de emergência
- histerectomia periparto
- planejada
- atonia uterina

Introduction

Peripartum hysterectomy (PPH) is an important surgical procedure that is typically used to prevent maternal mortality from uterine hemorrhage and sepsis. It was first performed at the end of the nineteenth century as a life-saving procedure.[1] The incidence of PPH varies between 0.2 and 6.09 for every thousand deliveries.[2,3] The important risk factors for PPH are age, previous cesarean sections, previous uterine surgery, labor induction, abnormalities in placental invasion, and uterine atony.[4,5] Recent studies[3,6] have reported that the most common indication for PPH was placental invasion anomalies, although uterine atony and uterine rupture were the most frequent reasons to perform PPH in the past.[7,8] The increasing trend in cesarean sections might change the indications in favor of anomalies in placental invasion.[9] Most PPH procedures are performed in an unplanned or emergency situation to prevent life-threatening hemorrhage after unsuccessful conservative approaches such as prostaglandins, tamponade, and compression sutures within 24 hour of a delivery. The morbidity or mortality rates increase with unprepared conditions such as lack of surgical experience and insufficient blood transfusion. Contrary to that, prenatally diagnosed and planned cesarean hysterectomy provides results in low intraoperative bleeding and complications.[10] It also enables surgeons to prepare safe surgical procedures, to prevent morbidities with no increase in intra-/postoperative complications.[11] The aim of the present study was to compare the intra-, postoperative, and neonatal outcomes of patients who underwent emergency or planned PPHs.

Methods

The present retrospective study was conducted in the Departments of Obstetrics and Gynecology of two hospitals (one tertiary center, and one government hospital) over a period of 23 years. The study was approved by the Research Ethics Committee of the School of Medicine of Eskisehir Osmangazi University (Ref. No: E.98130–2019/19). All women who underwent PPH were included in the study population. Peripartum hysterectomy was defined as hysterectomy performed after 24 weeks of gestation and at the time, or within 24 hours, of delivery. The data of the patients were collected from the medical records, which were reviewed for maternal characteristics such as age, gravidity, parity, gestational age, previous cesarean delivery, and mode of delivery. The preoperative laboratory parameters and indications for surgery were also recorded. The exclusion criteria were as follows: delivery before 24 weeks of gestation and hysterectomy after 24 hours of delivery. The type of the surgery, the intraoperative and postoperative complications, such as ureteral injury, bladder injury, retroperitoneal hematoma, nerve injury, and vessel injury, were investigated. The transfusion of blood products such as red blood cells and fresh frozen plasma performed during and after surgery were measured. The neonatal outcomes were also evaluated, such as birth weight and appearance, pulse, grimace, activity, and respiration (Apgar) scores. The patients were divided into the emergency and planned PPH groups, and the data were compared according to this categorization. Emergency PPH are performed in cases of uncontrollable bleeding with conservative treatment modalities, such as prostaglandins, oxytocics and baloon tamponade. Emergency hysterectomies are performed especially in cases of uncontrollable bleeding and shock, or in cases of previous hemodynamic or hemostatic restoration. Moreover, any type of vascular control is performed with an emergency hysterectomy if necessary. Planned PPH was defined as planned cesarean hysterectomy generally scheduled between the 34th and 37th weeks of gestation. We scheduled planned PPH with a dedicated team composed of an experienced gynecologic oncologist and a maternal-fetal medicine specialist. A preoperative evaluation was performed to determine the specific markers of abnormal placentation with the use of gray-scale and Doppler ultrasound. We administered antenatal corticosteroids before 34 weeks. We performed a midline vertical incision, and the uterus was incised at the fundus. The uterine incision was closed, and dissection of the retroperitoneum and bladder was carefully performed by an experienced surgical team that included a gynecologic oncologist. As much as possible, total abdominal hysterectomy was the main approach, but subtotal hysterectomy was performed in some cases.

The Statistical Package for the Social Sciences (SPSS, SPSS, Inc., Chicago, IL, United States) software, version 15.0, was

used to analyze the data. Demographic parameters and clinical outcomes were analyzed with mean ± standard deviation (SD) and median values. The Kolmogorov–Smirnov normality test was used to evalute the distribution of the parameters. Normally distributed data were analyzed by using independent samples *t*-test. The Mann-Whitney U test was used to compare the non-parametric continuous and categorical data. The percentages were compared with the Pearson Chi-squared test or the Fisher Exact test. Values of $p < 0.05$ were considered statistically significant.

Results

There were 34,020 deliveries during the study period. A total of 66 PPHs were performed, with an incidence of 1.9 for every thousand deliveries, and all cases of PPH were analyzed. The mean age of the patients was 31.3 ± 5.5 years. The gravidity ranged from 1 to 12, with a mean of 3.9 ± 2.4. The average gestational age was 35.7 ± 3.7 weeks. Of these 66 patients, 14 (21.2%) women delivered vaginally, and 52 (78.8%) women underwent cesarean sections. Half of the patients ($n = 33$; 50%) had at least 1 previous cesarean section. The most common indications for PPH among the sample were placenta accreta ($n = 26$; 39.4%) and uterine atony ($n = 20$; 30.3%). Overall, 24 (36.4%) patients underwent subtotal abdominal hsyterectomy, and 42 (63.6%) patients, total abdominal hysterectomy. Planned PPHs were performed in 31 (47%) patients, while emergency PPHs were performed in 35 (53%) cases. ►**Table 1** summarizes the demographic and clinical parameters of the emergency and planned PPH groups. The mean gestational age was significantly lower in the planned PPH group ($p = 0.002$). Moreover, more than 90% ($n = 28$) of the patients in the planned group delivered after 34 gestational weeks. The indications for PPH among the study groups are shown in ►**Table 2**. Uterine atony was the most common indication in the emergency group, whereas abnormal placentation was the most common indication in the planned group (57.1%, $n = 20$ and 67.7%, $n = 21$ respectively). We compared the blood transfusions, postoperative laboratory values, and intraoperative complications of both groups (►**Table 3**). The planned PPH group required the use of a significantly lower amount of blood products in the intra- and postoperative periods. The postoperative hemoglobin (Hb) and the differences in pre- and

Table 1 Demographic and preoperative parameters of the groups submitted toemergency and planned hysterectomies

	Emergency hysterectomy ($n = 35$)	Planned hysterectomy ($n = 31$)	*p*-value
Age (years)	31.9 ± 6.5	30.5 ± 4.1	0.18
Gravidity	3.9 ± 2.6	4.1 ± 2.1	0.36
Parity	2.9 ± 2.6	2.6 ± 1.8	0.94
Mean gestational age (weeks)	36.3 ± 4.9	35.2 ± 1.8	0.002
Gestational age (weeks) – n(%)			
< 28	2(6.3)	0(0)	0.169
28–34	5(15.6)	3(9.7)	
> 34	25(78.1)	28(90.3)	
Mode of delivery – n(%)			
Vaginal delivery	14(40)	0(0)	0.001
Cesarean delivery	21(60)	31(100)	
Previous cesarean section – n(%)	7(20.0)	26(83.9)	0.001
Preoperative hemoglobin (g/dL)	10.1 ± 2.2	10.8 ± 1.2	0.10
Preoperative hematocrit (%)	32.1 ± 5.8	32.4 ± 3.0	0.84
Preoperative platelet count ($\times 10^9$/L)	222.0 ± 73.6	203.2 ± 58.5	0.30

Table 2 Indications for peripartum hysterectomy

	Emergency hysterectomy ($n = 35$)	Planned hysterectomy ($n = 31$)	Overall ($n = 66$)
Uterine atony – n(%)	20(57.1)	0(0)	20(30.3)
Uterine rupture – n(%)	9(25.7)	0(0)	9(13.6)
Placenta previa – n(%)	1(2.9)	2(6.5)	3(4.5)
Placenta accreta – n(%)	5(14.3)	21(67.7)	26(39.4)
Placenta percreta – n(%)	0(0)	8(25.8)	8(12.1)

Table 3 Intra- and postoperative outcomes of the patients submitted to emergency and planned hysterectomies

	Emergency hysterectomy ($n = 35$)	Planned hysterectomy ($n = 31$)	*p*-value
Red blood cell transfusion – n(%)	35(100)	26(83.9)	0.014
Number of red blood cell transfusions (units)	6.0 ± 5.0	3.9 ± 3.7	0.06
Fresh frozen plasma transfusion – n(%)	34(97.1)	23(74.2)	0.007
Number of fresh frozen plasma transfusions (units)	5.9 ± 5.4	2.5 ± 2.1	0.001
Postoperative hemoglobin (g/dL)	8.3 ± 1.3	9.9 ± 1.3	< 0.001
Postoperative platelet count ($\times 10^9$/L)	119.0 ± 55.8	158.3 ± 44.3	0.12
Difference between pre- and postoperative hemoglobin (g/dL)	1.7 ± 1.5	0.9 ± 0.7	0.03
Difference between pre- and postoperative hemoglobin (after transfusions; g/dL)	7.8 ± 5.9	4.8 ± 4.6	0.02
Vessel injury – n(%)	0(0)	0(0)	1
Nerve injury – n(%)	1(3)	0(0)	0.39
Retroperitoneal hematoma – n(%)	1(3)	0(0)	0.40
Bladder injury – n(%)	4(11)	14(45)	0.38
Ureteral injury – n(%)	0(0)	1(3)	0.39
Duration of hospital stay (days)	8.2 ± 5.9	6.9 ± 3.5	0.57

Table 4 Neonatal outcomes of the sample

	Emergency hysterectomy ($n = 35$)	Planned hysterectomy ($n = 31$)	*p*-value
Birth weight (g)	3041 ± 1186	2564 ± 491	0.003
Apgar scores			
1 minute	4.9 ± 3.4	7.5 ± 1.9	0.001
5 minutes	6.5 ± 3.9	9.2 ± 1.1	0.006

postoperative Hb values were also significantly different between the study groups. The complication rates were similar in both groups. The duration of the hospital stay was shorter in the planned group, but it did not reach statistical significance. ►**Table 4** shows that the neonatal outcomes were significantly different between the groups. The mean birth weight was significantly lower in the planned group, and it might be related to the earlier gestational week at the time of the surgery. Although we have demonstrated the lower birth weight in the planned group, the Apgar scores of this group were significantly better than those of the emergency group ($p < 0.01$).

Discussion

The present study showed that the most common indication for PPH was placenta accreata, a subgroup of placental invasion anomalies. The planned PPHs resulted in a lower rate of morbidities and better neonatal outcomes compared with the emergency procedures, which, in turn, required a greater amount of blood products.

The incidence of PPH varies widely. In a large-scaled meta-analysis,[6] the incidence found was of 0.9 for every thousand deliveries. A retrospective cohort study[12] from Pakistan showed a higher incidence, of 4.01 for every thousand deliveries. We have also observed PPH with an incidence of 1.7 for every thousand deliveries in a previous study from our tertiary center.[13] There are several studies that have assessed PPHs, and the incidence may change among countries and centers depending on whether they have sufficient antenatal care for pregnancies. In some studies[7,14–17] from Turkey, the incidence of PPH was established between 0.3 and 5.38 for every thousand deliveries. Sharma et al.[3] found a much higher incidence, of 6.9 for every thousand deliveries. The incidence found in the present study was similar to those found in previous studies, and in accordance with other Turkish studies.[11,13,14,21,23] In the past, the most common indication used to be uterine atony.[7,8] However, recently, the main indication has been shifted from uterine atony to abnormal placentation.[18] The rising rates of cesarean delivery may result in placental pathologies, increasing the rates of PPH.[6,19–21] In a study published in 2016, van den Akker

et al.[6] evaluated ~ 8 million deliveries, and reported that placental abnormalities were the most common indication for PPH, followed by uterine atony. In a recent study, Kazi[12] found that emergency PPH was performed in cases of hemorrhage primarily due to uterine atony. Senturk et al.[17] suggested that the incidence of PPH was higher in Eastern Turkey, and the main indication was uterine atony and rupture. The increasing use of uterotonics and rate of cesarean sections may explain the shift on the main indication for PPH from uterine atony to abnormal invasive placentation.[3,6,19,22–24] Morbidly adherent placenta has gained prominent as an indication, especially in planned cesarean PPH.[3] Briery et al.[11] reported that uterine atony was the indication for emergency PPH in over half of the patients, and placenta accreta was the second most frequent indication. In a retrospective study, Sharma et al.[3] showed that placenta accreta was observed in all of the elective PPH patients. We found similar results in accordance to the recent literature.[3,6,11,12,17] The rate of cesarean sections has increased over the years; in the present study, it was of 63.6%. Therefore, placental abnormalities were present in 56% of patients. We have also determined that the indication for PPH was only abnormal placental pathologies in the planned group. We have performed total abdominal hysterectomy in 63.6% ($n = 42$) of the patients, with no significant differences between both study groups. Subtotal hysterectomy is more desirable for surgeons, because removal of the cervix may be difficult due to possible dilation in cases of PPH. As aforementioned, total abdominal hysterectomy was performed more frequently in the present study. Some studies[7,20] have demonstrated that subtotal abdominal hysterectomy is more suitable, especially in cases of abnormalities in placental invasion, and the morbidity was lower than that of cases of total abdominal hysterectomy. However, some researchers[5,8] have suggested the performance of total abdominal hysterectomy if the patient is in good condition, and they have indicated that this procedure should be considered to prevent hemorrhage from the cervix.

Studies[8,11] have established that intraoperative bleeding is higher in cases of emergency PPH compared with scheduled cases. In a recent prospective-cohort study, Seoud et al.[25] have observed lower volumes of intraoperative bleeding in the elective surgery group, and they have also found that a lower amount of blood products were transfused in the elective cases. In parallel with the higher blood loss, there is a higher amount of transfused blood products in PPH. In the present study, we observed that all of the patients in the emergency group received red blood cell transfusions, and transfusions were necessary in 83.9% ($n = 26$) of the planned surgery group ($p = 0.014$). We have also determined that lower volumes of fresh frozen plasma transfusion were required in the planned group. Wei et al.[26] reported a rate of 95% of red blood cell transfusion, and Sak et al.[27] reported a rate of 62.2% among placenta accreta patients. Briery et al.[11] compared the rates of transfusion of red blood cells between patients undergoning emergency and planned cesarean hysterectomies, and they observed rates of 66% and 33%, with a mean of 4.5 and 1.6 of transfused units respectively ($p < 0.05$). Seoud et al.,[25] in their prospective-cohort study, also found that elective surgery was associated with lower rates of blood transfusion compared with emergency surgery.[25] In another retrospective study,[3] the authors reported lower postoperative Hb values in the emergency surgery group compared with the planned group, but without statistical significance (7.8 ± 1.6 versus 8.9 ± 2.2 respectively; $p = 0.08$). In the present study, we have also found significantly lower levels of Hb in the emergency group. The transfused units of red blood cells and fresh frozen plasma were higher in the emergency group. Similar to our study, Seoud et al.[25] established that the transfusion rate and mean transfused units were higher in the emergency cases. We have also analyzed the difference between preoperative and postoperative Hb levels, and found lower differences in the planned cases compared with emergency cases. A higher rate of complications is expected in the emergency PPH group. Bladder injury, which is the most common complication, ranges from 3% to 20% in several studies.[3,7,12,17,23] In the present study, the incidence of bladder injury (27.2%, $n = 18$) was higher than that reported in the literature, and the planned group had a higher rate of bladder injury than emergency group, but this was not statistically significant. We believe that the higher rate may be related to the higher incidence of abnormal placental invasion in the planned group. Briery et al.[11] reported a higher incidence of postoperative complications in the group submitted to emergency cesarean hysterectomy. Two studies[11,25] have established that the length of the hospital stay was similar between the two groups, but Pettit et al.[28] reported a shorter hospital stay in the planned group. We have also observed a slightly longer hospital stay in the emergency group, which was not statistically significant, and was similar to the literature findings.

Neonatal outcomes are important in PPHs. In emergency procedures, these outcomes may be affected negatively, so we can improve the neonatal outcomes by performing planned PPHs in selected patients with proper timing. Seoud et al.[25] reported similar birth weight and Apgar scores among elective and emergency cases. Pettit et al.[28] also compared the neonatal outcomes and reported similar Apgar scores for both groups. Otherwise, they found later gestational weeks and higher birth weights in the planned group. Briery et al.[11] reported that the planned group had later gestational weeks, and higher fetal birth weight and Apgar scores compared with the emergency group, which were not statistically significant. On the contrary, we have observed significantly later gestational weeks and higher birth weight in the emergency group. We have also observed significantly higher Apgar scores in the planned group, although their gestational weeks were later, and the birth weight, lower than those of the emergency group. A possible explanation for that may be administration of antenatal corticosteroids to all of the patients in the planned group prior to delivery.

Emergency PPH is a life-saving procedure, but it results in some postoperative problems. Thus, planned PPH may improve the maternal and neonatal outcomes and decrease the complication rates. The prenatal diagnosis of abnormal placental invasion becomes significant for the performance

scheduled surgery. One third of the cases of placental accreta diagnosed prenatally still delivered in an unplanned manner.[28] We think that it is not possible to completely avoid emergency cases. The ideal delivery time for cases of suspected abnormal placentation is still controversial. There were more optimal outcomes regarding the cases of placenta accreta with delivery at the 34th gestational week.[29] The American College of Obstetricians and Gynecologists (ACOG) recently recommended delivery at 34 weeks to 35 weeks and 6 days, especially in cases of suspected placenta accreta.[30] The ACOG also suggests performing the deliveries in cases of placenta accreta with an expert team in a tertiary center.[10]

The main limitation of the present study was its retrospective nature. The data of the study population covers a very wide time interval, so cases of uterine atony were more present in older data, and cases of placental pathologies were more prominent in the more recent data. This might establish a selection bias for the present study. However, in the present study, we have comprehensively compared emergency and planned PPHs, and the size of the sample was not large enough according to previous studies.[15,16,28] One of the limitations is the lack of information about the level of expertise of the surgeons in both study groups. Another important limitation is that we have compared different indications for emergency and planned surgeries, such as uterine atony and anomalies in placental invasion; since in cases of uterine atony, the uterine anatomy is not distorted compared to placental invasion anomalies such as placenta accreata.

Conclusion

We have shown that planning the PHP prenatally improved the maternal and neonatal outcomes. The prenatal diagnosis of suspected cases provides some surgical preparations such as ureteral catheter placement during the surgery. According to the aforementioned ACOG recommendations, we make an effort to diagnose the suspected cases prenatally, and we also currently perform planned PHPs from 34 weeks to 35 weeks and 6 days of gestation with an expert multi-disciplinary team. Further prospective studies are needed to investigate the correlation of planned PHP and perinatal outcomes.

Contributors

All authors participated in the concept and design of the study, as well as in the analysis and interpretation of data, draft or revision of the manuscript, and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests

The author have no conflict of interests to declare.

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Editorial

Testosterone Therapy for Women: Still Many Questions to be Answered

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In recent years, the biological role of androgens in the female organism has aroused increasing interest. Women in the reproductive period and after menopause produce androgens that contribute to ovarian function, sexual function, bone metabolism, cognition, among other actions. Despite the evidence of involvement of its excess in reproductive health disorders, studies on its deficiency have increased.

Androgen levels in the female body vary with age. In addition to peripheral conversion mechanisms, ovaries and adrenals are responsible for the production and maintenance of circulating androgenic levels. After a peak at between 18 and 24 years of age, a slow decline begins during the reproductive period, around 30 years of age, and at 70–80 years of age, serum levels of androgens will represent 10 to 20% of levels found at the age of 30. In this process, menopause by itself does not represent a moment of accentuated androgenic decline.[1,2]

Testosterone is the most potent androgen circulating in the female body and generally the most dosed. Prescription rates have increased recently under the justification of alleviating the symptoms arising from its lack. The question is: how to characterize androgen deficiency in women? What is the evidence for its use?

Symptoms of androgen deficiency at different stages of life are nonspecific. Complaints of reduced arousal, fantasies, sexual desire and interest, and reduced sense of wellbeing and motivation have been cited. Rarefaction and thinning of pubic hair, loss of muscle and bone mass, in addition to persistent and unexplained fatigue have been mentioned as well. Most of these manifestations can be easily confused with signs of aging or overload with the rhythm of life. A biochemical characterization for the diagnosis of androgen deficiency is also not recognized. Testosterone measurement is often performed using low accuracy techniques for female serum levels. Although some laboratories already use more recent technology and better sensitivity that allow new questions about normal or reduced levels, the interpretation of such results is still controversial. Added to this is the fact that clinical effects of androgens are tissue-specific and not necessarily related to serum levels. Thus, important world societies are against the use of androgenic serum dosages as indicators of disorders resulting from the insufficiency of such hormones, especially as predictors of sexual dysfunction.[1–3]

To reinforce this fact, studies with women undergoing bilateral oophorectomy, hence with a drop in androgen production, did not demonstrate a strong correlation between postoperative testosterone levels and sexual function. Given the difficulty in characterizing their deficiency, when would there be an indication to prescribe androgenic supplementation?

Most studies evaluating the use of testosterone have been conducted in women with sexual complaints. Evidence that female sexual function is associated with androgenic action is mainly based on studies that observed improvement in hypoactive sexual desire disorder (HSDD) in postmenopausal women treated with testosterone with or without concomitant use of conventional estrogen therapy.[4]

The fact that female sexual dysfunctions are influenced by numerous clinical, surgical, interrelational and social conditions must be taken into account. Hormonal changes represent an extra factor and should be included in this context. Although the literature provides evidence of improvement in HSDD with the use of testosterone in postmenopausal women, androgenic serum levels have not been indicated as predictors of a positive or a negative outcome. According to literature data, postmenopausal women who received testosterone improved their sexual function score, although with only a slight increase in the number of satisfying sexual episodes. Likewise, testosterone replacement has shown to be effective in women undergoing bilateral oophorectomy. Thus, women with HSDD, after excluding other causes, represent the most accepted indication for testosterone supplementation.[3–6]

Other debatable indications for using testosterone are for promoting wellbeing, mood and cognition. In postmenopausal

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women, evidence pointing to improvement in all these indications is insufficient. In this same group of women, studies also do not support the use of testosterone in physiological doses aimed at beneficial effects on bone mass or the distribution of body fat, muscle strength or body composition.[3]

The benefits of androgen replacement in women during the reproductive period are also inconclusive, with divergent acceptance among world societies in the case of well-characterized HSDD.[4,7]

Although interest in the use of androgens is on the rise, we emphasize that robust evidence guiding their indication is not growing at the same speed. Until new evidence emerges, we recommend that physicians choose according to each individual and prescribe androgens sparingly always using physiological doses, respecting current scientific knowledge, and guide and discuss with their patients about the relative ignorance of the risks and benefits of using androgens, in particular regarding long-term safety.

Many world societies have manifested in this direction. The National Commission Specialized in Endocrine Gynecology (Portuguese acronym: CNEGE) of FEBRASGO, the Brazilian Federation of Gynecology and Obstetrics Associations, performed an extensive literature review and pointed out their positions on this very debatable subject. These positions are being published in two articles divided according to recommendations for women's reproductive phase or climacteric with the aim to help health professionals in decision-making, whether for patient assessment or the indication of androgen therapy, its dosage and reassessment of results.[8,9]

Conflicts of Interest:
None to declare.

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Short and Medium-term Outcomes of Omphalocele and Gastroschisis: A Survey from a Tertiary Center

Resultados a curto e médio prazo do onfalocelo e gastrosquisis: uma investigação de um centro terciário

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Abstract

Objective To characterize and compare the outcomes of omphalocele and gastroschisis from birth to 2 years of follow-up in a recent cohort at a tertiary center.

Methods This is a retrospective clinical record review of all patients with gastroschisis and omphalocele admitted to the Neonatal Intensive Care Unit between January 2009 and December 2019.

Results There were 38 patients, 13 of whom had omphalocele, and 25 of whom had gastroschisis. Associated anomalies were present in 6 patients (46.2%) with omphalocele and in 10 (41.7%) patients with gastroschisis. Compared with patients with omphalocele, those with gastroschisis had younger mothers (24.7 versus 29.6 years; $p = 0.033$), were born earlier (36 versus 37 weeks, $p = 0.006$), had lower birth weight (2365 ± 430.4 versus 2944.2 ± 571.9 g; $p = 0.001$), and had a longer hospital stay (24 versus 9 days, $p = 0.001$). The neonatal survival rate was 92.3% for omphalocele and 91.7% for gastroschisis. Thirty-four patients were followed-up over a median of 24 months; 13 patients with gastroschisis (59.1%) and 8 patients with omphalocele (66.7%) had at least one adverse event, mainly umbilical hernia (27.3% vs 41.7%), intestinal obstruction (31.8% vs 8.3%), or additional surgical interventions (27.3% vs 33.3%).

Keywords
- omphalocele
- gastroschisis
- anomalies
- abdominal-wall defect
- morbidity

[*] *Both authors have contributed equally to this work and share first authorship.*

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Conclusion Despite the high proportion of prematurity, low birth weight, and protracted recovery, gastroschisis and omphalocele (without chromosomal abnormalities) may achieve very high survival rates; on the other hand, complications may develop in the first years of life. Thus, a very positive perspective in terms of survival should be transmitted to future parents, but they should also be informed that substantial morbidity may occur in the medium term.

Resumo

Objetivo Caracterizar e comparar os desfechos do onfalocelo e gastrosquisis desde o nascimento até aos 2 anos de seguimento numa coorte recente de um centro terciário.
Métodos Este é um estudo retrospectivo em que foi feita uma revisão dos registos clínicos de todos os pacientes com gastrosquisis e onfalocelo que foram internados na unidade de cuidados intensivos neonatais, entre janeiro de 2009 e dezembro de 2019.
Resultados Identificamos 38 pacientes, 13 dos quais tinham onfalocelo e 25 dos quais tinham gastrosquisis. Anomalias associadas estavam presentes em 6 pacientes (46.2%) com onfalocelo e 10 (41.7%) com gastrosquisis. Comparativamente com os pacientes com onfalocelo, os pacientes com gastrosquisis tinham mães mais jovens (24.7 versus 29.6 anos; $p = 0.033$), nasceram mais precocemente (36 versus 37 semanas, $p = 0.006$), com menor peso ao nascimento ($2{,}365 \pm 430.4$ versus $2{,}944.2 \pm 571.9$ g; $p = 0.001$), e o internamento teve uma duração mais longa (24 versus 9 dias, $p = 0.001$). A taxa de sobrevivência neonatal foi de 92.3% para o onfalocelo e 91.7% para a gastrosquisis. Trinta e quatro pacientes foram seguidos durante um tempo mediano de seguimento de 24 meses: 13 com gastrosquisis (59.1%) e 8 com onfalocelo (66.7%) apresentaram pelo menos um evento adverso, sobretudo hérnia umbilical (27.3% vs 41.7%), obstrução intestinal (31.8% vs 8.3%) ou intervenções cirúrgicas adicionais (27.3% vs 33.3%).
Conclusão Apesar da alta proporção de prematuridade, de baixo peso e de recuperação lenta, os gastrosquisis, assim como os onfalocelos (sem anomalias cromossómicas), podem ter uma taxa de sobrevivência muito alta; por outro lado, nos primeiros anos de vida, podem surgir complicações não desprezíveis. Assim, aos futuros pais pode ser transmitida uma perspectiva muito positiva em termos de sobrevivência, embora eles também devam ser informados de que pode ocorrer morbidade substancial no médio prazo.

Palavras-chave
- onfalocele
- gastrosquisis
- anomalias
- defeito da parede abdominal
- morbidade

Introduction

Gastroschisis and omphalocele are the most common congenital abdominal wall defects, with a prevalence of ~ 2 to 4 per 10,000 live births, respectively.[1] The etiology of these defects remains poorly understood. In contrast to omphalocele, the prevalence of gastroschisis has been increasing worldwide in recent decades.[1]

Omphalocele is a midline abdominal wall defect in which varying amounts of bowel and liver, and occasionally other organs, protrude through the base of the umbilicus into a membranous sac. The intestines are generally morphologically and functionally normal.[2] Prognosis is determined mainly by the associated anomalies but also by the size of the defect and degree of liver exteriorization.[3,4] Omphalocele with co-occurring anomalies, which represents over 60% of cases of omphalocele, is associated with a high rate of pregnancy terminations and intrauterine fetal deaths and a significant rate of mortality in the neonatal period and at 1 year of age.[3,5,6] Infants with isolated omphalocele have the best survival rate.[5,6]

Gastroschisis is as an abdominal wall defected, in which bowel and sometimes other abdominal organs herniate into the amniotic cavity without a membranous protective sac. The prognosis of infants with gastroschisis is primarily determined by the degree of intestinal injury.[2,7] In contrast to omphalocele, the bowel in patients with gastroschisis is usually damaged due to chronic exposure to amniotic fluid, which results in a varying period of bowel dysmotility after birth, requiring prolonged parenteral nutrition and hospitalization.[8–10] Associated anomalies are present in 8 to 34% of cases, most of them in the gastrointestinal tract.[8,11] Extraintestinal and chromosomal abnormalities or recognizable syndromes are rare.[8]

Despite advances in prenatal diagnosis, surgical management and neonatal critical care over the last decades have resulted in improvement of survival rates of infants born with gastroschisis and omphalocele, the survivors are still at

significant risk of short and long-term adverse outcomes.[3,12] These include growth delay, neurodevelopmental deficiencies, recurrent abdominal pain, feeding difficulties, pulmonary insufficiency, recurrent infections, umbilical revision for hernia or scar repair, bowel obstruction requiring surgical treatment, and other surgical problems.[3,13] Efforts have been made to identify prenatal risk factors associated with gastroschisis and omphalocele,[14] the optimal timing and route of delivery,[15,16] immediate *vs* staged repair,[17,18] and other factors that may be amenable to improve outcomes as well to reduce the treatment costs. However, many of these issues still lacks consensus.[7,8,10]

The aim of the present study was to retrospectively review recent live births with gastroschisis and omphalocele, managed at our tertiary care center, regarding demographic features, associated anomalies, neonatal outcomes, and progress of the survivors until 2 years of age.

Methods

This is a retrospective study of all patients with gastroschisis and omphalocele that were born alive and were admitted to the Neonatal Intensive Care Unit of Centro Hospitalar Universitário de São João (CHUSJ), a tertiary center in Portugal, between January 2009 and December 2019. Elective terminations, spontaneous miscarriages, and intrauterine fetal deaths were excluded from our study. The present study received approval from the ethics committee of CHUSJ.

All data were obtained from the medical records of patients. Maternal information included age, parity, and previous abortions. Obstetric data included diagnosis (if prenatal, gestational age) and complications (amniotic fluid volume alterations, intrauterine growth restriction, gestational diabetes, and other). For the purposes of this study, intrauterine growth restriction (IUGR) was defined as birth weight below the 10th percentile. Gestational age at birth, mode of delivery, gender, birth weight, resuscitation, meconium aspiration, APGAR scores, herniated organs, time and type of surgical repair, and other surgeries during the first hospitalization were also obtained.

The morbidity indicators evaluated were length of hospital stay, duration of parenteral nutrition, time to initiate enteral feeding, need of mechanical ventilation, ventilator duration, complications (intestinal occlusion, necrotizing enterocolitis, and sepsis among others), and discharge with parenteral nutrition. Data of co-occurring major anomalies were also collected. We defined a major congenital anomaly as an anomaly that create significant medical problems for the patient or that require specific surgical or medical management.[19,20] Anomalies considered physiologic (e.g., patent foramen ovale), transient or minor, were excluded. The classification of omphaloceles in giant/large or small was based on the defect size and on the qualitative descriptions ("small," "large" and "giant") used by pediatric surgeons in surgical reports. Giant omphalocele was defined as a defect with a diameter greater than 5 cm and/or containing greater than 75% of the liver in the sac.[3] Complex gastroschisis was defined as gastroschisis associated with at least one of the following intestinal complications: atresia, volvulus, perforation, and necrosis.

The follow-up during the first 2 years of life focused on the following variables: presence of umbilical hernia, intestinal obstruction, surgical interventions, need for parenteral nutrition, need for supplemental oxygen, and anthropometric parameters (weight and length).

The outcomes of patients born with gastroschisis were compared with those of patients born with omphalocele. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ($\pm$ standard deviation) or median (P25–P75), in normal or skewed distribution, respectively. Categorical variables were described by absolute (n) and relative frequencies (%). For comparisons, parametric (independent *t*-test) and non-parametric (Mann-Whitney U test), tests were used for continuous variables with normal or skewed distribution, respectively. The Fisher exact test was used for comparisons involving categorical variables. Statistical significance was set at 5%. This study is reported in line with the STROBE checklist for observational studies.[21]

Results

There was a total of 38 patients, 13 with omphalocele and 25 with gastroschisis. All but two (one with omphalocele and one with gastroschisis) were diagnosed prenatally. One newborn with gastroschisis was transferred to another hospital on the 6th day of life and not subsequently followed-up at our institution.

Maternal and neonatal demographic data are summarized in ►**Table 1**. Maternal age was significantly lower for gastroschisis. Although not reaching statistical significance, there was a higher proportion of primigravida mothers in the gastroschisis group. There was no significant difference between omphalocele and gastroschisis regarding mother's history of previous abortions either.

There were 2 (5.3%) multiple pregnancies, both with twins, discordant for the defect (1 with gastroschisis and 1 with omphalocele). Abnormal amniotic fluid volume (oligohydramnios or polyhydramnios) and IUGR were present in 2 (15.4%) and 3 (23.1%) omphalocele pregnancies, respectively. For the 22 gastroschisis pregnancies with available fetal ultrasound information, 2 (9.1%) had abnormal amniotic fluid volume and 7 (31.8%) had IUGR.

Two patients with omphalocele were delivered vaginally, while the other patients were delivered by elective or emergency cesarean section. At birth, patients with gastroschisis presented a significantly lower gestational age than patients with omphalocele. This reflects the higher proportion of preterm deliveries associated with gastroschisis (80%) when compared with omphalocele (53.8%). Birth weight was significantly lower for patients with gastroschisis than for those with omphalocele. For both defects, there was a similar preponderance of males.

Visceral content exteriorized through the abdominal wall defect at birth and associated anomalies are shown

Table 1 Maternal and neonatal demographics

	Total ($n = 38$)	Omphalocele ($n = 13$)	Gastroschisis ($n = 25$)	*P*-value
Maternal age (years)	26.4 ± 6.8	29.6 ± 5.8	24.7 ± 6.8	0.033
Gestational age at diagnosis (weeks)	20 [13–24]	21 [12–22]	19 [13–27]	0.803
Primigravida	25 (65.8%)	7 (53.8%)	18 (72%)	0.301
Previous abortions	10 (26.3%)	4 (30.8%)	6 (25%)	0.709
Gestational age at delivery (weeks)	36 [35–37]	37 [36–38]	36 [34–36]	0.006
Mode of delivery				
vaginal	2 (5.3%)	2 (15.4%)	0	0.111
cesarean section	36 (94.7%)	11 (84.6%)	25 (100%)	
Gender				
Male	23 (60.5%)	7 (53.8%)	16 (64%)	0.728
Female	15 (39.5%)	6 (46.2%)	9 (36%)	
Birth weight (grams)	2,563.4 ± 551.1	2,944.2 ± 571.9	2,365 ± 430.4	0.001

Values are given as mean ± SD, median [P25 – P75] or n (%).

Table 2 Viscera exteriorized and associated anomalies

	Total ($n = 38$)	Omphalocele ($n = 13$)	Gastroschisis ($n = 25$)
Viscera exteriorized			
Bowel (only)	20 (52.6%)	6 (46.1%)	14 (56%)
Liver (only)	3 (7.9%)	3 (23.1%)	–
Bowel + liver	3 (7.9%)	3 (23.1%)	–
Bowel + liver + stomach + spleen	1 (2.6%)	1 (7.7%)	–
Bowel + stomach	5 (13.2%)	–	5 (20%)
Bowel + bladder and/or gonads	6 (15.8%)	–	6 (24%)
Associated anomalies, total *	16 (43.2%)	6 (46.2%)	10 (41.7%)
Beckwith-Wiedemann syndrome	2 (5.4%)	2 (15.4%)	–
Gastrointestinal anomalies, total	6 (16.2%)	–	6 (25%)
Bowel atresia	3 (8.1%)	–	3 (12.5%)
Enteric duplication cyst	1 (2.7%)	–	1 (4.2%)
Meckel diverticulum	2 (5.4%)	–	2 (8.3%)
Cardiac anomalies, total	3 (8.1%)	2 (15.4%)	1 (4.2%)
VSD	1 (2.7%)	1 (7.7%)	–
ASD	2 (5.4%)	1 (7.7%)	1 (4.2%)
Int-IVC	1 (2.7%)	1 (7.7%)	–
Central nervous system anomalies, total	4 (10.8%)	3 (23.1%)	1 (4.2%)
ACC	1 (2.7%)	1 (7.7%)	–
Nasal glial heterotopy	1 (2.7%)	1 (7.7%)	–
Hydrocephaly	1 (2.7%)	–	1 (4.2%)
Microcephaly	1 (2.7%)	1 (7.7%)	–
Cryptorchidism	3 (8.1%)	1 (7.7%)	2 (8.3%)
Hydronephrosis	1 (2.7%)	–	1 (4.2%)
Syndactyly	2 (5.4%)	–	2 (8.3%)

Abbreviations: ACC, agenesis of the corpus callosum; ASD, atrial septal defect; Int-IVC, interrupted inferior vena cava; VSD, ventral septal defect
Values are given as n (%)
*$n = 24$ for associated anomalies with gastroschisis due to missing information from 1 patient transferred to another hospital

Table 3 Comparison of clinical outcomes between patients with omphalocele and gastroschisis

	Total ($n = 38$)	Omphalocele ($n = 13$)	Gastroschisis ($n = 25$)	*P*-value
Resuscitation at birth	6 (15.8%)	3 (23.1%)	3 (12.0%)	0.392
APGAR Score				
1st minute < 7	4 (10.5%)	2 (15.4%)	2 (8%)	0.595
5th minute < 7	2 (5.3%)	1 (7.7%)	1 (4%)	1.000
Type of surgery				
Primary closure	33 (86.8%)	12 (92.3%)	21 (84%)	0.643
Staged closure (silo)	5 (13.2%)	1 (7.7%)	4 (16%)	
More than 1 surgery during hospital stay *, ¶	7 (18.9%)	2 (15.4%)	5 (20.8%)	1.000
Hospital stay (days) *	20 [11.5–31.5]	9 [5.5–17.5]	24 [15.8–36.8]	0.001
Need for mechanical ventilation	34 (89.5%)	11 (84.6%)	23 (92%)	0.595
Ventilator duration (days)	3 [1.8–5]	2 [1–3.5]	4 [2–6]	0.052
Parenteral nutrition duration (days) *	16 [9–27.5]	8 [3–13.5]	22.5 [14–34.5]	< 0.001
Initiation of enteral feeding (days of life) *	9.5 [4.8–14.5]	4 [2–5.5]	12 [9.5–19.5]	< 0.001
Complications during hospital stay, total*				
Sepsis	8 (21.6%)	1 (7.7%)	7 (29.2%)	0.216
Intestinal occlusion	2 (5.4%)	0	2 (8.3%)	0.532
Neonatal death *	3 (8.1%)	1 (7.7%)	2 (8.3%)	1.000

Values are given as median [P25–P75] or n (%)

*$n = 24$ for gastroschisis due to missing information from 1 patient transferred to another hospital

¶For omphalocele: silo placement after failed primary closure ($n = 1$), inguinal hernia repair and orchidopexy ($n = 1$). For gastroschisis: silo removal with or without intestinal atresia repair ($n = 3$), surgery for adhesion-related bowel obstruction ($n = 1$), surgical wound debridement ($n = 1$), intestinal atresia repair ($n = 1$)

in ►**Table 2**. Associated anomalies were present in 6 patients (46.2%) with omphalocele and in 10 (41.7%) with gastroschisis. Two male patients with gastroschisis had balanced translocations (t [6;8] [q13; p23.1] and t [2/9]) that were not associated with any known phenotype, and, therefore, were not included in the analysis. The translocation t(6;8)(q13; p23.1) was likely associated with infertility since the mother had had 5 previous pregnancy losses. Anomalies in the gastrointestinal tract were found only in patients with gastroschisis, the majority being bowel atresias. Of the 6 patients (24%) with complex gastroschisis, 2 presented with bowel atresia only, 1 presented with bowel atresia and perforation, and the other 3 presented with bowel perforation either alone or with other complications that define complex gastroschisis.

All patients with omphalocele had a normal karyotype. Genetic syndromes were found exclusively in patients with omphalocele (2 patients diagnosed with Beckwith-Wiedemann syndrome). There was a third patient with omphalocele and multiple anomalies in several organs, including one hemivertebrae, several cardiac malformations (mesocardia, ASD, interrupted inferior vena cava with azygos continuation to superior vena cava), and several facial abnormalities associated with Duane type 1 syndrome. There were 4 omphaloceles considered giant (30.8%), 3 of which had no associated anomalies. No patient had rupture of the omphalocele sac. One patient with a small omphalocele presented with ileum stenosis at birth.

Most patients had surgical repair of the abdominal wall defect on the first day of life, regardless of the type of the defect. Only one patient with omphalocele had surgery on the second day of life. Primary closure was achieved in 86.8% of the patients (►**Table 3**). Two patients (1 with complex gastroschisis and 1 with giant omphalocele) required silo placement after failed primary repair due to abdominal compartment syndrome. Both have died. For the other 3 patients (1 patient with complex and 2 with simple gastroschisis, respectively) who underwent staged closure, the mean time with silo was 10.7 days. Two patients with large omphaloceles required the use of a polytetrafluoroethylene (PTFE) patch. Intestinal atresia was repaired either in a second operation after primary closure (1 patient with complex gastroschisis) or during secondary abdominal closure (1 patient with complex gastroschisis). Intestinal stenosis (1 patient with complex gastroschisis and 1 patient with omphalocele) was repaired during primary closure.

Overall, patients with gastroschisis had a higher rate of complications during the hospital stay, as shown in ►**Table 3**. Sepsis and intestinal occlusion were more frequent, but without statistical significance, in patients with gastroschisis. Necrotizing enterocolitis was not found in any of the patients. Gastroschisis was significantly associated with a longer duration of parenteral nutrition and longer time to initiate enteral feeding. Patients with gastroschisis were hospitalized twice as long as patients with omphalocele. One of the patients with complex gastroschisis (bowel

Table 4 Adverse outcomes during the follow-up

	Total ($n = 34$)	Omphalocele ($n = 12$)	Gastroschisis ($n = 22$)	*P*-value
Patients with adverse outcomes	21 (61.8%)	8 (66.7%)	13 (59.1%)	0.727
Umbilical hernia	11 (32.4%)	5 (41.7%)	6 (27.3%)	0.459
Intestinal occlusion episodes	8 (23.5%)	1 (8.3%)	7 (31.8%)	0.210
Surgical interventions ¶	10 (29.4%)	4 (33.3%)	6 (27.3%)	0.714
Parenteral nutrition	1 (2.9%)	0	1 (4.5%)	1.000
Supplemental oxygen	1 (2.9%)	1 (8.3%)	0	0.353

Values are given as n (%)
¶The surgical interventions are listed in ►**Supplementary Table S1**

perforation only), who had an associated enteric duplication cyst, underwent a massive bowel resection during the primary repair surgery and developed ultra-short gut syndrome. One patient with Beckwith-Wiedemann syndrome, who had been born preterm (33 weeks) and with bronchopulmonary dysplasia, was discharged on nasogastric feeds and supplemental oxygen.

The neonatal survival rate was 92.3% for omphalocele and 91.7% for gastroschisis. All the three deaths occurred in the neonatal period and involved preterm neonates. Two deaths were of patients with gastroschisis. One of them presented complex gastroschisis with bowel and bladder exteriorized; the patient underwent silo placement and died on day 3 of life. The second patient was born by cesarean section in another hospital and suffered perinatal asphyxia. The death occurred on day 16 of life and was related with severe hypoxic-ischemic encephalopathy. The third patient was a twin born with a giant omphalocele containing the bowel, stomach, liver, and spleen. After failed primary closure, a silo was applied, but the patient died on day 3 of life.

Thirty-four patients were followed-up, with a median follow-up time of 24 months (range 11–24), and the outcomes are summarized in ►**Table 4**. Thirteen patients with gastroschisis (59.1%) and 8 patients with omphalocele (66.7%) had at least one adverse event during the follow-up. Ten patients (29.4%) needed further surgical interventions due to diverse comorbidities, and the details are given in ►**Supplementary Table S1** of the supplementary material. Seven patients with gastroschisis (31.8%) suffered intestinal obstruction episodes, with adhesions being the cause in 3 of them. Of the 5 surviving patients with complex gastroschisis, 3 underwent surgery for bowel obstruction during the follow-up period. Only 1 patient with omphalocele (8.3%) had bowel obstruction, and it was caused by an intestinal volvulus. The patient with complex gastroschisis that had ultra-short gut syndrome remained hospitalized for 788 days due to several complications (intestinal obstruction episodes and catheter-related infections) and lack of family support. Although it was possible to make progress to oral feeding, it was not possible to wean parenteral nutrition; therefore, one serial transverse enteroplasty (STEP) procedure was performed at 10 months. Despite that, the patient continued to be dependent on parenteral nutrition with irregular enteral tolerance during the follow-up period of our study. The patient with Beckwith-Wiedemann syndrome and bronchopulmonary dysplasia received supplemental oxygen until 1 year of age.

Anthropometric data at 2 years of follow-up was available for 7 patients with omphalocele and 15 patients with gastroschisis. Only 1 patient with omphalocele (patient 2 in ►**Supplementary Table S1**) that had been born with both weight and length below the 10th percentile was still below that percentile at 2 years of age. Of the 15 patients with gastroschisis, 3 had both weight and length at birth below the 10th percentile, 1 had birth length below the 10th percentile, and 1 had birth weight below the 10th percentile. Only 1 patient with gastroschisis had the length below the 10th percentile at 2 years of age, indicating improvement in the growth between birth and follow-up for most children.

Discussion

This study examines the detailed short and medium-term outcome of 38 live births with omphalocele and gastroschisis. This represents approximately an institutional prevalence of 10 cases per 10,000 live births; however, our center is a referral one for antenatal diagnosis and therapy; that figure is probably indicative of an estimated prevalence of 3 to 5 cases per 10,000 live births in the country, as reported by others.[5,22] The etiology of these anterior abdominal wall defects and the associated risk factors remain controversial. Young maternal age has been recognized as one of the strongest risk factors for gastroschisis.[1,14] Consistent with this, the mothers of fetuses with gastroschisis were markedly younger (average 24.7 years) than mothers with fetuses with omphalocele (29.6 years) in our cohort of patients. For omphalocele, both young and advanced maternal age have been identified as risk factors.[5,14]

The majority of patients in our cohort of cases were delivered at preterm. Gastroschisis patients were born earlier and with lower birth weight than those with omphalocele, which is consistent with other studies.[11,23] All patients with gastroschisis and 84.6% of the patients with omphalocele were delivered by caesarean section. The observed rate for cesarean delivery was high, and this is mainly explained by the fact that a planned delivery in a tertiary care center, with access to appropriate neonatal and pediatric surgical services, is more readily achieved by caesarean section than by

vaginal delivery. There is also a fear of some obstetricians of inducing birth dystocia or injury of the exposed abdominal viscera during vaginal delivery.[7] However, several studies failed to demonstrate that cesarean section is superior to vaginal delivery for neonates with omphalocele and gastroschisis.[7,22,24]

The choice of the method to reduce the exteriorized organs and close the fascial defect depends on several factors, namely the size of the defect, patient stability, gestational maturity, and the presence of associated anomalies. Many surgeons recommend primary closure, when feasible, to be done within a few hours after birth.[8] This is also the preferred strategy at our center. Our primary abdominal closure rate of 86.8% is similar to other published rates.[4,23,25] Staged repair with silo placement may be preferable for the unstable neonate, large defects and when gastroschisis is associated with significant intestinal damage.[4,7] In our study, one patient with a giant omphalocele and one patient with a large and complex gastroschisis developed compartment syndrome after primary closure and were converted to a staged reduction. Both patients died. This highlights the difficulties in managing patients with large defects as there is lack of strong evidence for decision-making. According to Lee et al.,[26] initial primary closure should never be attempted for giant omphaloceles, while other studies report that immediate closure with or without the use of a synthetic patch is possible.[4,27]

The length of hospitalization was significantly longer for patients with gastroschisis than for patients with omphalocele. The factors that contributed to this difference included the later onset of bowel function in patients with gastroschisis, as indicated by their significantly longer time in parenteral nutrition and to initiate enteral feeding, compared with patients with omphalocele. Furthermore, although not reaching statistical significance, patients with gastroschisis were more likely to have complications during hospitalization, namely sepsis. Our findings are in line with other studies that have shown that patients with gastroschisis generally have a more complicated neonatal course than those with omphalocele.[11] This is related to the expected bowel dysmotility and deficient nutrient absorption associated with gastroschisis, while patients with omphalocele typically have a normal or less impaired bowel function after birth.[2] Therefore, a longer period of parenteral nutrition is generally required for infants with gastroschisis while they wait for the recovery of gut function. During this period, patients are at risk of having complications associated with the parenteral nutrition, namely catheter-related sepsis, and liver disease.[28] In our cohort of patients with gastroschisis, 24% had complex gastroschisis, which is in line with other studies.[29] These patients typically have worse outcomes, and our findings confirm this.

Patients with omphalocele are more frequently diagnosed with associated anomalies compared with those with gastroschisis.[7,11] However, in our cohort of patients, we found that the proportion of patients diagnosed with associated anomalies was similar in omphalocele (46.2%) and in gastroschisis (41.7%). Given that elective terminations and intrauterine fetal deaths were excluded from our study, the proportion of patients with omphalocele and associated anomalies is lower than otherwise would have been expected. This also explains the absence of omphalocele cases with chromosomal defects. Similarly, Heider et al.[30] found that by excluding elective terminations and spontaneous miscarriages, the rate of associated anomalies in a cohort of 36 cases of omphalocele was 31%. We found a pattern of anomalies associated with each defect similar to what is reported in the literature.[6,8,11,31] Patients with omphalocele were more likely to have genetic syndromes and central nervous system anomalies, while gastrointestinal anomalies were more commonly associated with gastroschisis.

Survival rates greater than 90% have been reported for gastroschisis.[12,32] Our data corroborates this finding. We also report a high survival rate (92.3%) for omphalocele, and this is explained by the absence of cases with abnormal karyotype and the high proportion of isolated omphaloceles (53.8%) in our cohort of cases. Previously, Marshall et al.[5] reported a survival rate of 92% for patients with isolated omphalocele, and this value decreased to 38.8% for patients with chromosomal anomalies. Furthermore, excluding one case with bronchopulmonary dysplasia, none of the other survivors with omphalocele had significant cardiopulmonary complications during hospital stay. Thus, our group of patients with omphalocele may represent a selected subset of cases with low postoperative morbidity and mortality.

Medium-term morbidity was evaluated through examination of the outcomes listed in ►**Table 4** for a median follow-up of 24 months, and through evaluation of the anthropometric parameters at 2 years of age. Infants with omphalocele and with gastroschisis typically show an early growth delay that improves over time in most cases.[3,10,20] We also observed an improvement of growth parameters from birth to 2 years of age, such that only 2 patients (1 with omphalocele and 1 with gastroschisis) had length and/or weight below the 10th percentile at 2 years of age.

None of the outcomes in ►**Table 4** were significantly different between gastroschisis and omphalocele. A higher proportion of patients with gastroschisis (31.8% versus 8.3%) had bowel obstruction during the follow-up period, mainly due to intestinal adhesions. Adhesive small bowel obstruction is a frequent and serious complication in the first year of life, particularly in patients with gastroschisis.[12,33] Van Eijck et al.[33] reported a series of 55 patients with gastroschisis and 92 patients with omphalocele, in which 25% and 13%, respectively, developed adhesive small bowel obstruction. The higher propensity of gastroschisis for adhesive small bowel obstruction is postulated to be a consequence of the inflammatory reaction of the bowel serosa following prolonged exposure to the amniotic fluid, and the hypoperistalsis that characterizes the newborns with gastroschisis also favors adhesion formation.[33]

One of the most severe complications of anterior abdominal wall defects is short gut syndrome, which is the most common cause of intestinal failure in children.[34] Bowel atresia and other gastrointestinal anomalies, midgut volvulus, or necrotizing enterocolitis can predispose patients with

gastroschisis and omphalocele to short bowel syndrome.[7,10] This condition can be handled with pharmacologic interventions and intestinal lengthening procedures with the ultimate goal of avoiding intestinal transplantation. In our study, one patient with complex gastroschisis who developed ultra-short gut syndrome and underwent one STEP procedure at 10 months was still dependent on total parenteral nutrition at 2 years of age.

Umbilical hernia is a well-known complication following repair of congenital abdominal defects.[12,35] The presence of umbilical hernia, abdominal scars or the lack of an umbilicus is known to cause psychosocial stress in some children and their parents.[13,23] Henrich et al.[23] reported a series of 15 patients with omphalocele and 20 patients with gastroschisis in whom 20% and 15%, respectively, developed a ventral hernia. In our study, we found a high proportion of patients with omphalocele (41.7%) and gastroschisis (27.3%) who developed an umbilical hernia. An expectant approach may be considered as the hernia resolves spontaneously in many patients.[35] In our study, only one patient underwent hernia repair during the follow-up period. For gastroschisis, the most consistent risk factor for umbilical hernia is sutureless closure,[35] but this method is not used at our center. Hawkins et al.[17] compared primary closure with SILO closure and found an equivalent hernia rate between primary closure and longer duration of SILO reduction, with SILO placed for less than 5 days associated with the lowest incidence of ventral hernia.[17] Given that, in our study, a small number of patients (3 survivors) underwent secondary closure, we cannot take conclusions about the impact of the repair method on the development of umbilical hernia.

Our results support a hopeful information in terms of survival to be transmitted to future parents of a child born with gastroschisis or with omphalocele with a normal karyotype. However, during prenatal counseling, parents should be informed that neonates with gastroschisis and omphalocele are at risk for serious complications, including longer duration of parenteral feeding, presence of other anomalies requiring more urgent treatment (e.g., bowel atresia), need of reoperation and prolonged hospital stays. Furthermore, some survivors may experience a non-negligible morbidity in the first 2 years of life, as explained above.

There are some limitations to our study, which include those of any retrospective analysis, such as selection bias, potential confounders, incomplete or missing data, and unmeasured factors that could have changed the results. In addition, this study does not contemplate all the mortality commonly associated with omphalocele because we included only live births. The sample is relatively small, but it is from a single center with standardized procedures of care, allowing a comprehensive and detailed characterization of the natural history and outcomes of these abdominal wall defects.

Conclusion

Our study presents a comprehensive overview of the management and outcome of live births with gastroschisis and omphalocele in a large tertiary center. The present study corroborates that, when compared with omphalocele, patients with gastroschisis had younger mothers, lower gestational age and weight at birth, and a more prolonged hospitalization course. Both gastroschisis and omphalocele (with no chromosomal abnormalities) were associated with survival rates greater than 90%; however, significant morbidity may occur in the medium term.

Contributors

All the authors participated in the concept and design of the present study. Marques A. T. and Estevão-Costa J. have performed the analysis and interpretation of data and the writing of the article. All the authors contributed to critical review of the intellectual content and have approved the manuscript as submitted.

Conflict of Interests

The authors have no conflict of interests to declare.

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Is There Any Effect of the Physician Performing Embryo Transfer in IVF-ICSI Treatment: A Prospective Cohort Study

Existe algum efeito do médico que realiza a transferência de embriões no tratamento de FIV-ICSI: Um estudo de coorte prospectivo

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Abstract

Objective To evaluate whether there is an effect of the physician who transfers the embryos on pregnancy rates in in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) treatment.

Methods A total of 757 participants were analyzed between 2012 and 2017. Participants were classified according to 3 physicians who transferred the embryos: ([group 1 = 164 patients]; [group 2 = 233 patients]; [group 3 = 360 patients]). Baseline parameters and IVF-ICSI outcomes were compared between the groups.

Results No differences were determined between the groups regarding the baseline parameters (age, age subgroups [20–29, 30–39, and $\geq$ 40 years old)], body mass index (BMI), smoking status, infertility period, cause of infertility, baseline follicle stimulating hormone, luteinizing hormone, estradiol (E_2), thyroid stimulating hormone, prolactin levels, antral follicle count, duration of stimulation, stimulation protocol, gonadotropin dose required, maximum E_2 levels, progesterone levels, endometrial thickness on human chorionic gonadotropin (hCG) administration and transfer days ($p > 0.05$). The numbers of oocytes retrieved, metaphase II (MII), 2 pronucleus (2PN), transferred embryo, fertilization rate, day of embryo transfer, the catheter effect and embryo transfer technique, and clinical pregnancy rates (CPRs) were also comparable between the groups ($p > 0.05$).

Conclusion Our data suggests that the physician who transfers the embryos has no impact on CPRs in patients who have undergone IVF-ICSI, but further studies with more participants are required to elucidate this situation.

Keywords
- assisted reproductive technology
- embryo transfer
- infertility physicians
- pregnancy rate

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Resumo

Objetivo Avaliar se há ou não efeito do médico que realiza a transferência de embriões nas taxas de gravidez no tratamento com fertilização in vitro-injeção intracitoplasmática de espermatozoide (FIV-ICSI, na sigla em inglês).

Métodos Um total de 757 participantes foram analisados entre 2012 e 2017. Os participantes foram classificados de acordo com 3 médicos que transferiram os embriões: ([grupo 1 = 164 pacientes]; [grupo 2 = 233 pacientes]; [grupo 3 = 360 pacientes]). Parâmetros basais e resultados de FIV-ICSI foram comparados entre os grupos.

Resultados Nenhuma diferença foi determinada entre os grupos nos parâmetros basais (idade, subgrupos de idade [20-29, 30-39 e ≥ 40 anos)], índice de massa corporal (IMC), tabagismo, período de infertilidade, causa da infertilidade, hormônio folículo estimulante basal , hormônio luteinizante, estradiol (E2), hormônio estimulador da tireoide, níveis de prolactina, contagem de folículos antrais, duração da estimulação, protocolo de estimulação, dose de gonadotrofina necessária, níveis máximos de E2, níveis de progesterona e espessura endometrial na administração de hCG e nos dias de transferência ($p > 0,05$). O número de oócitos recuperados, MII e 2PN, embrião transferido, taxa de fertilização, dia da transferência do embrião, o efeito do cateter e a técnica de transferência de embrião e taxas clínicas de gravidez (RCPs) também foram comparáveis entre os grupos ($p > 0,05$).

Conclusão Nossos dados sugerem que o médico que transfere os embriões não tem impacto sobre as RCPs em pacientes que se submeteram a FIV-ICSI, mas mais estudos com mais participantes são necessários para elucidar esta situação.

Palavras-chave

- tecnologia reprodutiva assistida
- transferência de embrião
- médicos de infertilidade
- taxa de gravidez

Introduction

Despite all of the developments in assisted reproductive technology (ART) since the first live birth following in vitro fertilization (IVF) in 1978, pregnancy rates have remained at between ~ 35 and 45%.[1–5] In ART cycles, the method of embryo transfer (ET) is important for clinical pregnancy success in addition to features such as age, endometrial receptivity of the infertile woman, and embryo quality.[6–9] It has been claimed that faulty ET is responsible for between 25 and 30% of failed implantations, related either to the catheter application technique or to the experience of the clinician performing the ET procedure.[5,6,10] To minimize possible negative effects of different physicians on the clinical pregnancy rate (CPR) in ET, these procedures have been standardized by assisted reproduction clinics. Nevertheless, some studies have suggested that the physician who performs the ET may affect CPR success.[11–13] In the present study, we aimed to evaluate the effect of the physician who transfers the embryos on pregnancy rates in IVF-intracytoplasmic sperm injection (IVF-ICSI) treatment.

Methods

Study Participants and Data Collection

The present prospective study was performed at the Reproductive Endocrinology Department of the Ali Kemal Belviranli Maternal Women's Health and Children's Hospital. Outcomes of 757 fresh ICSI cycles were reviewed between January 2012 and December 2017. The inclusion criteria were participants aged between 20 and 44 years old, body mass index (BMI) between 18 and 35 kg/m^2, regular menstrual cycles, no uterine abnormalities in the ultrasound, and normal baseline hormonal levels. Participants were excluded from the study if they were ≥ 45 years, with a BMI ≥ 35 kg/m^2, or had any significant illness or metabolic disorders. Ethical board approval was granted from the institutional review board (2012/57). Written and oral informed consent was given from the participants. Data were obtained for age, BMI (kg/m^2), smoking status, infertility period, cause of infertility, baseline at day 3 for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) levels, thyroid-stimulating hormone (TSH), prolactin, antral follicle count, stimulation parameters, IVF-ICSI outcomes, and CPR.

Ovarian Stimulation and Oocyte Retrieval

Controlled ovulation stimulation was negotiated using the gonadotropin-releasing hormone agonist (GnRHa) or the flexible gonadotropin-releasing hormone antagonist (GnRHant) protocol.

Embryo Transfer Procedure

Three senior physicians performed the ETs accompanied by ultrasonographic guidance (USG) (Logiq 200 Pro, General Electric, Seoul, South Korea) using an ET catheter system. A sterile speculum was introduced in the vagina in the lithotomy position, then the vagina and the cervix were cleaned using sterile cotton swabs. An embryologist loaded the embryos into a soft transfer catheter that was given to the

ET physician, who deposited the embryos ~ 10 mm from the uterine fundus under USG. The catheter was gently removed after 5 seconds. In cases of ET with external guidance, an initial catheter with inner sheath was inserted into the external cervical os, and then advanced through the cervical canal and the internal os to 10 mm of the uterine fundus under USG. The internal sheath was withdrawn, and a second catheter loaded with embryos was introduced in its place and advanced to ~ 10 mm from the uterine fundus, where the embryos were deposited. Difficult transfers required the use of a stylet in addition to this form of external guidance. All catheters were immediately checked for retained embryos and blood, and the patient remained in the Trendelenburg position for ~ 10 minutes. Patients who used the tenaculum were excluded from the study. Progesterone in the form of Crinone 8% gel (Serono, Istanbul, Turkey) at a daily dose of 90 mg for 14 days was given for luteal phase support. Baseline parameters and IVF-ICSI outcomes were compared between the groups. Clinical pregnancy was accepted as those with a gestational sac accompanying fetal heartbeat on ultrasound examination at between 4 and 5 weeks after the ET. The CPR was defined as the number of clinical pregnancy cycles/number of embryo transfer cycles × 100%. The number of embryos transferred (≤ 2 per patient) complied with the Turkish national regulations. The subjects were classified according to 3 physicians who transferred the embryos: ([group 1 = 164 patients]; [group 2 = 233 patients]; [group 3 = 360 patients]).

Statistical Analysis

The statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to examine the continuous variables with normal and non-normal distributions. The one-way analysis of variance (ANOVA) was preferred for the normally distributed continuous variables, while the Kruskal-Wallis test was used for the non-normally distributed continuous variables. Categorical data were analyzed by the Pearson chi-squared test, and the Fisher exact test was applied if the expected frequency was < 5 in $> 20\%$ of all

Table 1 Demographic and stimulation characteristics of the patients

		Group 1 ($n = 164$)	Group 2 ($n = 233$)	Group 3 ($n = 360$)	*p-value*
Age (years old)		30.31 ± 5.48	29.21 ± 4.54	29.77 ± 4.31	0.069
Age (years old) subgroups	20–29 (%)	52.4%	59.6%	54.2%	0.529
	30–39 (%)	45.1%	38.6%	44.4%	
	≥ 40 (%)	2.4%	1.8%	1.4%	
BMI (kg/m^2)		26.16 ± 4.67	25.50 ± 4.31	26.18 ± 4.82	0.190
Smoking rate (%)		4.5%	6.4%	9.7%	0.110
Duration of infertility (years)		6.42 ± 4.02	6.49 ± 3.18	6.30 ± 3.49	0.410
Etiology of infertility (%)	Male factor	40.2%	41.7%	31.9%	
	Tubal factor	4.3%	1.8%	1.4%	0.069
	Unexplained	35.4%	37.7%	42.5%	
	Poor responder	20.1%	18.8%	24.2%	
Baseline-FSH (IU/mL)		6.94 ± 1.94	7.08 ± 2.19	7.29 ± 2.49	0.103
Baseline-LH (IU/mL)		5.14 ± 2.71	5.48 ± 2.93	5.77 ± 2.97	0.064
Baseline-estradiol (pg/mL)		43.27 ± 13.15	45.62 ± 16.54	44.79 ± 17.36	0.124
Antral follicle count		6.61 ± 2.48	6.63 ± 2.38	6.28 ± 2.58	0.395
TSH (μIU/mL)		2.15 ± 1.04	2.20 ± 1.07	2.19 ± 1.17	0.885
Prolactin (ng/mL)		14.74 ± 7.19	15.62 ± 7.93	15.53 ± 10.20	0.224
Stimulation protocol (%)	Long	24.5%	21.1%	17.1%	
	Antagonist	75.5%	78.9%	80.8%	0.118
Duration of stimulation (days)		10.27 ± 1.42	9.93 ± 1.84	10.13 ± 1.61	0.101
Gonadotropin dose (IU)		2037.62 ± 705.15	1861.35 ± 902.89	1921.41 ± 816.44	0.109
Estradiol levels on day hCG (pg/mL)		2051.67 ± 1110.13	2002.62 ± 1109.04	1859.54 ± 1177.84	0.126
Progesterone levels on day hCG (pg/mL)		0.86 ± 0.38	0.85 ± 0.40	0.79 ± 0.39	0.098
Endometrial thickness on day hCG (mm)		10.56 ± 1.64	10.51 ± 1.61	10.27 ± 1.89	0.130
Endometrial thickness on transfer day (mm)		10.62 ± 1.78	11.01 ± 1.73	10.61 ± 1.90	0.105

Abbreviations: BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropine; TSH, thyroid stimulating hormone.
*Statistically significant.

cells. The continuous variables were presented as mean ± standard deviation (SD), and the categorical variables were presented as the number of cases and percentages. The Bonferroni adjustment was performed to control the type I errors for all possible multiple comparisons. A p-value < 0.05 was accepted as statistically significant.

Results

A total of 56 patients were excluded from the study, specifically those ≥ 45 years old ($n = 19$), with BMI ≥ 35kg/m^2 ($n = 14$), with systemic disease ($n = 9$), endocrine or metabolic disorders ($n = 6$), use of tenaculum ($n = 5$), and concomitant medication ($n = 3$). The remaining 757 participants were classified into the three ET groups and their outcomes were analyzed (►**Fig. 1**).

A comparison of the sociodemographic and stimulation characteristics of the participants is provided in ►**Table 1**. There was no difference between the groups regarding age, age subgroups (20–29, 30–39, and ≥ 40 years old), BMI, smoking status, infertility period, cause of infertility, baseline FSH, LH, E_2, TSH, prolactin levels, antral follicle count, stimulation day, stimulation protocol, gonadotropin dose required, maximum E_2 and progesterone levels, and endometrial thickness on hCG administration and transfer days ($p > 0.05$).

The reproductive outcomes of the participants are summarized in ►**Table 2**. The numbers of oocytes retrieved, MII and 2PN, transferred embryo, fertilization rate, the ET day, the catheter effect and ET technique, and the CPR were comparable between the groups ($p > 0.05$).

Discussion

The present study aimed to investigate whether there is an effect of the physician who transfers the embryos on pregnancy rates in IVF-ICSI treatment. We found no such impact in the present study. There are several studies on this topic with contradictory results; some have shown that the physician factor can have as significant an effect on CPR in IVF-ICSI cycles as clinical and embryological features,[6,14,15] but contrasting results have also been reported.[12,16,17]

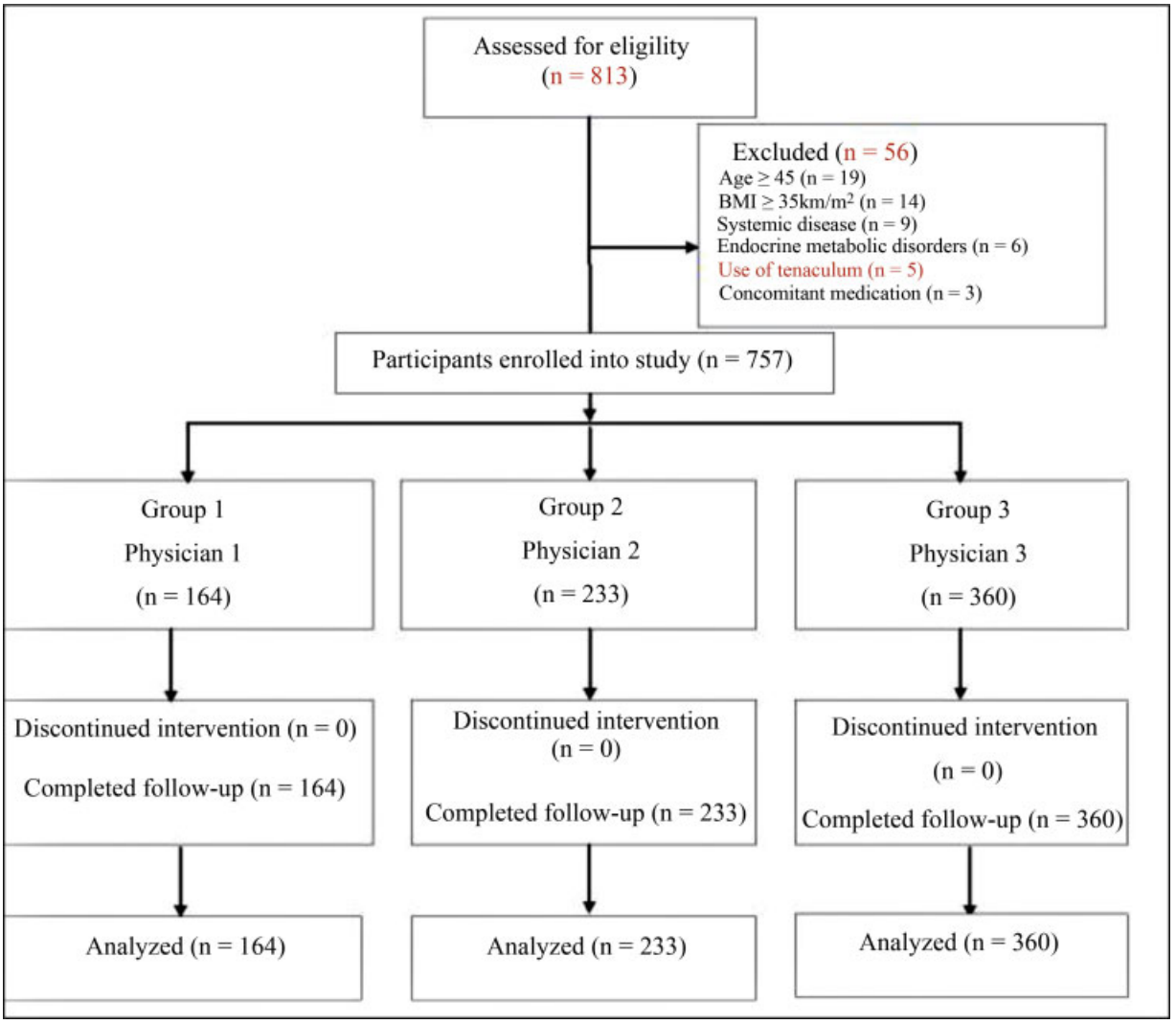

Fig. 1 Enrollment and follow-up of the study subjects.

Table 2 Laboratory and reproductive outcome parameters of the patients

		Group 1 ($n = 164$)	Group 2 ($n = 233$)	Group 3 ($n = 360$)	*p-value*
Number of oocytes retrieved		9.67 ± 6.59	8.92 ± 4.87	9.16 ± 5.39	0.112
Number of MII oocytes		8.02 ± 4.65	7.30 ± 4.22	7.10 ± 4.38	0.144
2 Pronucleus		5.19 ± 3.43	4.65 ± 3.08	4.86 ± 3.32	0.276
Fertilization rate (%)		63.98 ± 22.30	66.80 ± 23.88	65.35 ± 25.01	0.424
Grade I embryo (%)		64.8%	67.9%	66.7%	0.821
Number of embryos transferred		1.21 ± 0.40	1.18 ± 0.86	1.17 ± 0.38	0.821
Days of embryo transfer (%)	2	12.6%	4.5%	3.1%	
	3	78.0%	83.5%	87.1%	0.193
	5	9.4%	12.1%	9.8%	
Embryo transfer technique (%)	Easy transfer with a soft catheter	21.1%	18.3%	20.8%	
	After external guidance transfer	69.1%	73.3%	70.1%	0.118
	Difficult transfer with a stylet	9.8%	8.4%	9.1%	
The presence of blood in the catheter (%)		2.4%	3.1%	3.6%	0.466
Clinical pregnancy rate (%)		34.8%	37.7%	35.1%	0.771

Hearns-Stokes et al.[17] found that CPR was statistically different, at 17.0 and 54.3%, according to the physician performing the procedure in their evaluation of 854 fresh ETs in 617 IVF-ICSI cycles. However, possible confounding factors such as age and embryo quality, which may have caused this significant difference, were not analyzed. In another study, 1,850 IVF-ICSI cycles were retrospectively evaluated over 2 years, and CPR rates ranged between 13.2 and 37.4% among the physicians who had performed the ETs. When standard training was provided to the physicians with low CPRs in the 1st year, the rates increased.[12] However, other factors that could affect the CPR were once more not taken into account in the statistical analysis.

In some Nordic countries, ET is performed by midwives and physicians to share the workload, and in a study comparing 102 ETs split equally among the groups, no difference was found in terms of CPR, at 31.0 and 29.0%, respectively.[18] In a study of 679 nurses and 92 physicians in the United Kingdom, 771 ETs were evaluated and the CPR rate was found to be higher in the nurse group, at 36.2 versus 29.4%.[11] Since the ET procedures in our IVF center were all performed by physicians, these comparisons could not be performed in our study.

In a study evaluating 204 ETs performed by 5 trainee providers, no significant CPR difference was found between them.[13] Since our clinic does not train IVF physicians, no such comparison was performed on our data. Elsewhere, a study comparing the effect on CPR of 2 physicians performing 485 ETs found no difference, at 36.1 and 20.6%.[16] Similarly, in a further study that evaluated 977 ETs performed by 6 physicians, no difference was found between them in terms of CPR.[5]

Over the past 10 years, significant efforts have been made to develop standardized and atraumatic ET procedures to minimize the provider effect on CPR.[6,19] In our IVF clinic, for example, a definitive procedure is implemented and performed by experienced and senior physicians; more specifically, USG is used to guide and expel the embryos into the endometrial cavity ~ 10 mm from the uterine fundus on full bladder. Although ET is always performed by an experienced physician, it should be kept in mind that there are many possible confounding factors that can alter CPR, such as the presence of blood or mucus. These were excluded from the present study. Ultimately, there was no difference between the groups in terms of confounding factors. We subsequently explored the effects of different ET physicians in IVF-ICSI treatment, and found that it has no effect on CPR.

The strong point of the present study consists of its prospective design, the adequate number of subjects in each group, and the prototypical sample from central Turkey. The results can be generalized to most of the population of the country. However, the potential limitations of the study are that it was conducted in a tertiary care institution and that the cumulative CPR was not evaluated because no frozen ETs were included.

Conclusion

In conclusion, our data show that the pregnancy rates of patients who underwent IVF-ICSI treatment at our clinic were not impacted by the physician factor of who transferred the embryos.

Contributors
All authors participated in the concept and design of the study, as well as in the analysis and interpretation of data; draft or revision of the manuscript; and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests

The authors have no conflict of interests to declare.

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Epidemiological Survey on the Perception of Adverse Effects in Women Using Contraceptive Methods in Brazil

Pesquisa epidemiológica sobre a percepção dos efeitos adversos dos métodos contraceptivos por mulheres no Brasil

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Abstract

Objective The present study aimed to understand patient perception of the adverse effects of contraceptives to improve health care and adherence to treatment.

Methods An online questionnaire was available for women in Brazil to respond to assess their perception of adverse effects and their relationship with contraceptive methods.

Results Of all 536 women who responded, 346 (64.6%) reported current contraceptive use. One hundred and twenty-two (122–34.8%) women reported having already stopped using contraception because of the adverse effects. As for the contraceptive method used, the most frequent was the combined oral contraceptive (212–39.6%). When we calculated the relative risk for headache, there was a relative risk of 2.1282 (1.3425–3.3739; 95% CI), suggesting that the use of pills increases the risk of headache, as well as edema, in which a relative risk of 1.4435 (1.0177–2.0474; 95% CI) was observed. For low libido, the use of oral hormonal contraceptives was also shown to be a risk factor since its relative risk was 1.8805 (1.3527–2.6142; 95% CI). As for acne, the use of hormonal contraceptives proved to be a protective factor, with a relative risk of 0.3015 (0.1789–0.5082; 95% CI).

Conclusion The choice of a contraceptive method must always be individualized, and the patients must be equal participants in the process knowing the expected benefits and harms of each method and hormone, when present.

Keywords

- contraception
- hormonal contraception
- drug-related side effects and adverse reactions
- gynecology
- epidemiology

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Resumo

Objetivo Este estudo é destinado a entender a percepção de pacientes sobre os efeitos adversos dos métodos contraceptivos para aprimorar o atendimento médico e a aderência das mulheres ao tratamento.

Métodos Um questionário online foi disponibilizado para que mulheres no Brasil respondessem a fim de avaliar a sua percepção em relação aos efeitos adversos e a associação desses aos métodos contraceptivos.

Resultados Das 536 mulheres que responderam, 346 (64,5%) alegaram uso atual de método contraceptivo. Cento e vinte e duas (122–34,8%) mulheres disseram que já haviam parado o uso de métodos contraceptivos devido aos seus efeitos adversos. Quanto ao método contraceptivo em uso, o mais frequentemente utilizado foi o contraceptivo hormonal oral combinado (212–39,6%). Quando calculamos o risco relativo para cefaleia, foi encontrado um risco relativo de 2,1282 (1,3425–3,3739; 95% intervalo de confiança [IC]), sugerindo que o uso das pílulas aumenta o risco de ocorrência desse efeito adverso, bem como de edema, cujo risco relativo foi de 1,4435 (1,0177–2,0474; 95% IC). Em relação à redução da libido, o uso de contraceptivo hormonal oral combinado foi também considerado um fator de risco, pois seu risco relativo foi 1,8805 (1,3527–2,6142; 95% IC). No que se refere à acne, o uso de contraceptivos hormonais demonstrou ser um fator de proteção, com risco relativo de 0,3015 (0,1789–0,5082; 95% IC).

Conclusão A escolha de um método contraceptivo deve sempre ser individualizada, e as pacientes devem participar igualmente nesse processo sabendo dos benefícios e malefícios esperados de cada método e hormônio, quando presente.

Palavras-chave

- contracepção
- contracepção hormonal
- efeitos colaterais e reações adversas relacionadas ao uso de medicamentos
- ginecologia
- epidemiologia

Introduction

Prevention of pregnancy can be achieved by inhibiting ovulation, fertilization, and/or implantation using hormonal or non-hormonal methods. Hormonal contraception can be accomplished through oral contraceptive pills, transdermal patches, vaginal rings, subcutaneous implants, intramuscular injections, or intrauterine devices.[1]

In 2015, it was estimated that almost 650 million women worldwide used oral contraceptives.[2] However, despite its broad use, only a few use it, as it is prescribed by its gynecologist.[3] In a 2015 research, only 56% women reported being protected by a contraceptive method at the moment of their last vaginal intercourse.[4]

Long-acting reversible contraception methods (LARCs) are known to be the most effective due to not being dependent on the active participation of the patient—as is the case with the pill—and because of its long-acting mechanism, whether through liberation of progestogens, as in hormonal intrauterine devices (IUDs) and intradermal implants, or induction of an inflammatory response to hinder the process of fecundation, as in the copper and silver IUDs.[5]

However, women worldwide are more likely to use oral contraceptive pills or male condoms.[4] Contraceptive pills can be composed by two types of hormones, ethinyl estradiol or estradiol valerate paired with a form of progestogen, or by only one type, progestogen.[6]

Even though both types of pills can inhibit follicle-stimulating hormone (FSH) and luteinizing hormone (LH) sufficiently to prevent ovulation, the combined pills have greater antigonadotrophic and ovulation-inhibition effects. The progestogen component is effective in blocking the midcycle rise in LH secretion, which inhibits ovulation. On the other hand, ethinyl estradiol is mainly used due to its beneficial effect of preventing irregular shedding of the endometrium.[7]

In contraception, the most used hormones are estradiol, estradiol valerate, and ethinyl estradiol, as shown in ►**Table 1**. The dosage of estrogen has been decreased over the years to reduce the risk of cardiovascular disorders. However, reducing the estrogen dose leads to a less favorable control of the menstrual bleeding.[8]

Progestogens are classically characterized according to their structural origins, and the main ones can be seen in ►**Table 2**. They can bind to androgens, glucocorticoids, and mineralocorticoid receptors. According to its structure and activated receptors, each progestogen is associated with a greater or lesser frequency of adverse effects.[9]

Contraceptive methods may cause other effects that are dependent on the type and dose of the estrogenic and progestogenic components. These effects are often the reason a particular method is chosen. Among them, the most notable are the improvement in the appearance of hirsutism and acne when ethinylestradiol is used in combination with antiandrogenic progestogen.[10,11]

Table 1 Estrogens, their origin, and their uses in gynecology

Estrogen	Origin	Contraception use	Therapy hormone use
Estrone	Natural	No	No
Estradiol	Natural	Oral	No
Estriol	Natural	No	Oral, topical vaginal
Estetrol	Natural	Oral (under study)	Oral (under study)
Ethinylestradiol	synthetic	Oral, vaginal ring, adhesive	No
Promestriene	synthetic	No	Topical vaginal
Estradiol Valerate	synthetic	Oral, monthly injectable	Oral

Table 2 Main progestogens used in gynecology and their effects

	Antiestrogenic	Antiandrogenic	Glucocorticoid	Antimineralocorticoid
Cyproterone	+	++	+	−
Chlormadinone	+	+	+	−
Dienogest	+-	+	−	−
Drospirenone	+	+	−	+
Gestodene	+	−	+	+
Levonorgestrel	+	−	−	−
Nomegestrol	+	+-	−	−

+ strong action; +- moderate action; - weak action

Worldwide, the most common reasons for the non-use of contraception and the discontinuation of the method are fear of side effects and health concerns.[11,12] However, data about this topic in Brazil are scarce.

Even in women with high awareness, statements such as "IUDs are an abortive method" and "amenorrhea is prejudicial to health" are extremely common. These myths and misconceptions must be addressed by the medical assistant.[13]

The present study aimed to understand patient perception of the adverse effects of contraceptives to improve health care and adherence to treatment.

Methods

The method of selection for the population of this study was convenience sampling. Since the number of women in reproductive age in our region is $\sim$ 43 million, we wanted a sample of at least 385 women.

Women of reproductive age over 18 from a city in Brazil who had already had contact with the local university hospital, either as a patient, doctor, academic, or employee and who were using or had used any type of contraceptive methods were invited to answer an electronic questionnaire through an online link. All women who had an online contact registered in our database ($n = 1{,}274$) received an email with the invitation to answer an online questionnaire. Five hundred and thirty-six women (536) filled the online questionnaire, after signing the informed consent form.

The questionnaire was divided into three parts. The first part evaluated the patient's demographic data. The second performed a brief medical screening to assess if there were any comorbidities. The questions in the second part were intended to assess whether such symptoms existed prior to the use of the method, whether they were related to the menstrual cycle and whether they improved or worsened with the use of the contraceptive method. Finally, the last part analyzed the use of contraceptive methods and their correlation with adverse effects. It evaluated whether the patient currently uses contraception, what dosage, frequency and time of use, reason for discontinuing use, and it also questioned previous use of emergency contraception. So, the relationship between contraceptives and the main adverse effects reported by patients (headache, edema, mastalgia, and low sexual libido) could be evaluated.

To better understand the perception of the patients, all side effects (edema, headache, acne and mastalgia) were reported by self-diagnosis. No complaints were excluded, even if the women had hyperandrogenism or migraine, since we wanted to evaluate if they perceived an improvement or worsening of their symptoms after using the contraceptive method.

On the online questionnaire, the diagnosis of low libido was based on the deficiency or absence of sexual fantasies and desire for sexual activity or in cases in which the deficiency causes marked distress or interpersonal difficulty in more than half of sexual intercourse in the month. Having

that in mind, women could mark that option if they thought it was well-suited to their complaints.

This project was approved by legal ethics committee under CAAE 34836620.2.0000.5133.

Results

The mean age of the women who answered the questionnaire was 24.08 years, and the median of 23 years, with the highest age being a single woman aged 51 years, and the lowest fourteen women aged 18 years. The most reported profession was student (reported by 264 women, which corresponded to 49.3% of the total), followed by doctor (35 women—6.5%), teacher (11 women—2.1%), and lawyer (11 women—2.1%).

Eighty-nine (89—16.6%) of the women reported having some comorbidity, with the most frequent being asthma (present in 21—3.9%), followed by polycystic ovary syndrome (12—2.2%), and mood disorders (8—1.5%). Other reported comorbidities were hypothyroidism (6.7%), hyperthyroidism (1.1%), unspecified thrombophilia (1.1%), diabetes mellitus (2 women), systemic arterial hypertension (2.2%), migraine (3.3%), endometriosis (4.4).

Of all 536 women who participated in the study, 346 (64.6%) reported current use of a contraceptive method, 79 (14.7%) said they had already used it, but were no longer doing it, and 11 (2.1%) reported never having used contraception. In those who currently used it, the average use of the same contraceptive was 5.5 years, and the median was 5 years, with the lowest being 25 women who had not completed even 1 year of use (4.7%), and the highest being a woman who has used the same method for 25 years (0.2%). All those patients who had previously used contraceptives and discontinued their use (100%) were using combined oral contraceptives.

Three hundred and fifty-one (351—65.5%) patients reported having stopped using contraception for more than a month at some point. They reported the most frequent reason was the presence of side effects (122—34.8%), followed by not using it right (20—5.7%), no more need for contraception (19—5.4%), fear of frequent use of hormone (6—1.7%), and pregnancy (2—0.5%).

The most frequently used method was the combined oral contraceptive (212—39.6%), followed by the concomitant use of combined oral contraceptive and condom (93—17.4%), levonorgestrel-releasing intrauterine system (LRIS) (26—4.9), copper IUD (19—3.5), condom (18—3.4%), monthly injectable contraceptive (4—0.7%), contraceptive quarterly injectable (2—0.4%), implant (2–0.4%), and withdrawal (1—0.2%). In addition, 277 (51.7%) participants reported having used the morning-after pill at least once, even during the use of regular contraception.

Among women using hormonal pills, the most used combinations were 3 mg of drospirenone and 0.02 mg of ethinylestradiol (68 women—12.7%); 2 mg of cyproterone acetate combined with 0.035 mg of ethinylestradiol (63 patients—11.8%); 3 mg of drospirenone associated with 0.03 mg of ethinylestradiol (25 women—4.7%); 0.060 mg of gestodene with 0.015 mg of ethinylestradiol (17 women—3.2%); dienogest and estradiol valerate (13 women—2.4%); 0.075 mg of gestodene associated with 0.03 mg of ethinylestradiol (12 women—2.2%); 0.15 mg of levonorgestrel associated with 0.03 mg of ethinylestradiol (11 women—2.1%); and 2 mg chlormadinone acetate plus 0.03 mg ethinyl estradiol (10 women—1.9%). Other combinations mentioned were 0.075 mg of gestodene associated with 0.02 of ethinylestradiol (8 women—1.5%); 0.075 mcg of desogestrel (9 women—1.7%); 0.15 mcg of desogestrel associated with 0.020 of ethinylestradiol (7 women—1.3%); 2.5 mg of nomegestrol acetate associated with 1.5 mg of estradiol (3 women—0.6%); and 2 mg of chlormadinone acetate associated with 0.020 mg of ethinylestradiol.

As for side effects, 110 (20.5%) women reported headache using a contraceptive method, 72 women (13.4%) reported spotting. Among those with spotting, 22 (30.5%) reported feeling uncomfortable, but not enough to suspend the use of the method. On the other hand, 7 (9.7%) answered that they stopped using the pill due to the side effects. When evaluating which combination the patients were using, those ones most related to spotting were the combination of 0.02 mg ethinylestradiol to 3 mg drospirenone (15 patients); 0.03 mg ethinylestradiol with 0.075 mg gestodene (6 patients); 0.03 mg of ethinylestradiol combined with 3 mg of drospirenone (6 patients) (►**Tables 3**, **4**, and **5**).

When the relative risk was calculated regarding the use of hormonal contraceptives for spotting and mastalgia, there was no statistical significance at the 95% confidence level. However, when calculated for headache, there was a relative risk of 2.1282 (1.3425–3.3739; 95% CI), suggesting that the use of pills increases the risk of headache as well as edema, for which a relative risk of 1.4435 (1.0177–2.0474; 95% CI) was observed. For low libido, the use of oral hormonal contraceptives was also shown to be a risk factor since its relative risk was 1.8805 (1.3527–2.6142; 95% CI). As for acne, the use of hormonal contraceptives proved to be a protective factor, with a relative risk of 0.3015 (0.1789–0.5082; 95% CI).

As for contraceptive methods other than the pill, the only one that showed any statistically significant calculation was the LRIS, which proved to be a risk factor for acne, with a relative risk of 6.8077 (4.3107–10.7510; 95% CI). However, it is important to note that the calculations were hampered by the low number of patients reporting the use of such method.

Discussion

Women are increasingly becoming the protagonist in choosing their contraceptive method. However, this is the first study in this region to evaluate the methods collateral effects according to each specific formulation. Not only that, but it is also one of the few studies in which patients could make a self-diagnosis, which helped us understand their feelings in relation to the contraceptive methods.

Despite using an online questionnaire and a convenience sample, our findings were very similar to those of the

Table 3 Percentage of adverse effects after using the pill and its composition

	0.03 mg ethinyl-estradiol + 0.075 mg gestodene	0.03 mg ethinyl-estradiol + 3 mg drospirenone	0.015 mg ethinyl-estradiol + 0.060 mg gestodene	0.035 mg ethinyl-estradiol + 2 mg cyproterone acetate	0.030 mg ethinyl-estradiol + 2 mg chlormadinone acetate	0.020 mg ethinyl-estradiol + 3 mg drospirenone	Estradiol valerate + dienogest
Spotting	42% (6)	24% (6)	5.9% (1)	7.9% (5)	20% (2)	22% (15)	31% (4)
Headache	36% (5)	20% (5)	12% (2)	33% (21)	40% (4)	31% (21)	30% (4)
Acne	0	0	0	3.2% (2)	0	2.9% (2)	7.6% (1)
Mastalgia	29% (4)	16% (4)	18% (3)	19% (12)	20% (2)	24% (16)	7.6% (1)
Edema	21% (3)	20% (5)	41% (7)	43% (27)	40% (4)	31% (21)	23% (3)
Low libido	78% (11)	48% (12)	59% (10)	44% (28)	30% (3)	46% (31)	23% (3)
Total users	14	25	17	63	10	68	13

Table 4 Percentage of adverse effects in women who used a contraceptive method other than the pill

	IUD	LRIS	Condom	Monthly injectable	Quarterly injectable	Implant
Spotting	16% (3)	27% (7)	0	12.5% (1)	25% (1)	50% (1)
Headache	0	0	5,5% (1)	12.5% (1)	50% (2)	0
Acne	32% (6)	58% (15)	11% (2)	12.5% (1)	0	50% (1)
Mastalgia	5% (1)	15% (4)	33% (6)	0	25% (1)	0
Edema	26% (5)	19% (5)	22% (4)	25% (2)	0	50% (1)
Low libido	5% (1)	19% (5)	11% (2)	37.5% (3)	50% (2)	50% (1)
Total users	19	26	18	8	4	2

Abbreviations: IUD, intrauterine device; LRIS, levonorgestrel-releasing intrauterine system.

Table 5 Women who reported improvement in symptoms after using contraceptive pills

	0.03 mg ethinyl-estradiol + 0.075 mg gestodene	0.03 mg ethinyl-estradiol + 3 mg drospirenone	0.015 mg ethinyl-estradiol + 0.060 mg gestodene	0.035 mg ethinyl-estradiol + 2 mg cyproterone acetate	0.030 mg ethinyl-estradiol + 2 mg chlormadinone acetate	0.020 mg ethinylestradiol + 3 mg drospirenone	Estradiol valerate + dienogest
Spotting	0	8% (2)	12% (2)	6.4% (4)	0	4.4% (3)	0
Headache	71% (10)	56% (14)	47% (8)	79% (50)	70% (7)	62% (42)	62% (8)
Acne	7.1% (1)	24% (6)	29% (5)	14% (9)	10% (1)	21% (14)	38% (5)
Mastalgia	0	12% (3)	0	11% (7)	20% (2)	18% (12)	31% (4)
Edema	0	4.0% (1)	0	1.6% (1)	0	3% (2)	0
Total users	14	25	17	63	10	68	13

literature worldwide, such as the mean age of users as 25 years old, the contraceptive pills as the most used method, and the main reason for dissatisfaction and discontinuation use of a contraceptive method.[13–16]

Although the pill is still the most used contraceptive method, the frequency of women using LARCs is increasing. Nevertheless, because of various myths and misconceptions this transition is happening at a slow pace in Brazil. One of the main reasons for this is the decrease in the use of hormonal methods and the increase in methods which are either hormone-free or have a lower hormone dosage, which can result in lower side effects.[17,18]

In view of the cardiovascular risk caused by estrogen, vasculopathic patients, such as those with hypertension, diabetes, obesity, and dyslipidemia, should avoid the use of hormonal methods, which may explain why the

prevalence of these comorbidities was so low in our study.[15,16]

Unplanned pregnancies are more common in women who are not satisfied with the contraceptive method they are using.[19] In our study, whose results agree with those of the literature, the main reason for dissatisfaction with a contraceptive method was adverse effects, such as spotting, headache, and low libido.[20]

While progesterone is the hormone ultimately responsible for preventing pregnancy, the estrogen component helps regulating menstrual bleeding.[16] However, in our study, the findings regarding irregular bleeding, such as spotting, were more prevalent in women who used lower doses of estrogen, such as 0.020 mg. And, despite the use of a higher dose, a relevant number of women using 0.030 mg of ethinylestradiol with drospirenone also reported spotting. This finding can indicate that the control of menstrual bleeding is not only dependent on estrogen dosage but also on the progestogen used to compose the pill. Due to its antiestrogenic effect, the progestogen may impact the effect of estrogen, which makes sense since drospirenone has a strong antiestrogenic action as has already been suggested by some studies.[21]

Another important adverse effect related to the use of contraceptives is headache, as shown in our study, which can be caused mainly by using combined pills.[22] It seems that every primary headache—as tension, migraine, and trigeminal-autonomous—is more prevalent in women, because female hormones have a main role on migraine.[23]

In our study, women who used hormonal methods reported more headache than those who did not used any hormonal method. Moreover, among those using hormonal methods, patients who used a higher estrogen dose seemed to have had more headaches than those who used less than 0.02 mg of ethynyl estradiol. However, the exact relationship between headache and hormone dosages remains unknown, and it should be a topic of future research.[24]

Unlike headaches, acne is more prevalent in those who do not use a hormonal method. And, unlike headaches, this relationship is already fully understood.[25] Acne is more frequent in women with hyperandrogenism, since the androgens not only regulate lipogenesis in sebocytes but also influence inflammation in acne and convert progesterone in testosterone.[24] Therefore, for women with acne, the best methods are those with a great antiandrogenic effect, such as cyproterone, which was observed in our study.

Mastalgia in women under contraceptive therapy is controversial, and, as shown in our study, it does not appear to suffer the influence of hormones.[26] The truth is that the reason why mastalgia happens is still unknown, even in women who do not use hormonal methods.[27] Regarding edema, drospirenone derivatives have emerged as an important treatment. Due to their antimineralocorticoid effects, they stimulate diuresis.[28] However, we must keep in mind that it is difficult to assess edema, especially when the study is performed based on patient report, as was our case.

Finally, one of the main patient complaints in relation to hormonal contraceptives is low libido. It is also one of the main reasons for discontinuation of the use of hormones and for switching to other methods, such as IUDs.[29] As seen in our study, it appears that women have a greater decrease in libido when using progestogens with greater antiestrogenic effect, such as gestodene, and it is a minor complaint in patients using pills containing dienogest, which has a minor antiestrogenic effect.

Despite this, more studies are needed, as the present study did not obtain a representative sample of the population in Brazil, since the majority of its population were white women and those in the medical field. Not only that, but as the women completed the questionnaire at home, some questions could have been misunderstood.

Conclusion

It is essential to understand the relationship of women with their contraceptive methods to be able to provide better medical care, since unplanned and unwanted pregnancies can often result from the inadequate use of contraceptive methods due to dissatisfaction with the method. We also must keep in mind that contraceptive methods have other effects beyond preventing fecundation. They can also have secondary beneficial effects, such as: prevention of acne and irregular bleeding and management of dysmenorrhea. All the effects must be taken into consideration when prescribing any type of method. Moreover, the choice of a contraceptive method must always be individualized, and the patients must be equal participants in the process. They must be aware of the possible adverse effects of each method and must be willing to try more than once to find the ideal one.

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

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

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Performance of the Fracture Risk Assessment Tool Associated with Muscle Mass Measurements and Handgrip to Screen for the Risk of Osteoporosis in Young Postmenopausal Women

Desempenho da ferramenta de avaliação de risco de fraturas associada à medida de massa muscular e à preensão manual no rastreio de risco de osteoporose em mulheres jovens pós-menopáusicas

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Abstract

Objective To evaluate the improvement in screening accuracy of the Fracture Risk Assessment Tool (FRAX) for the risk of developing osteoporosis among young postmenopausal women by associating with it clinical muscle mass measures.

Methods A sample of postmenopausal women was submitted to calcaneal quantitative ultrasound (QUS), application of the FRAX questionnaire, and screening for the risk of developing sarcopenia at a health fair held in the city of São Bernardo do Campo in 2019. The sample also underwent anthropometric measurements, muscle mass, walking speed and handgrip tests. A major osteoporotic fracture (MOF) risk $\geq$ 8.5% on the FRAX, a classification of medium risk on the clinical guideline of the National Osteoporosis Guideline Group (NOGG), and a QUS T-score $\leq$ -1.8 sd were considered risks of having low bone mass, and QUS T-score $\leq$ -2.5sd, risk of having fractures.

Results In total, 198 women were evaluated, with a median age of 64 $\pm$ 7.7 years, median body mass index (BMI) of 27.3 $\pm$ 5.3 kg/m^2 and median QUS T-score of -1.3 ± 1.3 sd. The accuracy of the FRAX with a MOF risk $\geq$ 8.5% to identify women with T-scores $\leq$ -1.8 sd was poor, with an area under the curve (AUC) of 0.604 (95% confidence interval [95%CI]: 0.509–0.694) for women under 65 years of age, and of 0.642 (95%CI: 0.571–0.709) when age was not considered. Including data on muscle mass in the statistical analysis led to a significant improvement for the group of women

Keywords
- osteoporosis
- menopause
- FRAX
- NOGG
- sarcopenia

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under 65 years of age, with an AUC of 0,705 (95%CI: 0.612–0.786). The ability of the high-risk NOGG tool to identify T-scores $\leq$ -1.8 sd was limited.

Conclusion Clinical muscle mass measurements increased the accuracy of the FRAX to screen for osteoporosis in women aged under 65 years.

Resumo

Objetivo Avaliar a melhora da precisão da Fracture Risk Assessment Tool (Ferramenta de Avaliação do Risco de Fraturas, FRAX, em inglês) no rastreio do risco de desenvolver osteoporose em mulheres jovens pós-menopáusicas com a associação de medidas clínicas de massa muscular e preensão manual.

Métodos Uma amostra de mulheres pós-menopáusicas foi submetida a ultrassom quantitativo (USQ) de calcâneo, à aplicação do questionário FRAX, e rastreadas quanto ao risco de desenvolver sarcopenia em uma feira de saúde realizada em 2019 em São Bernardo do Campo. Além disso, a amostra também foi submetida a antropometria, e a testes de massa muscular, velocidade de marcha, e preensão manual. Um risco de grandes fraturas osteoporóticas (GFOs) $\geq$ 8,5% no FRAX, classificação de médio risco nas diretrizes clínicas do National Osteoporosis Guideline Group (NOGG), e *T-score* no USQ $\leq$ -1,8 dp foram considerados riscos de ter baixa massa óssea, e *T-score* no QUS $\leq$ -2,5 sd, risco de ter fraturas.

Resultados Ao todo, 198 mulheres foram avaliadas, com idade média de 64 $\pm$ 7,7 anos, índice de massa corporal (IMC) médio de 27,3 $\pm$ 5,3 kg/m^2, e *T-score* médio no USQ de -1,3 $\pm$ 1,3 sd. A precisão do FRAX com um risco de GFO $\geq$ 8,5% para identificar mulheres com *T-score* $\leq$ -1,8 dp foi precária, com uma área sob a curva (ASC) de 0,604 (intervalo de confiança de 95% [IC95%]: 0,509–0,694), para mulheres menores de 65 anos de idade, e de 0,642 (IC95%: 0,571–0,709) quando a idade não foi considerada. A inclusão de dados da massa muscular na análise estatística levou a uma melhora significativa no grupo menor de 65 anos de idade, com uma ASC de 0,705 (IC95%: 0,612–0,786). A habilidade da ferramenta NOGG de alto risco para identificar *T-scores* $\leq$ -1,8 dp foi limitada.

Conclusão As medidas clínicas da massa muscular aumentaram a precisão do FRAX no rastreio de osteoporose em mulheres menores de 65 anos de idade.

Palavras-chave
- osteoporose
- menopausa
- FRAX
- NOGG
- sarcopenia

Introduction

An increase in life expectancy and an aging population are associated with a higher prevalence of osteoporosis and fragility fractures. This certainly occurs in Brazil, where life expectancy has increased from 50 years in 1952 to 71 in 2010, and is estimated to be 80 years by 2050.[1,2]

One of the main challenges in osteoporosis care is the identification of individuals at a higher risk of incurring in fractures and, accordingly, the establishment of a preventive therapeutic approach. In last few years, clinical tools, associated or not to dual-energy X-ray absorptiometry (DXA), have been developed to improve the accuracy of fracture identification. The use of calcaneal quantitative ultrasound (QUS), a method more practical and less expensive than DXA, to predict the risk of fracture is also recommended. According to the World Health Organization (WHO), QUS cannot be used to diagnose osteoporosis or to monitor the effectiveness of the therapy. There are, however, studies[3,4] that confirm that QUS can predict fractures in elderly women, such as the one by Moayyeri et al.[3] (2012) a meta-analysis with a total follow-up of 279,124 people.

Clinical tools such as the Garvan fracture risk calculator, the QFracture risk calculator, and the Fracture Risk Assessment Tool (FRAX; https://www.sheffield.ac.uk/FRAX/) combine age and gender with clinical risk factors to estimate the risk of fracture in the next 5 or 10 years. There are also tools for osteoporosis screening, mainly for women younger than 65 years of age, as DXA is not universally recommended. Tools such as the Simple Calculated Osteoporosis Risk Estimate (SCORE), the Osteoporosis Self-Assessment Tool (OST), and the Osteoporosis Risk Assessment Instrument (ORAI), and even the FRAX, may be mentioned, as there is no standard for the analysis of this population.[5,6]

Brazilian guidelines recommend the use of the FRAX associated to the strategy for screening of the National Osteoporosis Guideline Group (NOGG), which enables the classification of individuals into high-, medium- and low-risk groups for fragility fractures. Those in the high-risk group should receive pharmacological treatment, those in

the medium-risk group should undergo DXA as screening for osteoporosis, and those in the low-risk group should be advised on their lifestyle habits.[7,8]

Although these strategies are recommended, very few studies[9] have evaluated their accuracy in identifying the risk of fracture and in tracking osteoporosis in the Brazilian population. In the young American postmenopausal population, the performance of the FRAX in identifying women with a risk of incurring in fractures was poor.[12] Simpler tools than the FRAX, such as the OST, have shown a better specificity, but they also demonstrate low sensitivity.[9–12]

The progressive loss of skeletal muscle mass and function in conjunction with aging is known as sarcopenia. It is considered a component of frailty syndrome leading to a higher risk of falling and fragility fractures. Its diagnosis is based on the assessment of muscle force and physical performance. The identification of individuals at risk of developing sarcopenia is simple, and it can be performed in ambulatory care.[13–15]

Osteoporosis and sarcopenia are usually connected to one another and both contribute to disability and frailty in the elderly. Nevertheless, clinical signs of sarcopenia or muscular mass evaluations are not incorporated in the clinical tools for the assessment of the risk of fracture.[15]

Therefore, the present study aims to evaluate the performance of the FRAX associated with skeletal muscular mass analyses in screening and diagnosing postmenopausal osteoporosis.

Methods

Population

In the present cross-sectional study, clinical data and supplementary exams were reviewed, after they were collected during the XXII Maratona da Saúde e Cidadania Dr. Claudio Zago, a health fair health held on April 13th, 2019, by the São Bernardo do Campo Rotary Club. In this event, the department of obstetrics and gynecology of Faculdade de Medicina do ABC (FMABC) invited postmenopausal women aged 50 years or older to take part in the activities in their booth. The activities comprised the application of structured clinical questionnaires on sarcopenia and osteoporosis, assessments of the height, weight, and circumferences of the arm, thigh, and calf, a walking speed test, the handgrip strength test, and the performance of a calcaneal QUS. The present study was approved by the Ethics in Research Committee of FMABC.

Procedures

Questionnaires

The subjects answered three specific questionnaires: the first one involved personal and clinical data, the second one was regarding the risk of bone fracture in 10 years (FRAX), and the third one was on the risk of developing sarcopenia. All questionnaires were applied by trained medicine students.

Clinical Questionnaire

The subjects were asked about their age, weight, height, ethnicity, time since the onset of menopause, previous use of hormone replacement therapy, smoking and/or drinking habits, the regularity of physical activity and muscle mass performance.

Sarcopenia Questionnaire

The subjects answered the Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire. Developed by American researchers, it identifies people with increased risk of developing sarcopenia through five questions approaching the areas in its name: strength, assistance with walking, rising from a chair, climbing stairs, and falls. Each answer is scored from 0 to 2, resulting in a final score ranging from 0 to 10. Scores ≥ 6 indicate a higher risk of developing sarcopenia.[14,16]

FRAX Questionnaire

All subjects were submitted to the FRAX-Brazil quationnaire. This clinical tool developed by the WHO matches clinical data and estimates the percentage risk of hip fracture and major fractures (clinical spinal, forearm, hip and shoulder fractures) for the following 10 years. In the present study, a risk of major osteoporotic fracture (MOF) $\geq 8.5\%$ on the FRAX was adopted as the criteria to perform a supplementary bone densitometry exam.[17]

NOGG Grading

Using the NOGG tool (available at https://www.sheffield.ac.uk/NOGG/), the subjects were classified in low-, medium- and high-risk groups. The NOGG tool recommends that people in the medium-risk group should undergo the bone density test to screen for osteoporosis. In the present study, we chose to group the individuals classified as medium- and high-risk according to the NOGG tool, considering that this is the population for whom densiometry should be requested or who should undergo pharmacological treatment.

Anthropometric and Muscle Mass Measurements

The measurements of height, weight and of the circumferences of the arm, thigh and calf were made with a measuring tape and a Geratherm scale. During weighing, the patients were guided to take off their coats and bags. The measurment of the circumferences was standardized as follows:[13,17–28]

Arm – midpoint between the lateral projection of the acromion process of the scapula and the lower margin of the ulnar olecranon.

Calf – at its widest point.

Thigh – midpoint on the trochanteric and the margin of the kneecap.

Assessment of Sarcopenia

The subjects were assessed according to the definition of sarcopenia of the European Working Group on Sarcopenia in Older People (EWGSOP).[14,16] To calculate the muscle mass (MM) in kilos (Kg) recomended by the EWGSOP, the

predictive equation described by Lee et al. [18] (2000) was used, in which:

- MM (Kg) = Ht x (0.00744 x AC^2 + 0.00088 x TC^2 + 0.00441 x CC^2) + 2.4 x gender – 0.048 × age + race + 7,8.

In the equation, Ht refers to the height in centimeters (cm), AC, to the arm circumference in cm, TC, to the thigh circumference in cm, and CC, to the calf circumference in cm. Regarding gender, the value of 1 is considered for men, and 0 for women; as for race, the values are -2.0 for Asians, 1.1 for African-Americans, and 0 for Whites or Hispanics. In the present study, the race score was adapted, considering -2.0 for Asians, 1.1 for people who considered themselves black or brown (*pardo* or *negro*, in Portuguese) and 0 for people who considered themselves white (*branco*, in Portuguese).

The skeletal MM index was calculated as MM divided by the squared height. Subjects with values between 5.5 kg/m^2 and 6.76 kg/m^2 were considered at risk of developing sarcopenia. The muscle strength was evaluated using an electronic handgrip, which estimates the person's muscle strength in kg based on the maximum strength reached in palm pressure. The measurements were recorded using the dominant arm, with the woman standing up straight, with both arms straight down and equidistant feet. The gadget was previously calibrated for females aged ~ 60 years. Women with results bellow 20 kg were considered at risk of developing sarcopenia.[19–21]

Finally, a walking speed test was used. The women would walk a distance of 6 m, in which the first meter was used to increase the walking speed, the 4 following meters were for timing the normal walking speed, and the last meter, for deceleration. Those with a time ≥ 0.8m/s were considered at risk of developing sarcopenia.

Calcaneal Quantitative Ultrasound (QUS)

All subjects underwent calcaneal QUS, with the GE Lunar Achilles Express ultrasonometer (GE Healthcare, Chicasgo, IL, US), through which the standard deviation values of bone mass related to the young adult population (T-score) can be obtained, as well as those with the same age (Z-score). In the present study, subjects with T-scores ≤ -1.8 sd were considered at risk of developing osteoporosis, and those with scores ≤ -2.5 sd, at risk of incurring in fractures.[29]

Statistical Analysis

The Microsoft Excel 2018 (Microsoft Corp. Redmond, WA, US), version 1910, was used to organize the data obtained, and the MedCalc Statistical Software (MedCalc Software bv, Ostend, Belgium), version 19.1, was used to conduct the statistical analysis. The Kolmogorov-Smirnov test was used to test the normal distribution of the numeric data. The continuous numeric data was expressed as means ± standard deviations, and the categorical data, as frequencies and percentages. The comparison of the groups was performed using the Student *t*-test for independent samples when the continuous numeric data followed a normal distribution, and the Wilcoxon test, for the data which did not follow a normal distribution. For the categorical data, the comparisons were made using the Chi-squared test. The diagnostic accuracy was evaluated through the area under the curve (AUC), following the methodology described by DeLong et al.[30] In all scenarios, a level of significance of 5% was adopted.

Results

A total of 200 patients were evaluated, 2 of whom were excluded for having weight higher than that allowed by the FRAX. The median age was of 64 ± 7.7 years, the median body mass index (BMI) was of 27.3 ± 5.3 kg/m^2, and the median T-score in the QUS was od -1.3 sd, (►**Table 1**). In the comparison of age groups, the population aged ≥ 65 years obtained inferior values, which was statistically significant, in the parameters related to fat, lean and bone mass, as well as in the SARC-F and physical performance (►**Table 1**).

The accuracy of using the FRAX with a MOF risk ≥ 8.5% for osteoporosis screening (T-score ≤ -1.8 sd) was poor (►**Fig. 1**, ►**Fig. 2**, ►**Table 2** and ►**Table 3**), with an AUC of 0.604 (95% confidence interval [95%CI]: 0.509–0.694) for women under 65 years of age, and of 0.642 (95%CI: 0.571–0.709) when age was not considered. Including MM data in the statistical analysis led to a significant improvement in the group of women under 65 years of age, with an AUC of 0.705 (95%CI: 0.612–0.786).

►**Table 4** shows that the NOGG tool had a sensitivity of 17% to identify individuals with QUS T-score ≤ -1.8 sd, as well as a specificity of 84%, a positive predictive value of 31%, and a negative predictive value of 71%.

Discussion

In the present study, e observed that the ability to identify low bone mass in women under 65 years of age was greater when measurements of the circumferences of the arm, calf, and thigh were associated with the FRAX with a MOF risk ≥ 8.5%.

Although studies are scare, especially regarding the population under 65 years of age, the relationship between MM measurements and and the risk of fracture has already been evaluated. Faulkner et al.[32] analyzed 8,074 women aged 67 years or older during 1,6 years, and found a correlation between the length of the hip axis and increased risk of trochanteric fracture (odds ratio [OR] = 1.6; 95%CI: 1.0–2.4) and femoral neck fracture (OR = 1.9; 95% CI 1.3–3.0). In another study, Farmer et al.,[31] who evaluated a population aged between 40 and 77 years, found a relationship of the arm muscle area and the thickness of the triceps skinfold with an increased risk for hip fractures.[12,31,32]

It stands out that the absolute risk of fracture for any bone density value among young postmenopausal women is small compared with the risk for those aged over 65 years. According to Doherty et al.,[33] the probability of vertebral or hip fracture at 5 years is of 03% and 0% respectively among women aged between 50 and 54 years, of 0.5% and 0.2% among those aged between 55 and 59 years, and of 1% and 0.2% among women aged between 55 and 64 years. The

Table 1 Clinical and anthropometric characteristics, diagnostic parameters of sarcopenia, and bone density of the study sample and comparison when divided by age group

	TOTAL	AGE			
		≤ 65 years (*N* = 115)	> 65 years (*N* = 83)	*p**	
	Mean ± standard deviation	Mean ± standard deviation	Mean ± standard deviation		
Weight (Kg)	65.8 ± 13.1	67.6 ± 14.1	63.8 ± 10.8	0.0170	
Height (m)	1.5 ± 0.1	1.55 ± 0.1	1.5 ± 0.1	< 0.0001	
BMI (Kg/m^2)	27.3 ± 5.3	27.7 ± 5.8	26.8 ± 4.4	< 0.0001	
AC (cm)	30 ± 4.4	30 ± 4.3	29 ± 4.4	< 0.0001	
TC (cm)	50 ± 6.3	51 ± 6.1	49.5 ± 6.5	< 0.0001	
CC (cm)	36 ± 4.0	37 ± 4.0	35 ± 4.0	< 0.0001	
MM (Kg)	27.7 ± 5.9	28.8 ± 5.9	26.1 ± 5.2	< 0.0001	
SMMI (Kg/m^2)	11.3 ± 2.3	11.8 ± 2.3	10.92 ± 2.0	< 0.0001	
Handgrip (Kg)	21 ± 5.5	22.3 ± 5.3	19.4 ± 5.5	< 0.0001	
GS (m/s)	0.89 ± 0.2	0.9 ± 0.2	0.85 ± 0.2	< 0.0001	
T-score on the calcaneal QUS	-1.3 ± 1.3	-1 ± 1.2	-1.6 ± 1.2	< 0.0001	
SARC-F	2 ± 2.3	1 ± 2.4	2 ± 2.2	< 0.0001	
		n (%)	n (%)	n (%)	*p***
Ethnicity	White	119 (60.1)	64 (55.7)	55 (66.3)	0.124
	Brown or Black	68 (34.3)	46 (40)	22 (26.5)	
	Asian	11 (5.5)	5 (4.3)	6 (7.2)	
Level of schooling	Illiterate	3 (1.5)	2 (1.7)	1 (1.2)	0.259
	Incomplete Primary Education	47 (23.7)	29 (25.2)	18 (21.7)	
	Complete Primary Education	31 (15.6)	15 (13.0)	16 (19.3)	
	Incomplete High School	72 (36.3)	47 (40.9)	25 (30.1)	
	Complete High School	16 (8.0)	10 (8.7)	6 (7.2)	
	Higher Education	29 (14.6)	12 (10.4)	17 (20.5)	
SARC-F ≥ 6	Yes	23 (11.6)	12 (10.4)	8 (9.6)	0.956
	No	174 (88.3)	103 (89.6)	75 (90.4)	
T-score ≤ -1.8 sd	Yes	58 (29.3)	23 (20)	35 (42.2)	0.001
	No	140 (70.7)	92 (80)	48 (57.9)	
Z-score ≤ -2.5 sd	Yes	27 (13.6%)	9 (7.8)	18 (21.7)	0.005
	No	171 (86.4%)	106 (92.2)	65 (78.3)	

; AC, arm circumference; BMI, body mass index, CC, calf circumference; MM, muscle mass; SMMI, skeletal muscle mass index; VM - gait speed; QUS, quantitative ultrasound; SARC-F, Strength, assistance with walking, rising from a chair, climbing stairs, and falls questionnaire; TC, thigh circumference.
Notes: *Correlation between age and the evaluated data through the Wilcoxon correlation test; **comparison between age over 65 years and ≤ 65 years by the Chi-squared test.

performance of universal screening with the bone densitometry test for all women over 50 years of age is an expensive and ineffective strategy. Accordingly, providing a more accurate screening alternative is critical as a public health strategy.

Currently, although numerous diagnosis tools have already been developed, there is no consensus as to which should be used, or even as to which guideline should be followed to identify low bone mass in young postmenopausal women. In 2014, Crandall et al[12] evaluated the diagnostic tools for this population, and obtained a FRAX AUC value of 0,60, which is considered low, and is similar to that found in the present study (0,604). When comparing it to other screening methods, the authors[12] found that the sensitivity and specificity of the OST, which uses only age and weight, was higher than those of the FRAX with a MOF risk ≥ 8.4%.

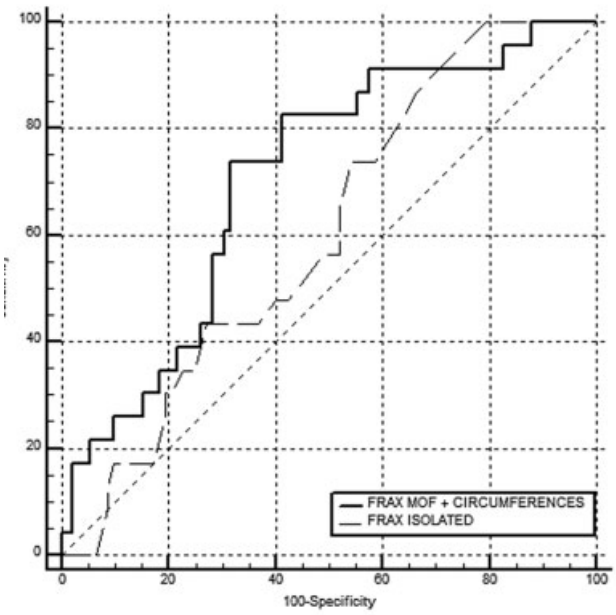

Fig. 1 Performance of the Fracture Risk Assessment Tool (FRAX) regarding the risk of major osteoporotic fracture (MOF) taken in isolation and associated with circumference measurements to identify women under 65 years of age with T-score $\leq$ -1.8 sd on calcaneal quantitative ultrasound (QUS).

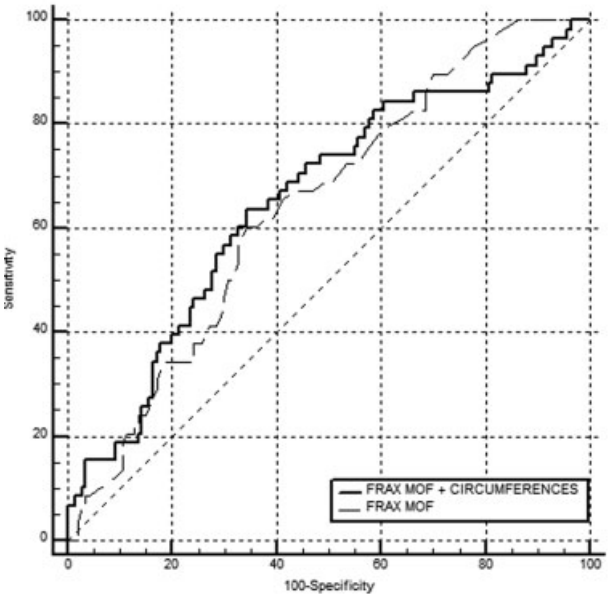

Fig. 2 Performance of the FRAX regarding the MOF risk taken in isolation and associated with circumference measurements to identify women with a QUS T-score $\leq$ -1,8 sd without considering age.

The mean of age of 64 years shows that the sample of the present study is representative of young postmenopausal women, the focus of the study, who, as expected, showed better performance, strength and MM. Despite this, 20% of this population presented T-scores $\leq$ -1.8 sd and 7.8% $\leq$ -2.5 sd in the QUS. This finding differs from the small fracture rate

Table 2 Analysis of ►**Figure 1**

	Area under the curve	Standard Error	95% Confidence Interval
FRAX MOF	0.604	0.059	0.509–0.694
FRAX MOF + CC	0.705	0.058	0.612–0.786

Abbreviations: CC, circumferences; FRAX, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture.

Table 3 Analysis of ►**Figure 2**

	AUC	Standard Error	95% CI
FRAX MOF	0.642	0.041	0.571–0.709
FRAX MOF + CC	0.654	0.043	0.583–0.720

Abbreviations: 95%CI, 95% confidence interval; AUC, area under the curve; CC, circumferences; FRAX, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture.

Table 4 Comparison between medium- or high-risk and low-risk subjects in the NOGG clinical guideline to identify individuals with T-score $\leq$ -1,8 sd on calcaneal qualitative ultrasound

	T-score $\leq$ -1,8 n (%)	T-score $>$ -1,8 n (%)	p^*
Medium- or high-risk on the NOGGclinical guideline	10 (5)	22 (11)	0.7910
Low-risk on the NOGG clinical guideline	48 (24)	118 (60)	

Abbreviation: NOGG, National Osteoporosis Guideline Group.

expected among this population in 5 years, as documented by Doherty et al.[33] in 2001, and it can be explained by the fact that the sample was not chosen at random, but consisted of women who saught medical assistance at a health fair.

The low performance of the NOGG tool when compard with the QUS can be explained by the fact that the majority of the women included in the study was young, with good bone mass levels. Another relevant factor is that only 32 patients, a low number, were classified as high-risk. In any case, there are few studies evaluating the performance of the NOGG tool among the Brazilian population, especially among women aged $\geq$ 65 years. Even though the QUS is not a standard for the diagnosis of osteoporosis, it presents high clinical applicability in terms of the prediction of fractures, as confirmed by Moayyeri et al.[3] in a study with a follow-up of more than 200 thousand person-years.

The results of the present study are substantial, considering that the sample comprised a significant number of the population, people from the community, and not previously

selected, as occurs with patients cared for in outpatient clinics. Nevertheless, the present research may be considered notable due to the fact that it is, perhaps, the first Brazilian study to correlate risk factors for sarcopenia with the diagnosis of osteoporosis or the risk of fracture. The results have a relevant potential for application in the medical practice.

The present study has several limitations. The ethnic groups included present different body fat distribution, a factor considered a bias by Lee et al.[18] during the development of the equation for the MM analysis. Further, the population evaluated was overweight, which interfered with the interpretation of the MM and sarcopenia results. Another fact considered relevant was that the population had anthropometric measurements taken in a non-standardized way in relation to their clothing, because it was an event open to the public, with a high flow of people. In addition, it is known that the QUS, a method used as a parameter to assess bone mass, is not a standard for the diagnosis. However, it is a tool that may be used at a health fair with a reasonable degree of accuracy. The present study will be repeated, with the possibility of inviting patients and applying bone densitometry in the future.

The association of measurements of the calf, arm and thigh improved the accuracy of the FRAX to detect individuals under 65 years of age with lower bone mass on the QUS. This demonstrates the importance of evaluating parameters related to MM in the identification of individuals at risk of developing osteoporosis or incurring in fragility fractures. Associating such measures with the FRAX tool, improving the performance of these strategies, has a great potential regarding osteoporosis care, especially among young postmenopausal women. Further studies are needed to confirm the findings of the present study and establish new approaches in the screening and diagnosis of the risk of fracture due to frailty.

Conclusion

The association of arm, thigh, and calf measurements increased the accuracy of the FRAX to screen for osteoporosis among women under 65 years of age.

Contributors

All authors participated in the concept and design of the study, in the analysis and interpretation of data, in the draft or revision of the manuscript, and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests

The authors have no conflict of interests to declare.

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Analysis of the Excess of Papanicolaou Tests in Brazil from 2006 to 2015

Análise do excesso de testes de Papanicolaou no Brasil entre 2006 e 2015

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Abstract

Objective To analyze the quantity of cervical smears, also designated Papanicolaou tests, between 2006 and 2015 in all the Federal units of Brazil, as well as to verify the quantity of exams collected outside the recommended age range and the economic impact of such excess.

Methods The data was collected from the Ministry of Health's database called *Sistema de Informação do Câncer do Colo de Útero* (SISCOLO), which contains all the test results collected nationwide by the Unified Health System (SUS, in the Portuguese acronym). From that, the number of exams and the age range of the women who underwent them were analyzed; besides, these numbers were stratified according to the state of where the exam was performed. The quantity of exams collected outside the recommended age range was verified, and, so, the economic impact generated was noted.

Results Between 2006 and 2015, 87,425,549 Papanicolaou tests were collected in Brazil. Of these, 20,215,052 tests were collected outside the age range recommended by the Brazilian Ministry of Health; this number corresponded to 23.12% of all exams. From such data, considering that each Pap smear collected by SUS generates a cost of BRL 7.30 to the government, according to the information in the *Tabela SUS* dated September 2018, there was a total charge of BRL 147,569,880 for tests collected outside the protocol.

Conclusion In Brazil, according to the Ministry of Health's protocol about the recommended practices on collecting Pap smears, whose newest edition dates of 2016, it is recommended that Pap smears are collected in women from a specific age range, in whom the potential diagnosing advantages overcome the onus of overdiagnosis or of a lesion with great regression potential. However, such protocols have not been correctly followed, promoting more than 20 million tests in excess, and an exorbitant cost for the Brazilian public health system. It is relevant to take measures to correctly use the official protocol, reducing the patients risks, as well as the economic impact for SUS.

Keywords
- Papanicolaou test
- uterine cervix
- cervical neoplasia
- public health

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Resumo

Objetivo Analisar a quantidade de exames cérvico-vaginais, também chamados de Teste de Papanicolau, entre os anos de 2006 e 2015 em todos os estados brasileiros, bem como verificar o número de exames realizados fora da faixa etária indicada, e o impacto econômico desse excesso.

Métodos Os dados foram coletados a partir da base de dados do Ministério da Saúde chamada Sistema de Informação do Câncer do Colo de Útero (SISCOLO), que reúne os resultados de exames realizados em todo o Brasil pelo sistema único de saúde (SUS). A partir disso, foi analisado o número de exames e a faixa-etária de realização dos mesmos; além disso, esses números foram estratificados de acordo com o estado brasileiro de origem do exame. Foi verificada a quantidade de exames fora da idade recomendada, e, assim, foi observado o impacto econômico gerado.

Resultado Entre 2006 e 2015, 87.425.549 exames de Papanicolau foram realizados no Brasil. Deste montante, 20.215.052 testes foram realizados fora da faixa-etária preconizada pelo Ministério da Saúde do Brasil, o que equivale a 23,12% do total. A partir desse número, considerando que cada exame cérvico -vaginal realizado pelo SUS gera um custo de R$ 7,30 para o governo, de acordo com informações na Tabela SUS datada de setembro de 2018, foram gastos R$ 147.569.880 em exames realizados sem indicação.

Conclusão No Brasil, no protocolo do Ministério da Saúde sobre as práticas adequadas em coleta de exames cérvico-vaginais, sendo sua edição mais recente de 2016, a recomendação é realizar o teste de Papanicolau em mulheres dentro de uma faixa-etária específica, na qual a chance de se diagnosticar uma lesão supera o ônus de um sobrediagnóstico ou uma lesão com grande potencial de regressão. Entretanto, essa recomendação não tem sido seguida corretamente, gerando mais de 20 milhões de exames excedentes e um custo monetário exorbitante para o sistema público de saúde. É importante que medidas sejam tomadas para que o protocolo seja empregado corretamente a fim de reduzir riscos para a paciente, bem como a redução de gastos desnecessários para o SUS.

Palavras-chave

- teste de Papanicolau
- colo do útero
- neoplasias do colo
- saúde pública

Introduction

Cervical cancer is a public health issue, even though it is an avoidable disease.[1,2] It is the third most frequent tumor in women worldwide[2] and the fourth cause of death for malign tumors in women around the world,[1] responsible for the death of 274 thousand women every year worldwide.[3]

In the past 30 years, a relationship between cervical cancer and human papillomavirus (HPV) has been established, justifying the disease's etiology.[4] Human papillomavirus infection may occur in up to 80% of women along their sexual life,[5] even though the infection alone is not sufficient for the cancer to evolve, so, mostly, the infection is transient and its natural course is spontaneous resolution, which can take from 6 months to 2 years.[6]

Considering the natural history of the disease and its great regression potential, the guidelines from the Brazilian Ministry of Health recommend starting to collect Pap smears at 25 years-old, if the patient has already initiated her sexual life, repeating the exam annually for the first 2 years, and, from then on, if there is no cytological abnormality with malign potential, the collections may be performed every 3 years and should be interrupted when the woman reaches 64 years old.[7] There is a tendency of many women to do the Pap test annually, although it is known that reduction of the cumulative incidence of cervix invasion lesions is 93.5% when the test is done annually and 90.8% when done triennially,[8] which justifies the Brazilian guidelines. The excess of Pap smears, especially in those women who are not in the age range recommended by the Ministry of Health, overtaxes the public health system, especially considering that Brazil is a developing country and has a continent-dimension territory. Furthermore, it is important to consider quaternary prevention, which enforces the need to avoid possible damages associated with unnecessary medical interventions, such as iatrogeny.

Therefore, the objective of the present study is to verify the quantity of cervical screenings collected between 2006 to 2015 in all Brazilian states and the number of exams from 2006 to 2015 that did not fill the age criteria recommended by the Brazilian Ministry of Health, including its economic impact.

Methods

This is a descriptive, transversal, and analytical study, and the data was collected from the Ministry of Health's online

database called *Sistema de Informação do Câncer do Colo de Útero* (SISCOLO), which contains all the test results collected nationwide by the Unified Health System (SUS, in the Portuguese acronym). The target population of this study was women, especially those under 25 years-old as well as those older than 64 years old, who do not fill the recommended age range recommended by the Ministry of Health. From such data, we analyzed the quantity of exams performed between 2006 and 2015, in all Brazilian states, and how many were not done according to the Brazilian Ministry of Health protocol, whose guideline has been in place since 1986, and the conduct suggested by this guideline has been endorsed in every normative actualization about oncotic cytology, with the latest edition being from 2016. Moreover, also between 2006 and 2015, we analyzed the quantity of exams in each Brazilian region, and the economic impact of these surpluses, considering the rationalization and the proper management of public resources.

Results

Based on the data collected from the SISCOLO platform, it became possible to accomplish a quantitative demographic analysis of age and geographic patterns of screening examinations on cervical cancer. In total, 87,425,549 Papanicolaou tests were collected throughout Brazil between 2006 and 2015. Such total number was stratified by age group and by Brazilian regions and states. Of that amount, 20,215,052 were made outside the Ministry of Health recommended age range, which consists in 23.12% of all collected exams during the evaluated period. It was observed that, considering absolute values, the Southeast region, in which the state of São Paulo stands out, had the highest number of exams during the period analyzed in this study, totalizing 39,801,111 Pap smears collected. Within that number, 9,166,999 of the Pap smears collected belong to women who are not in the age range recommended by the Brazilian Ministry of Health. The complete data about the number of Pap smears collected by year and by Federative unit is demonstrated in ►**Fig. 1**.

It is relevant to highlight that, considering relative values, the Southeast region also has the lead, especially when the relation between the total number of Pap smears collected from 2006 to 2015 and the region's absolute female population in 2010 are compared, to use the median of the evaluated period. However, only in 2010, when the ratio between the total Pap smears collected in that year and the absolute female population are compared, the South region (11.89%), followed by Southeast region (11.57%), has the lead. It is relevant that, in the statistics related to the Pap tests collected in 2010 and its relationship with the total female population in that year, the maximum amplitude between the percentages in the South, Southeast, Central-West and Northeast, not including the North, was low (1.28 percentage point), which demonstrate some kind of uniformity in the exams collection, according to each region's population. The North region, on the other hand, showed the ratio of Pap smears collected in such year/female population in 2010 of 7.71% (0.0771), representing a result considerably below the national average (10.97%), while the Northeast (10.61%) and Central-West regions (10.68%), even though their statistics were also below the national average, showed smaller

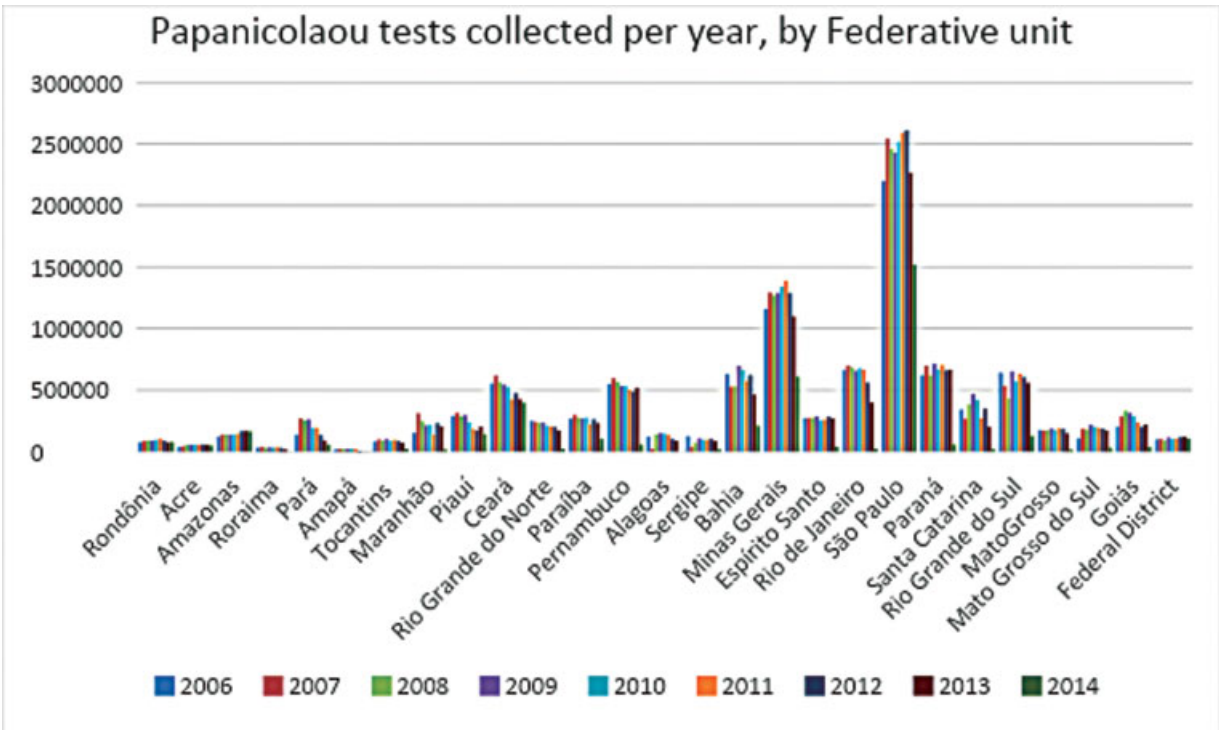

Fig. 1 Papanicolaou tests collected per year, by Federative unit.

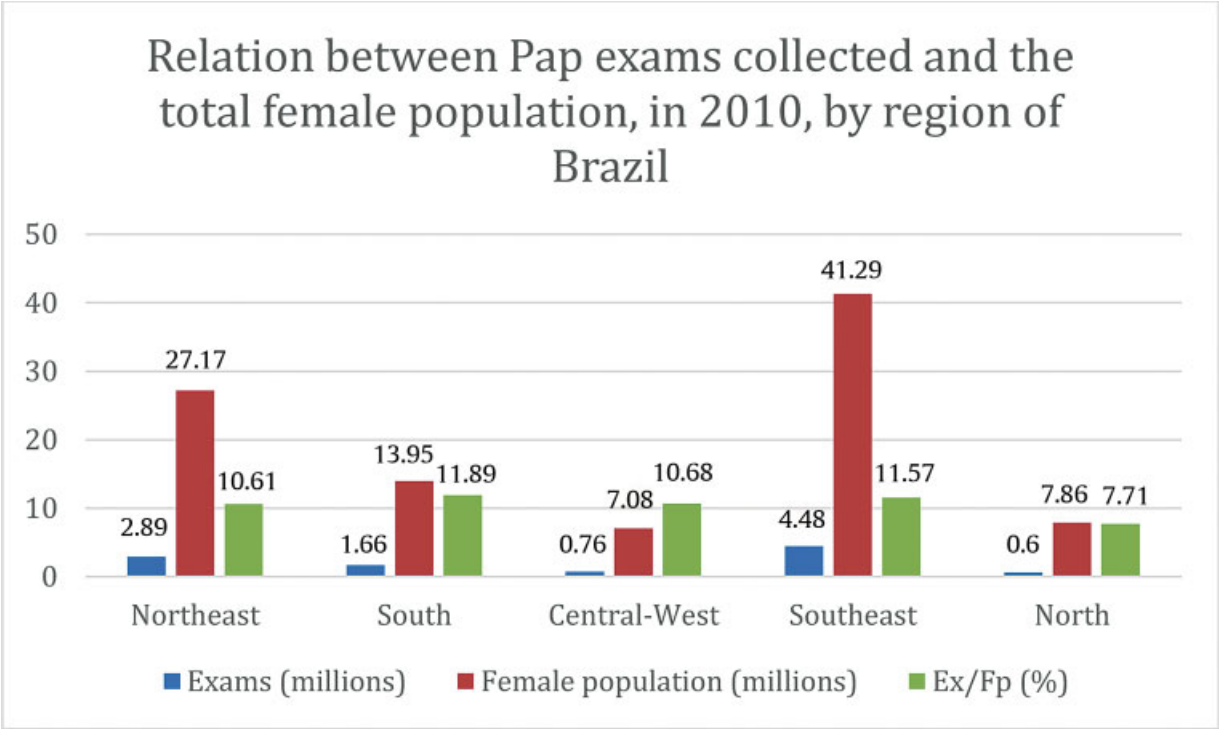

Fig. 2 Relation between Pap exams collected and the total female population, in 2010, by region of Brazil.

discrepancy. The detailed information about the relationship between the female population and the number of Pap smears collected in each region of Brazil can be found in ►**Fig. 2**.

In another analysis, now comparing the total number of Pap smears collected between 2006 and 2015 and the female population in 2010, the North region also presented the lowest percentage among the 5 regions of Brazil (67.62%). Such percentage was below the national average too (88.53%), as well as the Central-West (84.81%) and Northeast (86.23%) regions, though such regions do not show as much discrepancy in relation to the national average as the North region does. Low population density, presence of many isolated territories and populations, as well as difficult access to medical care are factors that may explain such results. When analyzing the Pap tests collected between 2006 and 2015, it was observed that a relevant percentage of all exams were collected in women of the age range < 24 years old or > 65 years old, that is, out of the age gap recommended by the Brazilian Ministry of Health. More than 20% of all Pap smears were collected outside such protocol, reaching 23.98% in the Northeast region, and presenting the lowest rate in the South region, with 22.04%. Thus, there is a maximum amplitude among regions of 1.94 percentage point, while the national average is 23.12%. It is relevant, addressing economics aspects of such topic, account the cost to the public health system budget induced by the needless exams collected. Since the value spent by SUS for each Pap smear collected is BRL 7.30, information acquired by the *Tabela SUS* dated September 2018, in which the values paid to the service providers referred to the procedures covered by SUS are shown, it becomes possible to evaluate the excessive amount of money spent on collecting such unnecessary Pap smears. The total cost with unnecessary exams collected in a manner inconsistent with the protocol from the Ministry of Health all over Brazil during the cited period was BRL 147,569,880. The information regarding each Brazilian region is graphically represented in ►**Fig. 3**.

Discussion

Cervical cancer represents the third most common tumor in the Brazilian female population, and it is the fourth type of cancer in the cancer mortality scale in that same population. Still, especially in underdeveloped and developing countries, it is considered a public health issue and a major concern worldwide.[9]

It is estimated that up to 80% of the sexually active population will acquire HPV over their lifetime. The article by de San José et al.[5] estimates that 291 millions of women have HPV and considers that 32% of them are infected by subtypes 16 and 18 , or both, which are known as high-grade oncogenics, and considering that, according to Ferlay et al.,[10] the annual incidence, worldwide, is 530 thousand cervical cancer cases per year, it can be inferred that the presence of HPV alone is not a sufficient factor for the development of cancer, and it can be even considered a rare outcome.

Human papillomavirus infection is usually transient and has spontaneous regression, which may happen between 6 months and 2 years after acquiring the infection.[6] It is believed that low-grade squamous intraepithelial lesions (LSILs) do not actually represent a precursor lesion of cancer,

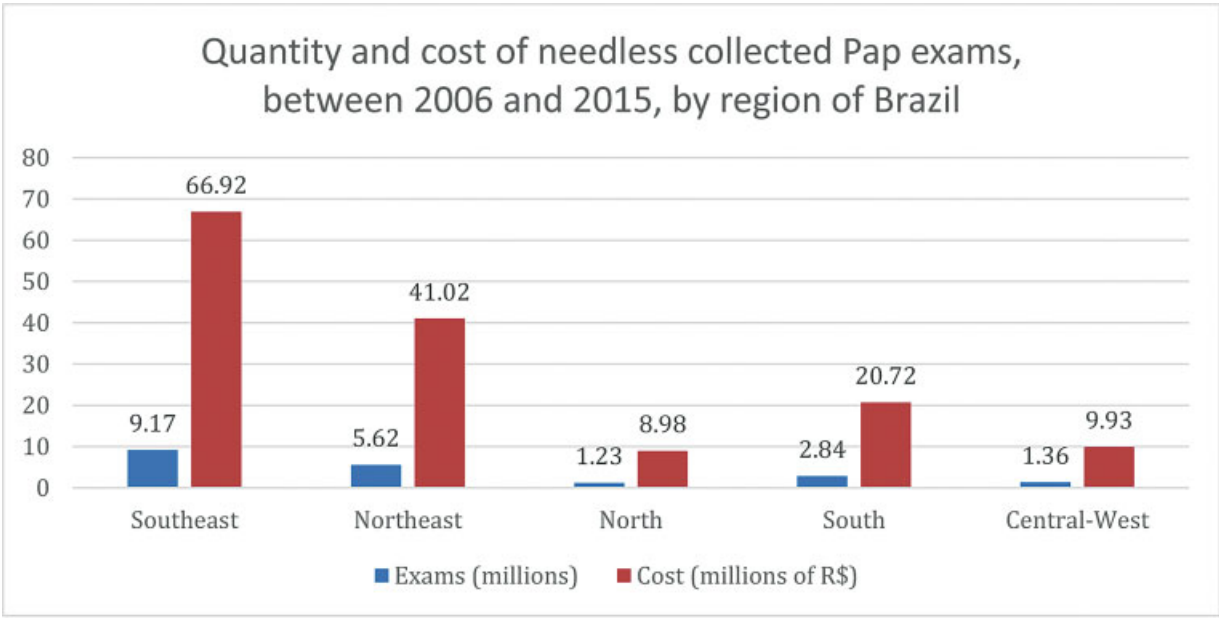

Fig. 3 Quantity and cost of needless collected Pap exams between 2006 and 2015 by region of Brazil.

but rather a cellular manifestation that denotes the virus infection, although high-grade squamous intraepithelial lesions have the potential to progress to cancer.[5]

When there is infection by subtype 16 and it persists, it is estimated that the risk of developing cervical intraepithelial neoplasia grade 3 (CIN 3) or a more serious injury in 3 years is 5% and, in 10 years, 20%.[11]

McCredie et al.[12] analyzed medical documents of a survey conducted in New Zealand between 1965 and 1974 in which patients with cervical cancer precursor lesions, in this case CIN 3, were not treated at the time, which was later considered unethical, and it was observed that the cumulative incidence of cervical cancer was 31.3% in 30 years, which corroborates the slow evolution of precursor lesions to cancer.

Recommendations of different societies worldwide are based on a study performed in 1986 by the International Agency of Research on Cancer,[13] which involved 8 countries and demonstrated that after a negative cervical cytology exam, in a 100% coverage population, there would be 93.5% reduction in the cumulative incidence of invasive cervical lesions in an annual screening, while in a triennial screening, the incidence reduction would be 90.8%.[8]

The highest risk for cervical cancer is found in the age group between 45 and 49 years—that is, not in young women, with a newly initiated sexual life—and mortality increases with advancing age.

An American study performed by Watson et al.[14] evidenced that among 10,846 cases of cervical cancer diagnosed, 1.1% belonged to women up to 24 years old. Statistically, therefore, there is good reason, considering collective health, for the cytological examination of cervical mucous to be made years after the initiation of sexual life, and not as soon as a woman reaches adulthood or even earlier, unless there are significant factors to do so.

Therefore, it is important to implement quaternary prevention. It is composed by a group of actions that aim to reduce damage caused by unnecessary medical interventions.[15]

The Center for Disease Control and Prevention (CDC), in its 2006 recommendations,[16] addresses the impact that the diagnosis of cancer precursor lesions may cause in teenagers. With this in mind, health attention to this group of women should instead emphasize the prevention of sexually transmitted diseases and contraception, considering that, at this age, the relationship between personal burden and preventative gain would be very high in favor of the burden. To confirm this statement, over 20% of the Papanicolaou tests made in Brazil between 2006 and 2015 were performed in women outside the age range recommended by the Ministry of Health patients were not between 25–64 years old). Given the fact that every Papanicolaou costs for the health system R $ 7.30 and considering the excessive number of unnecessary tests, its cost got to over R$ 147 million between the years of 2006 and 2015 in Brazil.

Vale et al.[17] measured, in two cities in the state of São Paulo, not only the number of smears collected outside the recommended age range, but also the number of exams collected biennial and annually, and not triennially, which is also contrary to the Brazilian Ministry of Health protocol. Such quantification promotes an accurate analysis of the real number, and proportion, of unnecessary smears collected. Such proportion, to give an example, has reached more than 60% of all Pap smears collected in the city of Amparo (SP) from 2001 to 2007. Therefore, an even bigger proportion than the one measured in this study considering only the age range.

The analysis by Van Ballegooijen et al.[18] of different screening patterns around the world, but specially in The Netherlands and Canada, demonstrated that, following some

protocols about the beginning and the end of screening age, the interval between exams and population's coverage, it is possible to acquire less deaths and more years of life gained even with fewer collected smears and, thus, less unnecessarily treated women. Such results, according to the authors, might be obtained using efficient screening patterns, which focus on periodicity, longer intervals between exams, larger attendance, and rationalization of exam's age range.

Following the Ministry of Health protocol on Pap smears has benefits not only to the patient and to public health, but for the health budget too. Eliminating such waste in exams can cause considerable cost savings. In the USA, for example, it is estimated that, in 2011, between 158 and 226 billion dollars were spent in unnecessary tests, surgeries, medications, etc.,[19] in which the unnecessary Papanicolaou tests are included.

Conclusion

Considering the fact that cervical cancer is a public health issue, and it is the third most common tumor on women around the world, it is evident the importance of means for early detection of such lesions and to make a precise diagnosis. As seen in this study, there is an enormous amount (over 20 million) of tests performed in women who are not in the age range suggested by the Ministry of Health, corresponding to 23% of the total amount. Hence, it is necessary to question why those tests are performed in such a way in the whole Brazilian territory, even including women younger than 11 years old and older than 80 years old. Considering that there is a protocol by the Brazilian Ministry of Health, which is endorsed by scientific evidence recognized by organs such as World Health Organization and the American CDC, it would be expected that doctors are more cautious about requesting tests such as cervical screening for women who do not fill the age criteria recommended. Therefore, it is recommended that the Brazilian Ministry of Health and SUS watch carefully those numbers and values, in order for measures such as professional training, especially in Basic Units of Health, so changes could be seen in the way those exams are collected in Brazil. Furthermore, it is important to highlight that, in this article, there were not available information to know if those tests are being done every 3 years, accordingly to the Brazilian's health system protocol, or every 1 or 2 years, which means that the amount of unnecessary Pap smears is probably even greater than that calculated, because of the number of exams collected disregarding the correct time gap between exams. There are no similar studies comparing the cost of Pap smears and its impact on women's mortality or on the public health's budget. There are, however, other studies and estimates on the burden to the health system of excessive tests, surgeries, and medications, which are responsible for huge waste of public or private resources. This study's data represent an organization tool that allows the medical community to rethink its clinical practice, especially considering that in a continental-size country such as Brazil, minimal changes mean a lot of money spent. Hopefully, especially in Basic Units of Health, Pap smears will be collected according to t guidelines of the Brazilian Ministry of Health.

Contributors
All the authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

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

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Assistance to Victims of Sexual Violence in a Referral Service: A 10-Year Experience

Assistência a vítimas de violência sexual em um serviço de referência: Uma experiência de 10 Anos

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Abstract

Objective To evaluate the assistance provided to women victims of sexual violence and their participation in the follow-up treatment after the traumatic event, presenting a sociodemographic profile, gynecological background, and circumstances of the event, and reporting the results, acceptance, and side effects of prophylaxis for sexually transmitted infections (STIs) and pregnancy.

Methods A retrospective cohort study comprising the period between 2007 and 2016. All women receiving medical care and clinical follow-up after a severe episode of sexual violence were included. Records of domestic violence, male victims, children, and adolescents who reported consensual sexual activity were excluded. The present study included descriptive statistics as frequencies and percentages.

Results A total of 867 medical records were reviewed and 444 cases of sexual violence were included. The age of the victims ranged from 10 to 77 years old, most of them self-declared white, with between 4 and 8 years of education, and denying having a sexual partner. Sexual violence occurred predominantly at night, on public thoroughfare, being committed by an unknown offender. Most victims were assisted at the referral service center within 72 hours after the violence, enabling the recommended prophylaxis. There was high acceptance of antiretroviral therapy (ART), although half of the users reported side effects. Seroconversion to human immunodeficiency virus (HIV) or to hepatitis B virus (HBV) was not detected in women undergoing prophylaxis.

Conclusion In the present cohort, the profile of victims of sexual violence was low-educated, young, white women. The traumatic event occurred predominantly at night, on public thoroughfare, being committed by an unknown offender. Assistance within the first 72 hours after sexual violence enables the healthcare center to provide prophylactic interventions against STIs and unwanted pregnancies.

Keywords
- sex offenses
- rape
- sexually transmitted diseases
- violence against women
- pregnancy unwanted

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Resumo

Objetivo Avaliar a assistência prestada às mulheres vítimas de violência sexual e seu acompanhamento após o evento traumático, caracterizando o perfil sociodemográfico, antecedentes ginecológicos e circunstâncias do evento, além de relatar a aceitação e os efeitos colaterais da profilaxia para infecções sexualmente transmissíveis (ISTs) e a ocorrência de gravidez resultante da violência sexual.

Métodos Estudo de coorte retrospectivo compreendendo o período entre 2007 e 2016. Foram incluídas todas as mulheres em acompanhamento médico e clínico após episódio de violência sexual. Foram excluídos registros de violência doméstica, vítimas do sexo masculino e crianças e adolescentes que relataram atividade sexual consensual. O estudo incluiu estatísticas descritivas, com frequências e percentuais.

Resultados Foram revisados 867 prontuários e 444 casos de violência sexual foram incluídos. A faixa etária foi 10 a 77 anos; a maioria das vítimas se autodeclarou branca, com entre 4 e 8 anos de escolaridade, e negou ter um parceiro sexual fixo. A violência sexual ocorreu predominantemente à noite, em via pública, por um agressor desconhecido. A maioria foi atendida no serviço de referência em até 72 horas após a violência, possibilitando profilaxias preconizadas. Houve alta aceitação da terapia antirretroviral (TARV), embora metade das usuárias relatasse efeitos colaterais. A soroconversão para o vírus da imunodeficiência humana (HIV, na sigla em inglês) ou para o vírus da hepatite B (HBV, na sigla em inglês) não foi detectada entre as vítimas.

Conclusão Nesta coorte, o perfil das vítimas de violência sexual foi de mulheres brancas, de baixa escolaridade, e jovens. O evento traumático ocorreu predominantemente à noite, em via pública, por um agressor desconhecido. A assistência nas primeiras 72 horas após a violência sexual permite que o serviço de saúde realize intervenções profiláticas contra ISTs e gravidez indesejada.

Palavras-chave

- delitos sexuais
- estupro
- doenças sexualmente transmissíveis
- violência contra a mulher
- gravidez não desejada

Introduction

According to the World Health Organization (WHO),[1] sexual violence is a serious public health problem, being defined as any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, using mental or physical coercion or aggression, in any setting, including but not limited to the household and work environments. In addition to the immediate risks resulting from sexual violence, such as sexually transmitted infections (STIs)[2,3] and unwanted pregnancies, a high percentage of victims develop mental health disorders in the medium- and long-term, with a strong tendency to present psychiatric disorders, social isolation, use of psychoactive substances, and suicide.[4,5]

National studies showed that 20% of the population have already experienced sexual violence.[6] This type of violence is twice as frequent in the female population, being estimated that up to 40% of women had a violent sexual experience.[6–9] In female adolescents, the prevalence of this type of violence is six times higher when compared with adult women.[10]

The elaboration of technical norms and clinical protocols for the reception, care, and notification of violence is based on the international guidelines of the WHO.[11,12] In Brazil, beginning in the 1980s, the Ministry of Health standardized assistance for people who suffered sexual violence. These guidelines were updated over the years, and the last ones were published in 2014[13] and 2015,[14] having been elaborated in partnership with the Health Departments of the federation units, as well as with scientific societies and social movements.

Health system organization and professional training are essential to improve the reception and healthcare of victims of violence, consequently decreasing its damages. The assistance in the health service must be immediate and, if possible, performed by a multidisciplinary team with the participation of physicians, nurses, social workers, and psychologists.[11–14] Thus, it is possible to welcome, assist, conduct clinical and laboratory tests, and administer emergency contraception and chemoprophylaxis for human immunodeficiency virus (HIV) and other STIs. Immediate prophylaxis is an effective measure that must be available in every health center assisting these victims. It is also possible to offer psychosocial support, being aware of the importance of training the professionals who work directly with these victims, improving their skills and technical capacity for the treatment of victims of sexual offense. However, there are few services in Brazil with a specialized profile, most of them linked to referral or university hospitals.[15]

Within this context, the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP, in the Portuguese acronym), Ribeirão Preto, state of São Paulo, Brazil, offers the Serviço de Atenção às Vítimas de Violência Doméstica e Agressão Sexual (Assistance Service for Victims of Domestic Violence and Sexual Assault [SEAVIDAS, in the Portuguese acronym]) to the population of the Regional Health Directorate (Direção

Regional de Saúde - DRS) XIII. This regional health service comprises 26 cities with an estimated population of 1,450,000 people, with 700,000 inhabitants in Ribeirão Preto, state of São Paulo, Brazil. This service is maintained with funding from the Government of the State of São Paulo, aiming at providing comprehensive health care to victims of domestic violence and sexual assault at the tertiary level, referred by primary health care centers, by social assistance units, by legal units or spontaneous search for care. In addition, the implemented structure is interdisciplinary and multiprofessional, with physicians, nurses, psychologists, and social workers providing appropriate care for the victims.

The patient flow recommended by the SEAVIDAS expects situations of violence classified as severe or chronic. Severe violence is characterized as occurring in the previous 72 hours (up to a maximum of 5 days) and requires immediate prophylaxis conducted in a hospital environment, in an emergency regime, not requiring the referral regulation system. After the initial reception, the victim joins the assistance service to continue a follow-up treatment for 6 months. Chronic violence is characterized as having occurred >72 hours before (or >5 days) and/or being recurrent. In these cases, the patients are received at the center referred via state regulation and receive assistance at an outpatient service unit. The SEAVIDAS also carries out the ending of the pregnancy resulting from sexual violence (according to Law 12,015/2009).[16]

The objectives of the present study are to characterize the sociodemographic profile of women victims of severe sexual violence treated at the SEAVIDAS-HCFMRPUSP, to know, from the first medical visit, the circumstances in which the violent event occurred, and to evaluate the effectiveness of the prophylaxis protocols for STIs and pregnancy resulting from rape, and the participation of the victims in the follow-up treatment after the violence.

Methods

This is a retrospective cohort study conducted between 2007 and 2016 that included all assistance provided to women at the SEAVIDAS-HCFMRP USP after an immediate act of sexual violence. Cases of domestic violence, physical or verbal violence without sexual offense, male victims, premenarchal girls, and girls <14 years of old who reported consensual sexual intercourse were excluded.

By reviewing the medical records, some variables in the assistance of severe episodes were evaluated, such as sociodemographic (age, origin, color/race, marital status, paid activity, education); medical (pregnancies, sexual activity, use of contraception, psychiatric conditions); circumstances of the abuse (place, time, number of offenders, relationship with the offender), and legal aspects (medical examination and police report). In the initial medical care, the time of arrival at the service, concurrence of trauma or physical aggression, previous diseases, and postexposure prophylaxis (contraception and STIs) were checked.

The SEAVIDAS assistance protocol for women victims of sexual violence is based on the Technical Guidelines of the Brazilian Ministry of Health.[13] It is a multidisciplinary service, with compulsory notification to health and police authorities. When the victim is <18 years old, a police report and a medical-legal report made by a physician from the Medical Examiner's Office (Instituto Médico Legal [IML, in the Portuguese acronym]) with evidence collection of vaginal content for future identification of the DNA of the offender are mandatory.

After anamnesis and physical examination, the patient undergoes a pregnancy test, hepatitis B surface antigen (HBsAg), hepatitis C, HIV, and syphilis serology, and biochemistry tests (liver enzymes, kidney function, blood glucose, and blood count). In the assistance service, the victim receives prophylaxis consisting of levonorgestrel or a copper intrauterine device (IUD) for emergency contraception; azithromycin and ceftriaxone for bacterial infections; hepatitis B virus (HBV) vaccine and immunoglobulin (according to vaccination status); HIV antiretroviral therapy (ART) provided by the Brazilian Ministry of Health; tetanus vaccine; and metronidazole for trichomoniasis.

The patients are reassessed in an outpatient setting 7 to 10 days after the traumatic event to analyze their emotional state, emergency room test results, and ART acceptance. Medical and psychological follow-up is also offered for 6 months after the violence, and STI serology is retested 3 and 6 months after the traumatic event. The described reception and interventions are fundamental to minimize the damage caused by sexual violence to the life of a woman.

The present study was approved by the Research Ethics Committee of the HCFMRP USP, under the number 2,283,582/2017.

Results

Between 2007 and 2016, 2,067 victims of some type of violence were treated at the SEAVIDAS-HCFMRP USP. Of these, 867 were victims of sexual violence, but after applying the inclusion and exclusion criteria, 444 medical records were analyzed for sexual violence against women at the SEAVIDAS-HCRP. This process is described in the flowchart in ►**Figure 1**.

►**Table 1** shows the profile of the 444 victims of sexual violence. The age group between 20 and 59 years old comprised the highest number of cases (49.55%), and the mean age of the victims was 24.1 years old (median of 20 years old). Most victims declared to be white, were from the city of Ribeirão Preto, state of São Paulo, Brazil, had between 4 and 8 years of education, did not have a paid activity, and did not have a steady sexual partner. Regarding their gynecological and obstetric histories, 155 victims (35.42%) denied having started sexual activity before the rape, 286 victims (65%) were nulliparous, and 325 (74.55%) did not use contraceptive methods. A diagnosis of psychiatric disorder prior to victimization (including use of psychoactive substances, cognitive impairment, and psychic comorbidities) was positive in 100 women (23.11%); however, it was

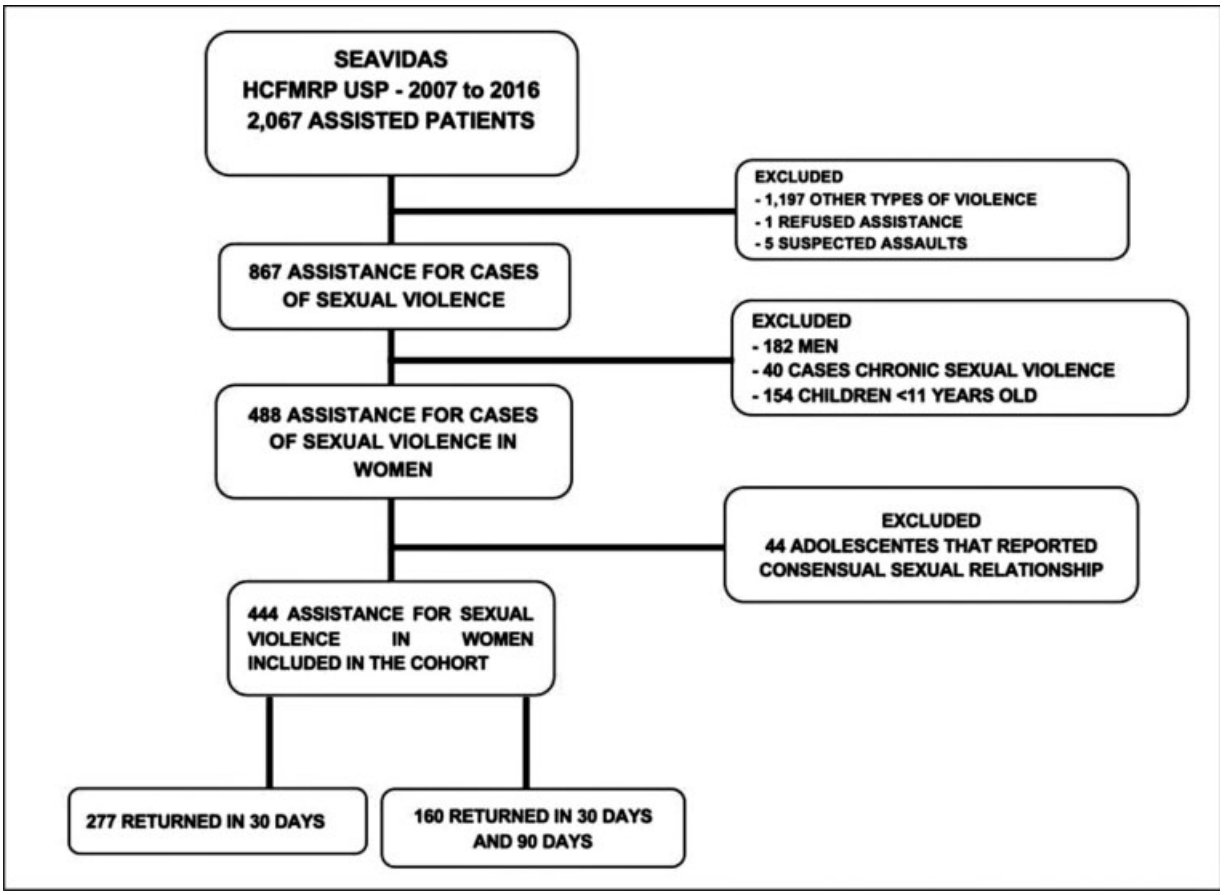

Fig. 1 Assistance flowchart for cases of violence at SEAVIDAS-HCRP between 2007 and 2016.

not possible to access data on the mental health follow-up of these patients.

►**Table 2** shows the circumstances of the sexual assault. Most of them happened at night, outdoors, with a single unknown offender. There was a record of use of psychoactive drugs, voluntary or forced by the offender, in 33 patients (7.69%), and of use of condoms by the offender in 14 victims (3.21%).

The time of arrival at the health center to receive assistance after sexual violence was up to 72 hours for 346 victims (77.9%), with 257 (57.9%) having been assisted within the first 24 hours after the violence. In the initial care, the medical team observed a concomitance of physical aggression in 170 women (38.2%), and the evidence of recent hymen rupture in 75 (16.9%) of these was confirmed by an expert physician. A police report and medical-legal evaluation were carried out for 391 (88.1%) victims of sexual violence treated at the SEAVIDAS-HCRP.

Regarding prophylaxis at the first visit, 14 victims (3.1%) had a previous diagnosis of STI or had a rapid reagent test. Of these, four women had HIV, four were chronic carriers of the HBV, and six patients had reagent serology for syphilis. Therefore, these women did not receive prophylaxis for these infections. Emergency contraception was administered to 296 (66.7%) victims, ceftriaxone, azithromycin, and hepatitis B vaccine to 386 (86.9%), and ART to 331 (74.5%), as shown in ►**Table 3**. Prophylaxis against trichomoniasis was prescribed in the outpatient visit 7 to 10 days after the traumatic event.

Regarding ART acceptance, out of the 331 victims who accepted it, 253 used the therapy adequately (76.4%). However, 23.6% of the victims did not complete the 28 days of prophylaxis. Of the victims who used ART correctly, 49.5% reported gastrointestinal side effects such as nausea, vomiting, epigastric pain or lack of appetite, and 13.9% reported neurological symptoms such as headache, insomnia, drowsiness, or dizziness. Two patients presented hematological changes (anemia or leukopenia), and the antiretroviral medications were changed.

The outpatient follow-up after the traumatic event showed that 227 women (51.1%) returned in the 1st month and 160 women (36%) returned in the 3rd month. The prophylaxis result did not show seroconversion to HIV or HBV infection in the women who repeated serology, and all 6 patients with a syphilis serological diagnosis underwent a follow-up with venereal disease research laboratory (VDRL) retest according to the protocol recommended by the Brazilian Ministry of Health. In this sample, pregnancy was diagnosed in a victim of sexual violence who had not received emergency contraception because she arrived at the health service 5 days after the traumatic event.

Discussion

A total of 444 cases of women victims of sexual violence within a 10-year period was studied. According to article 213

Table 1 Distribution of 444 women victims of sexual violence according to the sample characterization

Data	*n*	%
Age (years old)		
11–14	97	21.85%
15–19	117	26.35%
20–59	220	49.55%
≥ 60	10	2.25%
Color		
White	315	71.11%
Not white	128	28.89%
Education		
Illiterate	26	6.47%
4 to 8 years	205	51.00%
9 to 12 years	132	32.84%
Higher/technical education	39	9.70%
Paid activity		
Yes	134	31.16%
No	296	68.84%
Origin		
Ribeirão Preto	239	53.83%
DRS XIII cities	192	43.24%
Other cities	13	2.93%
Sexual partner		
Yes	53	12.18%
No	382	87.82%
Previous sexual activity		
Yes	155	35.42%
No	279	64.58%
Parity		
Nulliparous	286	65.00%
Primiparous	43	9.77%
Multiparous	111	25.23%
Use of contraception		
Yes	111	25.46%
No	325	74.54%
Psychiatric disorder		
Yes	100	23.11%
No	336	76.89%

Table 2 Distribution of 444 women victims of sexual violence according to the circumstances of the traumatic event

Data	*n*	Frequency
Time		
Day	126	30.9%
Night	197	66.9%
False imprisonment	9	2.2%
Place		
Outdoors	167	38.3%
Victim's house	91	20.9%
Offender's house	69	15.8%
Rural area	27	6.2%
Other	82	18.8%
Number of offenders		
1	267	82.4%
2	33	10.2%
≥ 3	24	7.4%
Relationship with the offender		
Unknown	264	59.4%
Known	180	40.6%
Current partner	12	6.7%
Former partner	21	11.7%
Other	147	81.6%
Use of psychoactive drugs		
Yes	33	7.69%
No	396	92.31%
Use of contraceptive in the act		
Yes	14	3.21%
No	422	96.79%

Table 3 Distribution of 444 women victims of sexual violence according to the received prophylaxis

Prophylaxis	*n*	%
Contraception	296	66.7%
STI		
ART	331	74.5%
Bacterial and HBV	386	86.9%

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; STI, sexually transmitted infection.

of the Brazilian Penal Code (1940), rape is the act of forcing someone, with violence or serious threat, to have carnal conjunction or to engage in or consent to a libidinous act.[16,17] The Brazilian Public Security Yearbook, published in 2020,[18] pointed out that there are 8 rapes per minute in Brazil. This number is certainly underestimated, as it corresponds to the number of cases reported to the police authorities. This underreporting is justified by the victim's fear of the offender, self-blame and shame, and the fear of being mistreated at police stations.[19] Although there are no consistent studies to confirm these numbers, estimates indicate that they can be up to 10 times higher, placing sexual violence as a public health problem worldwide.

The sociodemographic profile of the women treated at the SEAVIDAS-HCRP during the period studied was quite similar to the one described in the national and international literature, with a predominance of young women, self-

declared white, without paid activity, and without a steady sexual partner.[5,15] Although violence against women, especially sexual, can occur at any age, it is much more frequent in adolescents and young adults. In the present case series, despite the wide age range of the victims (11 to 77 years old), the mean age was 24.4 years old, with a predominant age range between 11 and 19 years old, which corresponded to 43.9% of the victims, confirming the high number of adolescents who suffer sexual violence. This high number was described in other studies and can partly be explained by the vulnerability of this population, by the fact that the offender is part of the family circle of the victim, and by the difficulty adolescents have in assessing the risk of exposing themselves to situations that may culminate in sexual violence.[10]

Although, under Brazilian law, sexual intercourse under the age of 14 is considered rape and classified as presumed violence (rape of a vulnerable individual) even with the consent of the victim,[16] the 44 girls $<$ 14 years old who reported consensual sexual intercourse were not included in this analysis, since they were not considered victims of a traumatic event.

Regarding education, half of the victims reported having studied between 4 and 8 years and 32.8% had between 9 and 12 years of education. Although the population of the present cohort consists predominantly of young women, the low level of education reported by 51% of the victims is noteworthy. Most victims did not have any paid activity and did not have a sexual partner at the time of the assault. This profile can possibly be explained by the high number of adolescents in the present case series, since it is a period when they change partners frequently, and do not have a steady relationship or a paid activity.

Moreover, regarding the profiles of the victims, approximately a quarter of them reported having some kind of psychiatric disorder prior to the traumatic event, pointing out the vulnerability of this population. It is known that the prevalence of any type of violence is higher in the female population, since women are victims in 85% of cases of violence, and psychiatric disorders are more frequent in this population.[20,21] Therefore, it can be concluded that women with mental health disorders are at a greater risk of suffering sexual violence and should receive special attention from health and social service teams with a focus on preventive measures. It is once again reiterated that the impact of violence on psychological and behavioral aspects can aggravate pre-existing situations and persist throughout life with a negative impact on future sexual relationships.[21–23]

In conclusion, the analyses of the origin of the victims of sexual violence treated at the SEAVIDAS-HCRP during the period studied showed the importance of the broad operation that this assistance service has in the region. Approximately half of the victims came from Ribeirão Preto, which is the largest city in this Regional Health Department, while 43% came from the other 25 cities in this Department. The structuring of a comprehensive health care system for people in situations of sexual violence is an important step to ensure healthcare promotion and prevention for this group.[13,14] For this flow to be established, the SEAVIDAS-HCRP conducted several activities to disseminate protocols and matrix support, in addition to training health professionals, playing a fundamental role in ensuring adequate reception and decreased damages for these victims.

The results of the present study indicate that most rapes occurred at night, in an external environment, and were committed by an unknown offender; these circumstances are similar to those described in other national studies, such as that by Labronici et al.[24] Although more than half of the cases of sexual violence (59.4%) were committed by an unknown offender, the high percentage of sexual violence committed by someone the victim knows (40.6%) is noteworthy. In the cases committed by a known offender, the current or former partner was responsible for 18.4% of the cases. These data are quite worrisome, as they point out that women suffer violence even in supposedly safe environments and raises the question of the invisibility of aggression within the marital relationship, as discussed by Schraiber et al.[25] and Dantas-Berger et al.[26] In these texts, the authors discuss intimate partner violence as a determinant of serious consequences and how proximity to the offender makes it difficult to report and seek the right care. These difficulties make it impossible for women to receive prophylaxis, losing the chance to prevent STIs and pregnancy.

The present study showed that a significant number of victims of sexual violence had also suffered physical violence at the first appointment. This data is highly relevant in the context of fighting violence against women, showing the need to support victims of violence. In addition, the forced or voluntary use of substances during the act occurred in 7.69% of the sample, demonstrating an additional vulnerability factor to which the patients may be exposed.

All victims were offered to file a police report (PR), which was mandatory for victims $<$ 18 years old. In the present study, $\sim$ 90% of rape cases had a filed a PR, a result above the national average, pointing out the importance of the partnership between the SEAVIDAS-HCRP and the Secretariat for Public Security. It is important to highlight that, when filling in the PR, the Medical Examiner's Office is informed to conduct a forensic medical examination; that is, the victim will be examined by a physician and material will be collected for eventual identification of the DNA of the offender. However, it is difficult to establish this flow due to the lack of specialized medical experts and to the delayed expert assistance, in addition to the lack of knowledge by police authorities in addressing the issue.[20] Notification to health authorities is also relevant in the preparation of public policies and healthcare, as observed by Gaspar et al.[27] in a research on the notification of sexual violence in Brazil between 2009 and 2013.

Sexual violence was the first sexual experience of a significant number of adolescents, as reported by the victims and observed by the recent hymen rupture on medical examination. This data corroborates the study by Facuri et al.,[28] which evaluated victims of sexual violence in a university referral service in the state of São Paulo, Brazil.

There is, therefore, great damage to the sexual health of these adolescents, since the literature reports that these women may develop risky sexual behaviors, especially for the acquisition of STIs, drug abuse, and psychiatric disorders.[22] In addition, this population is more likely to suffer repetitive violence, as seen by Delziovo et al.,[29] especially for being proportionally more attacked by someone closely related to them.

The SEAVIDAS-HCRP follows the protocol of the Brazilian Ministry of Health for prophylaxis procedures after sexual violence. The time interval between the violent act and the beginning of prophylaxis is essential both to indicate the use and to obtain the necessary effectiveness to reduce damages such as STIs and pregnancy resulting from rape. The present study showed that $\sim$ 80% of the victims of sexual violence arrived at the service for assistance within the first 72 hours, and more than half arrived within 24 hours after the traumatic event, optimizing the prescription of HIV ART and emergency contraception.

The acceptance to ART by the patients was considered adequate and higher than the one registered in similar studies in Brazil, such as the one by Figueiredo et al.,[30] and in the international literature, such as the studies by Linden et al.[31] and Muriuki et al.[32] It is also important to provide clinical and laboratory follow-up during the 28 days of medication use, since 2 patients needed to adapt the ART due to hematological changes.

During the 10 years of the survey conducted in the present study, different ART schemes were recommended by the Ministry of Health aiming at greater efficacy and reduced side effects. This factor makes it difficult to analyze side effects in the victims assessed in the present study, since the ART schemes used were different over the years. According to studies such as the one by Malinverni et al.,[33] the drugs used in ART can be a modifying factor for adequate use. However, the complete structuring of the SEAVIDAS-HCRP, based on multidisciplinary care, was fundamental for the high acceptance of the prescribed prophylaxis by victims of violence. This conclusion was also reported in the study by Nisida,[34] who observed an increased adequate use of prophylaxis in victims who were part of the multidisciplinary care offered by the reception service for victims of sexual violence in the city of São Paulo state of São Paulo, Brazil.

The results of the present study highlight that a small percentage of women participated in the outpatient monitoring, half of whom returned in the 1st month, and with only a third returning in the 3rd postviolence month. Follow-up is encouraged by the SEAVIDAS-HCRP team to monitor possible seroconversion to STIs and to detect women who will develop mental health disorders, such as depression or post-traumatic stress disorder, requiring a differentiated approach. However, after the prophylaxis is completed, many victims of violence do not return, possibly because when returning to the service they remember the trauma suffered.

The women who underwent follow-up had highly effective interventions, since no victim had seroconversion to HIV, to Hepatitis B or C, or syphilis. Only one patient developed pregnancy. This patient had not received emergency contraception, as she arrived at the service after the 5th day of the traumatic event. The pregnancy diagnosis occurred at $\sim$ 20th week and she decided not to terminate the pregnancy legally, even though this possibility was offered by the service. These results reinforce the importance of immediate assistance in the health service center, trained to intervene with prophylaxis, as was also observed in the studies by Facuri et al.[28] and Delziovo et al.,[29] conducted in large Brazilian cities and with a sample profile similar to the one used in the present survey.

The results of the present study corroborate the importance of the referral service fulfilling its function of welcoming and helping victims of sexual violence, both in the severe episode and in following-up these women in the first months after the traumatic event. The multidisciplinary characteristic of the service, including physicians, psychologists, social workers, and nurses, certainly contributes to the excellent results observed in the present study.[35] Furthermore, the fact that the SEAVIDAS-HCRP is linked to the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo makes it possible to insert this important topic in training sessions, especially for health professionals, in the context of undergraduate health courses as well as in medical and multiprofessional residency, sensitizing professionals to the importance of the topic and enabling them to provide the best and most effective care. In addition to this, it is essential to disseminate the service, to provide information at the places that help victims of violence, and to facilitate access to these services.

The main limitations of the present study are its retrospective nature, so it depends on data obtained from medical records. Another limitation is the short monitoring of victims of sexual violence. Data collection from medical records is flawed due to incomplete records, and a long-term follow-up could bring more information to the research.

Conclusion

In the present cohort, the profile of the victims is young, white women with low education. Regarding the traumatic event, it occurs more at night and is committed by an unknown offender. Acceptance to prophylaxis was high and achieved the desired effect with STI prevention, and a case of pregnancy was registered in a victim who did not receive emergency contraception. The results of the present study show that the organization of health services is essential to help victims of sexual violence and to have an established and safe referral flow for these victims.

Contributors
All authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

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

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Efficacy of Transversus Abdominis Plane Block in the Reduction of Pain and Opioid Requirement in Laparoscopic and Robot-assisted Hysterectomy: A Systematic Review and Meta-analysis

Eficácia do bloqueio transverso do plano abdominal na redução da dor e da necessidade de opioides em histerectomia laparoscópica e assistida por robô: Uma revisão sistemática e metanálise

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Abstract

Objective To summarize the available evidence of TAP Block in efficacy in laparoscopic or robotic hysterectomy.

Data Sources We searched databases and gray literature for randomized controlled trials in which transversus abdominis plane (TAP) block was compared with placebo or with no treatment in patients who underwent laparoscopic or robot-assisted hysterectomy.

Method of Study Selection Two researchers independently evaluated the eligibility of the selected articles.

Tabulation, Integration, and Results Seven studies were selected, involving 518 patients. Early postoperative pain showed a difference in the mean mean difference (MD): - 1.17 (95% confidence interval [CI]: - 1.87–0.46) in pain scale scores ($I^2 = 68\%$), which was statistically significant in favor of using TAP block, but without clinical relevance; late postoperative pain: DM 0.001 (95%CI: - 0.43–0.44; $I^2 = 69\%$); opioid requirement: DM 0.36 (95%CI: - 0.94–1.68; $I^2 = 80\%$); and incidence of nausea and vomiting with a difference of 95%CI = - 0.11 (- 0.215–0.006) in favor of TAP.

Keywords
- transversus abdominis plane block
- pain
- laparoscopic hysterectomy
- robotic-assisted hysterectomy
- opioid

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Conclusion With moderate strength of evidence, due to the high heterogeneity and imbalance in baseline characteristics among studies, the results indicate that TAP block should not be considered as a clinically relevant analgesic technique to improve postoperative pain in laparoscopic or robotic hysterectomy, despite statistical significance in early postoperative pain scale scores.
Clinical Trial Number and Registry: PROSPERO ID - CRD42018103573.

Resumo

Objetivo Resumir as evidências disponíveis sobre a eficácia do bloqueio TAP em histerectomia laparoscópica ou robótica.
Fontes de Dados Pesquisamos bancos de dados e literatura cinza por ensaios clínicos randomizados nos quais o bloqueio do plano transverso do abdome (TAP na sigla em inglês) foi comparado com placebo ou com nenhum tratamento em pacientes que foram submetidos a histerectomia laparoscópica ou assistida por robô.
Métodos de Seleção de Estudos Dois pesquisadores avaliaram independentemente a elegibilidade dos artigos selecionados.
Tabulação, Integração e Resultados Sete estudos foram selecionados envolvendo 518 pacientes. A dor pós-operatória precoce apresentou diferença nas médias (DM) de: -1 17 (intervalo de confiança [IC] de 95%: - 1 87–0 46) nos escores da escala de dor (I2 = 68%) o que foi estatisticamente significativo a favor do uso do bloqueio TAP mas sem relevância clínica; dor pós-operatória tardia: DM 0001 (IC95%: - 043–044; I2 = 69%); necessidade de opioides: DM 0 36 (95%CI: - 0 94–168; I2 = 80%); e incidência de náuseas e vômitos com diferença de 95% CI = - 011 (- 0215–0006) a favor do TAP.
Conclusão Com moderada força de evidência devido à alta heterogeneidade e ao desequilíbrio nas características basais entre os estudos os resultados indicam que o bloqueio do TAP não deve ser considerado como uma técnica analgésica clinicamente relevante para melhorar a dor pós-operatória em histerectomia laparoscópica ou robótica apesar da significância estatística nas pontuações da escala de dor pós-operatória inicial.
Número e Registro do Ensaio Clínico: PROSPERO ID - CRD42018103573.

Palavras-chave
- bloqueio do plano transverso do abdome
- dor
- histerectomia laparoscópica
- histerectomia robótica assistida
- opioide

Introduction

Hysterectomy is a surgical procedure often associated with significant postoperative pain. This could be attributed to injuries suffered in the pelvic plexus,[1] which is predominantly composed of neural structures in the sacral and lower lumbar segments, as well as to inflammation caused by direct trauma to tissues during the surgical procedure.[2] Therefore, it has been considered that the block in the transverse abdominal plane (TAP), which acts by blocking iliohypogastric, ilioinguinal, and lower thoracic spinal nerves, could be useful. However, the pain referred by patients after a hysterectomy is more of a visceral origin.

Despite laparoscopic and robotic hysterectomy being minimally invasive surgeries, only 60% of the patients feel satisfied with postoperative pain control in such gynecologic procedures.[3] The use of analgesics and of nonsteroidal anti-inflammatory drugs has been the first line recommendation for the management of postoperative pain after hysterectomy.[4] Hence, the use of analgesic medications, including opioids, which are associated with minor side effects (pruritus, nausea, and vomiting), as well as major side effects (respiratory depression and addiction),[5] are sometimes required, increasing postoperative morbidity and mortality.[6,7]

To reduce postoperative pain and opioid side effects, several strategies have been developed in the context of multimodal analgesia.[8] Among them is TAP[9] block, in which local anesthetic is injected into the neurovascular plane between the internal oblique and transversus muscles of the abdominal wall, with the goal of blocking the lower thoracic spinal nerves (T7-T12) and the iliohypogastric and ilioinguinal nerves (L1).[9]

Since TAP block was first described in 2001 by Rafi,[9] its efficacy has been evaluated in multiple clinical trials and compared with other analgesic techniques in patients undergoing abdominal and pelvic procedures, including hysterectomy performed through several approaches: abdominal,[10–12] laparoscopic,[13–18] and robot-assisted.[19–21]

Currently, there are only two available studies evaluating the efficacy of TAP block exclusively in the context of surgical approaches to hysterectomy. In the first meta-analysis, Tubog et al.[22] reported a reduction in pain during the first postoperative hours. On the other hand, a second meta-

analysis by Bacal et al.[23] showed that postoperative pain was reduced for 24 hours. Regarding opioid dosing, Tubog et al.[22] found that TAP block had opioid-sparing effects in all surgical approaches, while the study by Bacal et al.[23] reported the opioid-sparing effect of TAP block only in patients undergoing abdominal hysterectomy, but not in those undergoing laparoscopic hysterectomy. However, the results obtained presented a significant heterogeneity.

In the present systematic review and meta-analysis, we have evaluated the best available evidence of the efficacy of TAP block in reducing pain and opioid requirement exclusively in laparoscopic and robot-assisted hysterectomy, taking into account and exploring the substantial data heterogeneity identified when drawing conclusions.

Methods

The present study was designed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[24]

Protocol and Registration

The present review was based in a previously registered and developed review protocol, which was prepared following the Cochrane Handbook for Systematic Reviews of Interventions,[25] and may be found under PROSPERO ID: CRD42018103573.

Eligibility Criteria

The PICO format was used to locate the evidence addressing the clinical query; (P) patients who underwent laparoscopic or robot-assisted hysterectomy for benign or malignant disease; (I) intervened with TAP block in laparoscopic or robot-assisted hysterectomy; (C) compared with placebo or with no treatment; (O): studies measuring any pain scale and opioid requirement; (S) randomized, blinded clinical trials. Studies published until to July 31st, 2018, without language restriction, were considered eligible for the present analysis.

Information Sources and Search

We searched the following electronic databases, trial registers, and websites: PubMed, Embase, LILACS, Cochrane Database of Systematic Reviews (CDSR), Clinical trials Web site (www.clinicaltrials.gov), SCIELO, Google Scholar, and Open Gray. The search strategy in PubMed included the following terms: *transversus abdominis plane block* OR *TAP block* AND *hysterectomy*. The same strategy was used for other databases, changing only syntaxes.

Study Selection

After eliminating studies registered in more than one database, those considered irrelevant according to the inclusion criteria or due to repeated publication were also excluded. This was a two-step process; an initial screening of titles and abstracts, and a second screening that was performed by reading the full texts. Two of the review authors (C.C.L and Orjuela J. C.) independently performed this process, and disagreements were resolved by consensus.

Data Collection Process and Data Items

As a primary outcome, the efficacy of TAP block in terms of postoperative pain was evaluated. Pain was assessed by the visual analogue scale (VAS), in which scores range from 0 to 10, where 0 is absence of pain and 10 is the maximum perceived pain. Data from studies reporting scores from 0 to 100 were converted to 0 to 10 by dividing the scores by 10. Pain was assessed at 2 time points: early (1 to 4 hours after surgery) and late (24 hours after surgery). As a secondary outcome, we evaluated the use of opioid during the first 24 postoperative hours and the side effects of their use were described, specifically nausea, vomiting, and sedation. Likewise, quality of recovery was also reported.

Two of the review authors (C.C.L. and Orjuela J. C.) independently extracted the previously described data into a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet. The extracted data included: the country where the study was performed, approach, inclusion and exclusion criteria, evaluated outcomes, blinding, sequence generation and concealment, number of patients, type of intervention, technique used to administer block, medication used, comparison group intervention, patient characteristics (age, body mass index [BMI]), American Society of Anesthesiology (ASA) score, preoperative and postoperative pain evaluated trough the visual analogue scale (VAS) scale and evaluation of pain, and reporting of side effects associated with opioids (nausea, vomiting, drowsiness), as well as quality of recovery. In case the required measurements were not identified, or if the results were exclusively reported as figures, the authors of the studies were contacted, and if no response was obtained, data were estimated by means of WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/).

Risk of Bias in Individual Studies

Two of the review authors (C.C.L and Orjuela J. C.) independently assessed the included studies for risk of bias using the Cochrane "Risk of bias" assessment tool (RoB 2.0)[26] for the six following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result, and other bias. Each of the two review authors classified studies as being of high, undetermined, or low risk, according to the algorithm of the tool. This classification was discussed and consensual with a third investigator (Rojas-Gualdrón D. F.).

Summary of Measures, Synthesis of Results, and Statistical Analysis

The primary outcome was the mean difference between early (4 hours) and late (24 hours) postoperative pain scale scores. A reduction in the pain scale score of 2 to 2.7 points, or of 30 to 40%, was considered to be significant, according to meaningful pain reduction for the patients.[27–30] As secondary outcome, differences of mean total morphine use in the first 24 hours after surgery were analyzed. We did not need to apply opioid conversion, since all analyzed studies exclusively used morphine. In addition, the difference in proportion of adverse events (nausea/vomiting) was

analyzed in studies reporting this data. In case a study did not report means, but reported medians instead, estimations were made following the procedure described by Wan et al. based on sample size, medians, and interquartile ranges.[31]

Based on the reported outcomes in the studies classified as of low risk of bias, the weighted estimate was obtained together with 95% confidence intervals (CIs) by the weighted least squares method, which is more robust than conventional random effects in the presence of publication bias (small sample) and than fixed effects in the presence of heterogeneity.[32] Heterogeneity among studies was calculated by tau (absolute) and I^2 (relative).

Risk of Bias across Studies and Sensitivity Analyses

The individual contribution of each study to the heterogeneity among studies was evaluated by means of sensitivity analysis by calculating the I^2 value when each individual study was excluded, and the possibility that baseline heterogeneity could explain the observed heterogeneity among studies was analyzed following the method described by Hicks et al.[33] Risk of publication bias was assessed visually by funnel plot augmentation, and no statistical test was performed given the low number of studies included in the meta-analysis.[34]

Two sensitivity analyses were performed. First, the prediction interval was estimated to evaluate between study heteogenity in the mean difference scale,[34] and by augmented funnel plots, the possible scenarios of weighted outcomes when updating the meta-analysis were estimated and analyzed and were grouped according to the possible outcomes of the hypothesis with a significance level of 5% as follows: a) in favor of TAP block, b) in favor of placebo, c) insignificant difference.[34] Second, the weighted outcome was estimated using the random effects method to determine the influence of between study heterogenity on the primary meta analytic estimation.

The quality of evidence and strength of recommendations of the results obtained in the present systematic review and meta-analysis were rated following the Grading of Recommendations Assessment, Development and Evaluation GRADE criteria.[35]

Results

Study Selection

In our initial search, we identified 218 potentially relevant articles. Of those, 54 were identified in PubMed, 96 in Embase, 66 in Cochrane Library, 1 in LILACS, and 1 in gray literature. Of those, 31 were excluded after screening the title, 16 due to duplication, and thus 171 were selected for abstract reading. A total of 164 studies were excluded because they failed to meet the inclusion criteria. The remaining 7 studies[13–18,21] met the inclusion criteria and were included in our quantitative analysis, comprising 261 patients who underwent hysterectomy and were intervened with TAP block, who were compared with 257 patients who underwent hysterectomy and were intervened with sham block or who were not intervened. We documented the selection process with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA flow chart (►**Fig. 1**).

Study Characteristics

All of the analyzed studies were randomized control trials. Three of the studies[13,15,21] compared TAP block with sham block with saline, and the other four[14,16–18] with no treatment. In five of the studies,[13–16,18] TAP block was performed after laparoscopic hysterectomy; in addition the study by Kane et al.[14] from 2012 also included single-port hysterectomy, and the study by Bava et al.[17] from 2016 included laparoscopically-assisted vaginal hysterectomy, both of which are considered variants of laparoscopic hysterectomy and are all considered to be minimally invasive procedures. On the other hand, compared with the rest of the studies, which only included benign disease, the study by Torup et al.[21] from 2015 was performed exclusively in patients undergoing robot-assisted hysterectomy and included patients with malignant disease.

All of the analyzed studies reported postoperative pain scale scores as an outcome. Pain was assessed by the visual analogue scale (VAS) or by numeric rating scales. Six studies[13–16,18,21] assessed opioid requirement. The studies by Bava et al.[17] and Kane et al.[14], from 2016 and 2012, respectively, additionally included among their outcomes the postoperative quality of recovery using the QoR-40 survey. Four studies[16–18,21] specifically assessed the incidence of postoperative nausea and vomiting as side effects related to the use of opioids. Sedation associated to the use of opioids was evaluated in the studies by Bava et al.[17] and Guardabassi et al.[18]

The Ramsay sedation scale was used in five of the studies, which also reported the American Society for Anesthesiologists (ASA) classification,[13,15,16,18,21] and included patients classified as ASAI and ASAII, except in the studies by Ghisi et al.[16] and Torup et al.[21], which also included patients classified as ASAIII. In five of the studies,[13,14,18,21] ropivacaine was the anesthetic used to perform TAP block, while bupivacaine was used in the study by Calle et al.,[15] and Ghisi et al.[16] used levobupivacaine. In all of the analyzed studies, certified anesthesiologists performed the ultrasound-guided TAP block, except in the study by Calle et al.,[15] in which surgeons performed laparoscopic-guided TAP block upon completion of surgical intervention (►**Table 1**).

Risk of Bias within Studies

In six of the studies, proper randomization procedure was followed, with random sequence generation and concealment, with balanced baseline characteristics between groups, thus suggesting no issues in the randomization procedure. In the remaining study, the randomization procedure was considered unclear, since nonprobability sampling of consecutive case series was used.

All of the analyzed studies were assessed as having low risk of deviation bias due to the planned intervention, since there was no evidence of cointerventions or changes in the treatment protocol, the interventions were successfully performed, and the participants were adherent to the assigned intervention. All of the studies were judged as having low risk of bias due to loss of outcome information, taking into account that results were available for most participants, that the studies exhibited proportions of missing data $< 10\%$, and despite this their results were robust.

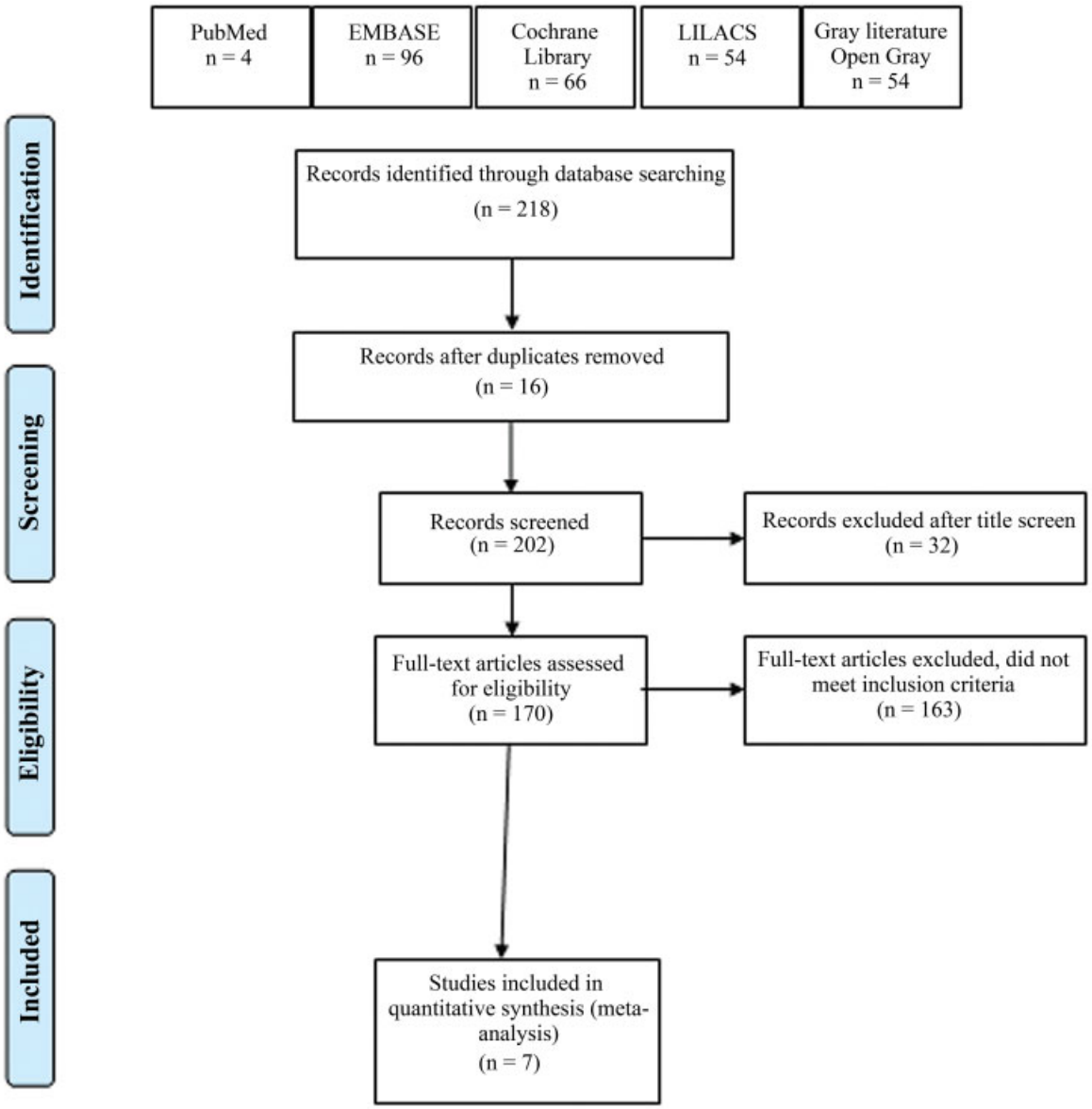

Fig. 1 PRISMA flow diagram.

Six of the seven studies were judged as having low risk of measurement bias, since the evaluators were not aware of the performed intervention and, therefore, this could not influence their results. We considered the study by Kane et al.[14] to have an unclear risk of measurement bias, since the research coordinator or members of the surgical team, who were not blinded to treatment allocation, were the ones conducting the interviews at the hospital or by phone to apply the QoR-40 questionnaire.

All seven studies were considered to have a low risk of selection bias because the reported results were those asked in the goals, and measurements were made with previously validated scales. Furthermore, five of the seven studies were judged as having low risk of overall bias, since a biased direction toward the alternative hypothesis was not defined. On the other hand, the remaining two studies were considered as having unclear overall bias, since in the study by Guardabassi et al.[18] flaws in the randomization procedure were identified, and in the study by Kane et al.[14] the quality of recovery questionnaire was applied by members of the research team that were aware of the treatment allocation of the patients (►**Table 2**).

Results of Individual Studies and Summary of Results

Study details, including demographic and operative characteristics are shown in ►**Table 1**. In the study by Calle et al.[15], the authors reported that patients receiving TAP block exhibited a statistically significant reduction in pain scale scores at time of hospital discharge compared with those in the placebo group ($p = 0.017$). However, they concluded that the role of TAP block for this procedure was questionable because of the lack of clinical significance due to the small difference identified.

De Oliveira et al.[13] reported that cumulative opioid consumption during the first 24 hours after surgery was lower in the 0.5% ropivacaine group compared with saline ($p = 0.003$). Linear regression showed an inverse relationship between

Table 1 Characteristics of included studies evaluating the efficacy of TAP block after hysterectomy

Study	Country	Type of surgery	Inclusion criteria	Exclusion criteria	Outcomes	Comparison group	Number TAP / Control Sequence generation and concealment	Blinding	Anesthetic drug dose (mg)	ASA	TAP block technique
Calle et al. (2014)[15]	Colombia Prado Clinic and CES University, Medellin	Laparoscopic	Patients with ASA surgical risk classification types 1 and 2; had no contraindications for administration of local anesthetics, NSAIDs, or acetaminophen; had an adequate level of understanding, i.e., being able to communicate by telephone and understand a numerical scale.	Change in the standard anesthetic technique, hospitalization following hysterectomy, previous medical history of allergy to local anesthetics, and not being able to be reached by telephone	Pain scale scores (VAS) at 24, 48, and 72 hours after surgery, opioid requirement after surgery	Placebo	100 / 97 Sequence was generated using computer-generated randomization list in blocks, which were placed in sealed envelopes	Triple blind: Patient, surgeon, and data analyst	Bupivacaine 0.25% (96)	I, II	Laparoscopic-guided
De Oliveira et al. (2011)[13]	United States of America Northwestern University, Chicago	Laparoscopic	Healthy women undergoing laparoscopic hysterectomy	Patients with previous history of allergy to local anesthetics, long-term use of opioid analgesics or corticosteroids, and pregnancy	Quality of Recovery (QoR-40) at 24h; pain numeric scale score at 30 minutes, 60 minutes, and 24 hours; time to opioid requirement and cumulative opioid consumption at 24 hours, and number of postoperative antiemetics	Placebo	22 / 23 Individuals were randomized into three groups using a computer-generated table of random numbers, and group assignments were sealed in sequentially numbered envelopes	Double blind: patients, anesthesia care providers	Ropivacaine 0.5% 100	I, II	Ultrasound
Ghisi et al. (2016)[16]	Italy Instituti Ospitalieri Cremona	Laparoscopic	Patients between 18 and 70 years old, undergoing elective total laparoscopic hysterectomy	Chronic opioid therapy in the previous 3 months before surgery, conversion to open surgical technique, BMI $>30\ kg/m^2$ or $<18\ kg/m^2$, postoperative recovery in intensive care unit, chronic therapy with antidepressants, known diagnosis of epilepsy or therapy with antiepileptic drugs, bilirubin level >3.0 mg/dL, aspartate aminotransferase and/or alanine aminotransferase >250 IU, creatinine level >1.4 mg/dL, pregnancy or lactation, known allergy to any drug used in the study, local infection at the block site, and drug or alcohol addiction.	Postoperative pain at rest and during movement using NRS of 0 to 10, at 2, 4, 6, and 24 hours. Morphine requirement 24 hours, incidence of postoperative nausea and vomiting (PONV) using the Apfel score	No block	22 / 22 Patients were randomized into two groups using computer-generated sequence of numbers placed in sealed envelopes	Single blind: observer (data collection)	Levobupivacaine 0.375% (75)	I - III	Ultrasound
Guardabassi et al. (2017)[18]	Argentina Hospital Italiano de Buenos Aires	Laparoscopic	Patients between 18 and 70 years old; BMI $<35\ kg/m^2$; undergoing total laparoscopic hysterectomy	Previous medical history of allergy to local anesthetics; psychiatric disorders or dementia, abdominal wall infection; chronic use of analgesics, chronic pain syndrome; diagnosed peripheral neuropathy; known allergy to analgesics or corticoids.	Pain NRS scores at 60 minutes, 2, 8, and 24 hours after surgery; opioid consumption during the first 24 postoperative hours; adverse effects on quality of sleep of the first night after surgery; episodes of nausea and vomit; Ramsay sedation scale	No block	20 / 20 Non-probability sampling of consecutive case series. Random assignment using sealed envelopes	Single-blind: Data analysts	Ropivacaína 0.5% (75)	I, II	Ultrasound

Table 1 (*Continued*)

Study	Country	Type of surgery	Inclusion criteria	Exclusion criteria	Outcomes	Comparison group	Number TAP / Control Sequence generation and concealment	Blinding	Anesthetic drug dose (mg)	ASA	TAP block technique
Bava et al. (2016)[17]	China Department of Anesthesiology and Operation, Hospital of People's Liberation Army. Xi'an	Laparoscopic and LAVH	Women scheduled for elective laparoscopic hysterectomy with benign lesions	Patients with preoperative use of analgesics were excluded due to potential impact on postoperative analgesia requirement; BMI > 30 kg/m^2; coagulopathy; contraindication for peripheral nerve block; any drug allergy	Pain, with NRS: 30 and 60 minutes, 4, 8, 12, and 24 hours PONV, Ramsay sedation scale Satisfaction scores	No block	35 / 36 Computer-generated randomization list in blocks, placed in sealed envelopes	Double-blind: blinded to patients and data analysts, but not to members of the surgical and anesthesia care teams	Ropivacaine 0.375% (112.5)	–	Ultrasound
Kane et al. (2012)[14]	United States of America Metrohealth Medical Center, Case Western Reserve University, Cleveland	Laparoscopic and single-port	All women undergoing laparoscopic hysterectomy by a single surgeon between April and September 2011 were approached to participate in this study.	Patients on chronic pain narcotic medications, or if they had allergy to local anesthetic.	Numeric visual analog scales for pain and opioid requirement at 2 and 24 hours after surgery; quality of recovery (QoR-40 survey) at postoperative day 1	No block	28 / 29 Computer-based block randomization	Single-blind: blinded to data analysts	Ropivacaine 0.5% with epinephrine (100)	–	Ultrasound

Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; NRS, non-randomized study; NSAIDS, nonsteroidal anti-inflammatory drugs; PONV, Postoperative nausea and vomiting.

opioid consumption and global quality of recovery at 24 hours in all three groups. Numerical pain rating scale scores in the recovery room were lower in the ropivacaine groups compared with saline. Thus, the authors concluded that preoperative TAP infiltration led to improved quality of recovery and analgesia in patients undergoing laparoscopic hysterectomy.

The study by Ghisi et al.[16] showed that morphine consumption was comparable between groups during their stay at the postanesthesia care unit and during the first 24 hours ($p = 0.154$; $p = 0.950$). Numeric rating scale (NRS) scores for pain at awakening were also comparable between groups ($p = 0.086$). This study concluded that ultrasound-guided TAP block did not reduce opioid consumption or pain scores at rest or movement during the first 24 hours after laparoscopic hysterectomy.

Similarly, the study by Guardabassi et al.[18] analyzed opioid consumption and scored pain using the visual numeric scale (VNS) during the first 24 postoperative hours, specifically at 60 minutes, 120 minutes, 8 hours, and 24 hours after surgery. The authors found no significant differences between groups in opioid consumption ($p = 0.2$) and reported that differences in pain scale scores were not statistically significant ($p > 0.1$) at the analyzed time points. Hence, they concluded that TAP block did not improve postoperative patient controlled opioid analgesia used for pain management in gynecologic laparoscopic surgery.

Bava et al.[17] reported that patients receiving TAP block exhibited a significantly lower NRS pain score compared with controls ($p < 0.05$), as well as a reduced postoperative analgesic requirement. Satisfaction scores were significantly higher in the TAP block group ($Z = 1.61$; $p < 0.01$), and length of stay and adverse effects were comparable between groups ($p > 0.05$). The authors concluded that, after laparoscopic hysterectomy, the joint use of TAP block and local anesthesia is a better analgesic approach compared with local anesthesia alone.

On the other hand, the study by Kane et al.[14] measured the early postoperative quality of recovery using validated QoR questionnaires and found no statistically significant improvement in scores of quality of recovery in the TAP block group (score 168; 125–195) compared with no block (score 169.5; 116–194) ($p = 0.533$). Furthermore, no statistically significant difference was found between groups in narcotic use, which was 11.7 mg (0–24) of morphine in the TAP block group versus 11.8 mg (0–27) ($p = 0.474$) in the no block group. Visual analog scale pain scores were also comparable between the TAP block (score 50.0; 0–100) and the no block group (score 60.0; 20–100) ($p = 0.447$). In conclusion, no statistically significant differences were identified in pain scores, narcotic use, or quality of recovery in patients receiving TAP block after hysterectomy. Moreover, the authors highlight that there was a significant increase in the time required in the posthysterectomy operating room for the placement of the ultrasound-guided TAP block.

The study by Torup et al.[21] found no differences between groups in median morphine consumption during the first 24 hours after surgery, VAS scores, and frequency of postoperative nausea and vomiting. Thus, in this study, TAP block, in

Table 2 Risk of bias domains and overall bias

Study (ref)	Randomization process	Deviation from planned intervention	Data on loss of results	Measurement of outcomes	Selection of reported outomes	Overall bias
Calle et al. (2014)[15]	Low	Low	Low	Low	Low	Low
De Oliveira et al. (2011)[13]	Low	Low	Low	Low	Low	Low
Ghisi et al. (2016)[16]	Low	Low	Low	Low	Low	Low
Guardabassi et al. (2017)[18]	Some concern	Low	Low	Low	Low	Some concern
Bava et al. (2016)[17]	Low	Low	Low	Low	Low	Low
Torup et al. (2015)[21]	Low	Low	Low	Low	Low	Low
Kane et al. (2012)[14]	Low	Low	Low	Some concern	Low	Some concern

addition to a basic analgesia regime with paracetamol and NSAIDs, did not provide further reduction in morphine consumption, in VAS pain scores, or in the frequency of nausea or vomiting after robot-assisted hysterectomy.

Early Postoperative Pain

This outcome was evaluated in all of the analyzed studies,[13–18,21] which altogether included a total of 518 patients. Our analysis showed that patients receiving TAP block reported statistically lower pain scale scores. Using the least squares method, the difference in means was of - 1.17 (95% confidence interval [CI]: - 1.87–- 0.46), with $I^2 = 68\%$ and $Tau^2 = 2.65$ (95% CI: 0.93–7.56), indicating intermediate heterogeneity.

Late Postoperative Pain

This outcome was evaluated in all of the analyzed studies,[13–18,21] which altogether included a total of 518 patients. Our analysis showed that there was no statistically significant difference in pain scale scores. Using the least squares method, the difference in pain scale scores between groups was not statistically significant between the 2 groups: 0.001 (95%CI: - 0.44–- 0.44), with $I^2 = 69\%$ and $Tau^2 = 2.75$ (95%CI: 0.96–7.84), indicating intermediate heterogeneity (►**Fig. 2**).

Opioid Requirement

Six of the 7 studies evaluated opioid requirement.[13–16,18,21] Using the least squares method, the difference in opioid consumption was of 0.37 (95%CI: - 0.95–1.68), with $I^2 = 80\%$ and $Tau^2 = 4.21$ (95%CI: 1.36–13.05), indicating high heterogeneity (►**Fig. 3**).

Nausea and Vomiting

Regarding presence of nausea and vomiting, our results indicate that this outcome showed a significant difference in favor of TAP block.

Risk of bias across studies and sensitivity analysis

A high level of heterogeneity was identified through the use of fixed and random effect models of meta-analysis, and therefore we explored baseline characteristics[33] and performed a meta-analysis to assess whether the identified heterogeneity could be attributed to methodological flaws, which showed no statistically significant differences between intervention and control groups.

Patient age was the only characteristic reported by all of the studies, and the difference between groups was of 0.84 (95%CI: - 0.17–1.86) with $I^2 = 17\%$. On the other hand, body mass index (BMI) was reported by 5 of the studies, and the difference of - 0.20 (95%CI: - 0.39–- 0.01; $I^2 = 25\%$), was statistically significant. Surgical time was reported by 4 studies, and the difference was of - 3.77 (95%CI: - 8.44–0.90; $I^2 = 0\%$).

Forest plots and funnel plot augmentations indicated robust results regarding precision and estimation of outcomes of TAP block regarding reduction of late postoperative pain and opioid requirement. The prediction interval showed that, given the current data, it is unlikely that new studies show opposite results. On the other hand, it is not clear whether the inclusion of new studies would change the results regarding the efficacy of TAP block in reducing early postoperative pain (►**Fig. 4**).

Discussion

Summary of Evidence

Over the past decade, minimally invasive surgery has gained relevance because of its advantages, including its association with less postoperative pain.[36] However, patients undergoing laparoscopic hysterectomy reported considerable pain of multifactorial origin, including somatic, visceral, and referred.[8] Consequently, these patients may require large amounts of opioid during the first 24 hours after surgery.[37]

Transversus abdominis plane block has been the matter of study in multiple trials, whose results have allowed its use in open and laparoscopic gynecological surgery. However, the results of studies reporting the efficacy of TAP block regarding reduction of pain and opioid requirement are contradictory, generating confusion in deciding whether to use it in clinical practice and to include it as part of multimodal analgesia protocols.

In the present meta-analysis, our results suggest that TAP block improves early postoperative pain scale scores, with a statistically significant difference of - 1.17 (95%CI: - 1.87–- 0.46), taking into account that a decrease of 1 point in pain

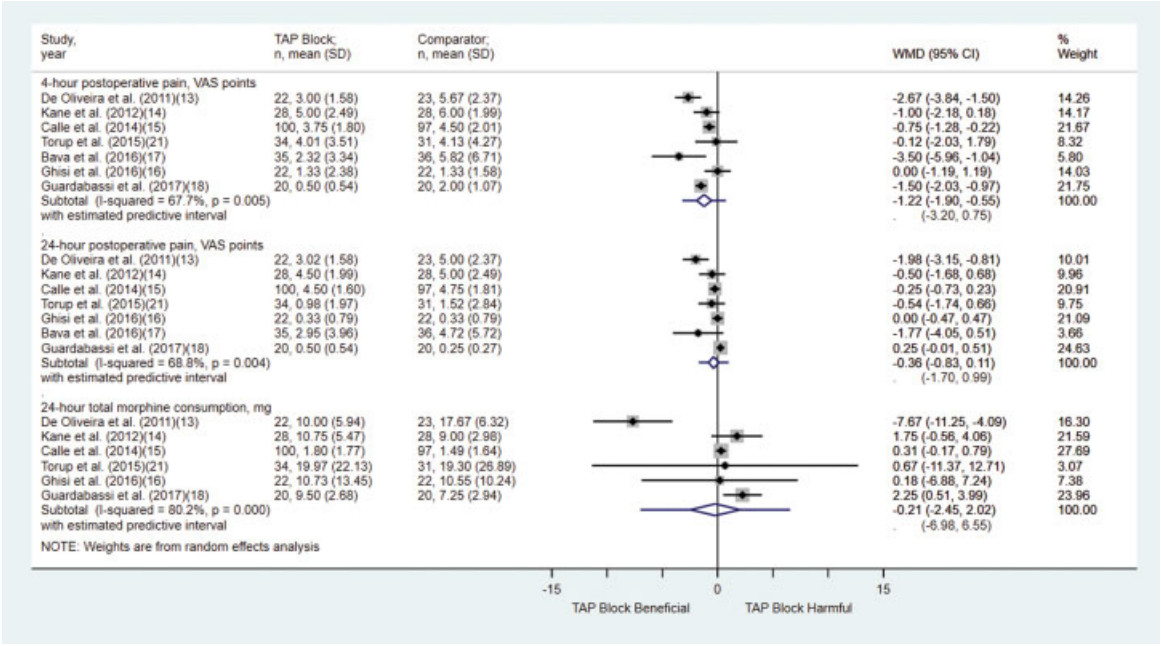

Fig. 2 Forest Plot: 4h postoperative pain, 24h postoperative pain.

scores, or of 15 to 20%, is considered as a minimum change, and to generate clinically significant improvement for patients, such as the lack of need to request rescue medication, pain scale scores should be reduced by 2 to 2.7 points, or by 30 to 40%.[27–30] Therefore, the clinical relevance of this finding is questionable, and the clinical benefit is unclear according to the prediction interval result.

Results of this outcome are similar to those found in other meta-analyses.[22,23] Differences in postoperative pain reduction did not go beyond the first 4 hours, and this difference was not significant 24 hours after surgery: 0.001 (95%CI: - 0.44–0.44), which is in agreement with the findings of the meta-analysis by Tubog et al.[22]

The type and dose of medications used in the different studies were equivalent; however, to explain the high level of heterogeneity identified, we conducted a sensitivity analysis excluding studies using bupivacaine[15] and levobupivacaine,[16] which showed the same results for the analyzed outcomes: early VAS score: - 1.65 (95%CI: - 2.47–- 0.83; Tau: 0.44; I^2: 55%); late VAS score: - 0.74 (95%CI: - 1.71–0.23; Tau: 0.85; I^2: 78%); and opioid requirement: - 0.80 (95%CI: - 5.33–3.74; Tau: 16.07; I^2: 88%).

Regarding presence of nausea and vomiting, our results indicate that this outcome showed a significant difference in favor of TAP block. In the meta-analysis by Bacal et al.,[23] due to the lack of consistency between studies, they were unable

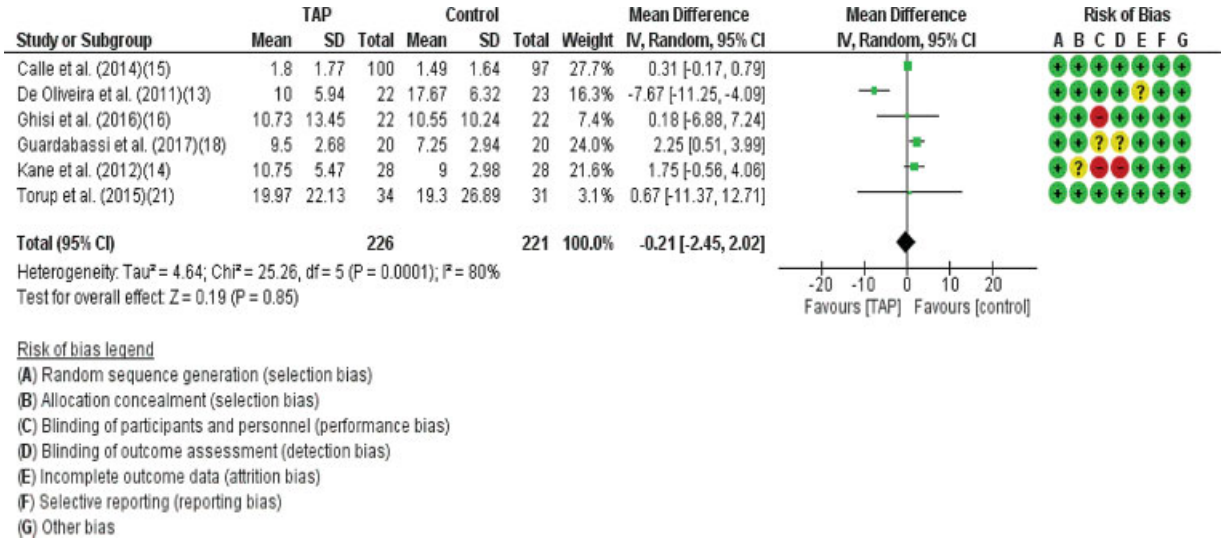

Fig. 3 Forest Plot: total morphine consumption.

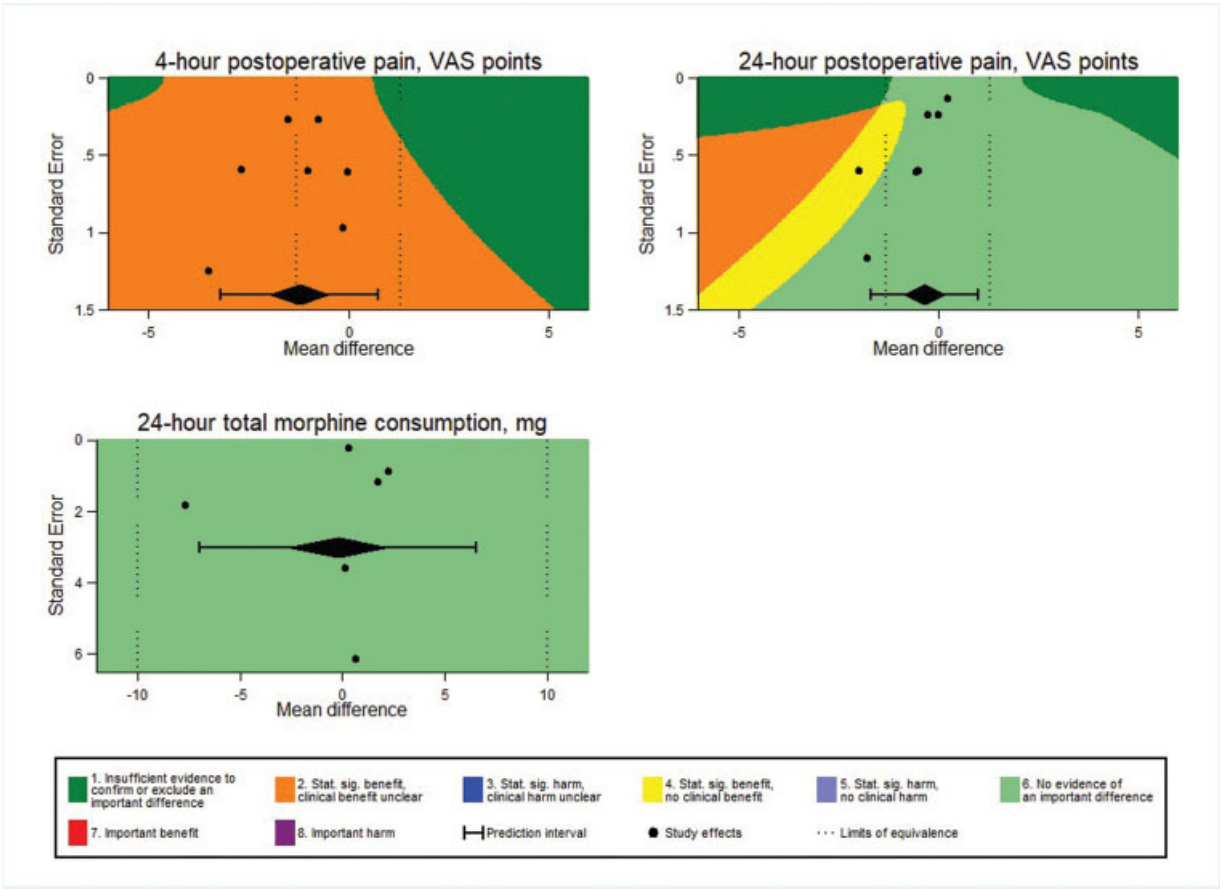

Fig. 4 Forest Plots and Funnel plot augmentation.

to evaluate the role of TAP block in the incidence of postoperative nausea and vomiting.

One of the strengths of the present study is the emphasis placed on our analysis to explain the high heterogeneity found between studies, and while it is not possible to conclude conclusively, we consider that the simple randomization process may play an important role in the persistence of such a high heterogeneity and affect the observed causal inference, which was taken into account when concluding about our findings.

Additional strengths include the exclusive use of clinical trials with systematic and methodological application of inclusion and exclusion criteria, whose quality was assessed by evaluation of risk of bias, which was low in general for all studies, and intermediate for two of the studies in relation to randomization in the study by Guardabassi et al.[18] and to outcome measurement in the study by Kane et al.[14]. However, this did not affect the reported results.

Among the limitations identified are the use of no block in four of the studies, which may lead to results that are less robust compared with placebo. Nonetheless, the results were similar for these two types of comparators. No particular study explains the obtained I^2 value, and the present meta-analysis was unable to explain the high heterogeneity between studies.

The comparability between studies may be affected by factors such as the use of different protocols regarding who did the intervention and measured outcomes, different blinding techniques, the report of a previous explanation to patients of the pain scales used, ambulatory management for some, and the intra- and postoperative analgesia regime used.

The analyzed studies did not report on comorbidities that may influence the intensity and duration of postoperative pain, such as endometriosis and chronic pelvic pain. Unfortunately, the only baseline characteristic reported by all studies was patient age, making the comparison of groups between studies challenging, as did the inconsistency in reporting adverse effects of opioid use; thus this should be taken into account in future studies.

Moreover, some of the studies did not perform an intent-to-treat analysis, which may affect the results. To obtain unreported measures, we contacted the corresponding author of three of the studies, of which only one replied. Therefore, the use of spreadsheets developed for graphs with unavailable numerical data was required.

Conclusion

In conclusion, the results obtained in the present meta-analysis indicate that TAP block improves early postoperative pain as indicated by the statistically significant difference; however, the clinical benefit of this difference is unclear. We did not find

relevant evidence to suggest that there were any significant differences in late postoperative pain and in opioid requirement in patients receiving TAP block. Based on the best available evidence to date, we conclude that TAP block should not be considered as an effective analgesic technique to improve postoperative pain in patients undergoing laparoscopic or robotic hysterectomy. This was concluded based on the obtained results, which showed a marginal analgesic efficacy in the early postoperative period albeit of unclear clinical relevance, and that this effect was not maintained over time nor decreased the opioid requirement. Nonetheless, since the evidence synthesis showed high heterogeneity and the baseline characteristics exhibited imbalance, the strength of the evidence resulting from the present meta-analysis is rated as moderate, as determined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, despite being randomized controlled clinical trials. On the other hand, regarding the small sample sizes in these trials, it is important that future studies take into consideration the use of efficient randomization methods in regard to balancing baseline characteristics. In addition, preoperative conditions that may modify outcomes, such as diseases associated with pelvic pain, should also be taken into account to generate stronger evidence.

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

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Underestimation Rate in the Percutaneous Diagnosis of Radial Scar/Complex Sclerosing Lesion of the Breast: Systematic Review

Taxa de subestimação no diagnóstico percutâneo de cicatriz radiada/lesão esclerosante complexa da mama: Revisão sistemática

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Abstract

Objective To evaluate the underestimation rate in breast surgical biopsy after the diagnosis of radial scar/complex sclerosing lesion through percutaneous biopsy.

Data Sources A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. The PubMed, SciELO, Cochrane, and Embase databases were consulted, with searches conducted through November 2020, using specific keywords (*radial scar* **OR** *complex sclerosing lesion*, *breast cancer*, *anatomopathological percutaneous biopsy* **AND/OR** *surgical biopsy*).

Data collection Study selection was conducted by two researchers experienced in preparing systematic reviews. The eight selected articles were fully read, and a comparative analysis was performed.

Study selection A total of 584 studies was extracted, 8 of which were selected. One of them included women who had undergone a percutaneous biopsy with a histological diagnosis of radial scar/complex sclerosing lesion and subsequently underwent surgical excision; the results were used to assess the underestimation rate of atypical and malignant lesions.

Data synthesis The overall underestimation rate in the 8 studies ranged from 1.3 to 40% and the invasive lesion underestimation rate varied from 0 to 10.5%.

Conclusion The histopathological diagnosis of a radial scar/complex sclerosing lesion on the breast is not definitive, and it may underestimate atypical and malignant lesions,

Keywords
- breast diseases
- breast neoplasms/diagnosis
- image-guided biopsy

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which require a different treatment, making surgical excision an important step in diagnostic evaluation.

Resumo

Objetivo Avaliar o grau de discordância entre biópsia percutânea e cirúrgica da mama em pacientes com diagnóstico de cicatriz radiada/lesão esclerosante complexa (CR/LEC) por meio de uma revisão sistemática.

Fontes dos dados Foi realizada uma revisão sistemática segundo as recomendações do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, na sigla em inglês). As bases de dados primárias consultadas foram PubMed, SciELO, Cochrane e Embase, com buscas conduzidas até novembro de 2020, utilizando palavras chaves específicas (*cicatriz radiada* OU *lesão esclerosante complexa*, *câncer de mama*, *anatomopatológico de biópsia percutânea* E/OU *biópsia cirúrgica*).

Seleção dos estudos A busca dos artigos resultou em um total de 584 estudos, sendo 8 selecionados, os quais incluíam mulheres submetidas a biópsia com diagnóstico histológico de CR/LEC e posteriormente submetidas a exérese cirúrgica para avaliar como desfecho o grau de subestimação de lesões atípicas e malignas.

Coleta de dados A seleção dos estudos foi conduzida por dois pesquisadores, com experiência na elaboração de revisão sistemática. Os oito artigos selecionados foram lidos na íntegra e submetidos a uma análise comparativa.

Síntese dos dados Cicatrizes radiadas/lesões esclerosante complexas foram associadas com lesões atípicas e malignas após a exérese cirúrgica. O grau de subestimação geral foi calculado pela porcentagem de lesões atípicas e malignas no anatomopatológico após a exérese cirúrgica dentre o total de CR/LEC diagnosticadas, enquanto o grau de subestimação de lesões invasoras foi calculado considerando-se apenas os carcinomas invasivos. O grau de subestimação geral dos estudos selecionados variou de 1,3 a 40%, e o de lesões invasoras de 0 a 10,5%.

Conclusão O diagnóstico histopatológico de CR/LEC na mama não é definitivo, podendo subestimar lesões atípicas e malignas, cujo tratamento é distinto, tornando a exérese cirúrgica etapa fundamental na investigação diagnóstica.

Palavras-chave
- doenças mamárias
- neoplasias da mama/diagnóstico
- biópsia guiada por imagem

Introduction

Radial scar/complex sclerosing lesion (RS/CSL) is a benign breast disease, characterized macroscopically by an architectural distortion of the breast tissue with radial spikes in the center and, microscopically, by a central area of fibroelastosis from which ducts and lobes radiate.[1,2] The distinction between both nomenclatures is based only on the size of the lesion: the radial scar measures < 1 cm and the complex sclerosing lesion is > 1 cm.[2] Most are microscopic, multiple, bilateral, and not palpable on clinical examination.

The implementation of screening programs and the consequent increase in the number of asymptomatic patients undergoing mammography contributed to a 3-fold increase in the detection of these lesions in percutaneous biopsies.[3] Due to its radiological and histological similarity to invasive cancer and its association with other atypical lesions, RS/CSL arouses the interest of researchers; however, the real need for surgical excision is questioned in view of a histopathological diagnosis enabled by percutaneous biopsy.

Once a histological diagnosis is reached after a percutaneous biopsy, the potential for intrinsic malignancy of the lesion must be considered. The lesion can develop into atypical proliferations, including atypical hyperplasia and invasive carcinoma. Besides, its coexistence with cancer and other high-risk lesions should be taken into account.[4] However, the pathogenesis of the lesion, as well as the reason the radial scar is associated with an increased risk of breast cancer, is still uncertain.[3]

Hence, the present study aims to assess the degree of disagreement between percutaneous and surgical biopsies in patients diagnosed with RS/CSL through the underestimation rate of atypical and malignant lesions diagnosed after surgical excision.

Methods

We conducted a systematic review for the assessment of the underestimation degree of malignant lesions based on a histological diagnosis of RS/CSL lesion after surgical excision and percutaneous biopsy. Studies evaluating RS/CSL with atypia by means of percutaneous biopsy were not included. The review followed the Preferred Reporting Items for

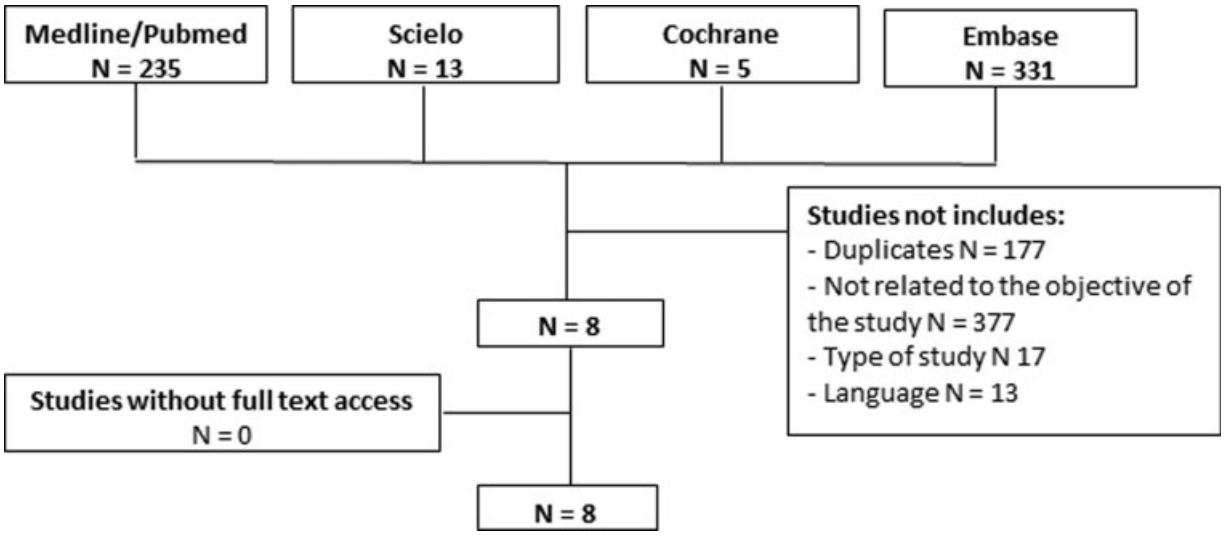

Fig. 1 Flow chart following the recommendations of PRISMA.

Systematic Reviews and Meta-Analysis (PRISMA) guidelines (►**Fig. 1**).[5] The recommendations were adapted from observational studies given the lack of clinical trials.

Pubmed/Medline: *radial scar* [All Fields] OR *complex sclerosing lesions* [All Fields] AND (*breast neoplasms* [MeSH Terms] OR (*breast* [All Fields] AND *neoplasms* [All Fields]) OR *breast neoplasms* [All Fields] OR (*breast* [All Fields] AND *cancer* [All Fields]) OR *breast cancer* [All Fields]) AND (*pathology* [Subheading] OR *pathology* [All Fields] OR *biopsy* [All Fields] OR *biopsy* [MeSH Terms]). Scielo: *radial scar*. Cochrane: *radial scar*. Embase: (*radial scar*/*exp* OR *radial scar* OR *complex sclerosing lesions*) AND (*breast cancer*/*exp* OR *breast cancer* OR (*breast*/*exp* OR *breast*) AND (*cancer*/*exp* OR *cancer*))) AND (*biopsy*'/*exp* OR *biopsy*). Article search and selection were conducted by two researchers experienced in preparing systematic reviews (Zanon A. B. B. and Maesaka J. Y.), with searches conducted through November 2020. Discrepancies in the selection of articles by these researchers were solved through group discussion with the participation of a third researcher (Chequin B. B.).

Results

The process of searching, identifying, and selecting articles is in ►**Fig. 1**. From a total of 584 articles, 8 studies were selected for inclusion in the final analysis. The main reasons for exclusion were the following: studies unrelated to the main objective of our review (female patients who underwent biopsy with a resultant histological diagnosis of RS/CSL and subsequently underwent surgical excision, enabling assessment of the underestimation degree of atypical and malignant lesions), type of studies (original studies only), duplicate articles, and articles not written in English or Portuguese. The 8 studies included 630 cases of RS/CSL on percutaneous biopsy, 442 of which subsequently underwent surgical excision (►**Table 1**). The mean age of the patients was 54 years old (range: 19 to 84 years old). The overall underestimation rate was calculated as the percentage of atypical and malignant lesions in the anatomopathological exam of the RS/CSLs that underwent surgical biopsy. The underestimation rate among the studies varied from 1.3 to 40% (►**Table 2**). The invasive lesion underestimation rate was calculated considering only invasive carcinomas in the anatomopathological exam of the RS/CSL that underwent surgical biopsy. The rate varied from 0 to 10.5%.

The mean age of the patients was 54.8 years old. There were 425 patients who underwent biopsies; of these, 95 (22%) were found to have RS/CSL on core needle biopsy and 77 had radial scar without evidence of atypia. Analysis of these 77 patients showed that the upgrade to the atypia rate was 31% (24 of 77) and to the carcinoma in situ rate was 9% (7/77). There was no upgrade to invasive carcinoma. Therefore, the overall underestimation rate was 40%.[6]

In Woodward et al.,[7] a retrospective review using a single institutional pathology and radiology database was conducted for all radial scars identified on core biopsy from January 2010 to January 2017. The mean age of the patients with benign biopsies was 52.9 years old. Sixty-six isolated RSs were identified and 44 underwent surgical excision. Fifteen upgraded to atypical lesions (flat epithelial hyperplasia [6], atypical ductal hyperplasia [5], lobular carcinoma in situ [2], atypical lobular hyperplasia [1], and atypical ductal hyperplasia/atypical lobular hyperplasia [1]) and 2 upgraded to malignancy (ductal carcinoma in situ [1] and invasive ductal carcinoma [1]). The overall underestimation rate was 38% and the invasive lesion underestimation rate was 2.2%.[7]

Gašljević et al.,[8] in a retrospective study using a database from the Slovenian National Breast Cancer Screening Program, checked all patients with a radial scar or a complex sclerosing lesion who underwent core needle biopsy between 2008 and 2018. The mean age was 61.5 years old. Of the 156 patients selected, 107 (68.6%) had radial scars or complex sclerosing lesions without atypia, and 76 of these patients underwent surgical excision. Seventy-five patients had nonmalignant lesions (atypical proliferative lesions, lobular neoplasia, and papilloma) on final excision and no patient had carcinoma

Table 1 Study selection

Author, year of publication	Type of study	RS/CSL diagnosed after percutaneous biopsy	Mean age (years old) (range)	RS/CSL that underwent surgical excision
Quinn et al. (2020)[6]	Retrospective	77	54.8 (50–64)	77
Woodward et al. (2020)[7]	Retrospective	66	55.6 (19–76)	44
Gašljević et al. (2020)[8]	Retrospective	107	61.5 (50–69)	76
Bacci et al. (2019)[9]	Retrospective	92	53.4 (25–83)	48
Mooney et al. (2016)[10]	Retrospective	54	53.2	25 (46%)
Matrai et al. (2015)[11]	Retrospective	77	51.4 (37–79)	77 (100%)
Nassar et al. (2015)[12]	Retrospective	100	50.2 (23–74)	38 (38%)
Stefenon et al. (2003)[1]	Retrospective	57	49 (31–84)	57(100%)
Final conclusion	–	630	54	442

Abbreviation: RS/CSL, radial scar/complex sclerosing lesion.

Table 2 Diagnosis after surgical excision

Author, year of publication	Atypia and LCIS	DCIS	Invasive carcinoma	Overall underestimation rate
Quinn et al. (2020)[6]	24/77 (31%)	7/77 (9%)	0/77 (0%)	31/77 (40%)
Woodward et al. (2020)[7]	15/44 (34%) 5ADH 1ALH 6FEA 2LCIS 1ADH/ALH	1/44 (2.2%)	1/44 (2.2%)	17/44 (38%)
Gašljević et al. (2020)[8]	0/76 (0%)	0/76 (0%)	1/76 (1.3%)	1/76 (1.3%)
Bacci et al. (2019)[9]	16/48 (33.3%) 6ADH 6ALH 8FEA	0/48 (0%)	0/48 (0%)	16/40 (33.3%)
Mooney et al. (2016)[10]	5/25 (20%) 2ADH 2ALH 1RSA	3/25 (12%)	1/25 (4%) 1ILC	9/25 (36%)
Matrai et al. (2015)[11]	9/77 (11.7%) 2ADH 1ALH 6LCIS	0/77 (0%)	0/77 (0%)	9/77 (11.7%)
Nassar et al. (2015)[12]	7/38 (18.4%) 1ADH 5ALH 1LCIS	2/38 (5.3%)	2/38 (5.3%)	11/38 (28.9%)
Stefenon et al. (2003)[1]	9/57 (15.8%) 5ADH 4ALH	0/57 (0%)	6/57 (10.5%)	15/57 (26.3%)
Final conclusion	85/442 (19.2%)	13/442 (2.9%)	11/442 (2.4%)	109/442 (24.6%)

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; FEA, flat epithelial hyperplasia; RSA, radial scar with atypia.
Quinn et al.[6] performed a retrospective review of articles retrieved from a breast screening database at one of the four national units in Ireland. Patients with a radial scar identified on core biopsy or surgical excision were selected. Radial scars without atypia (on core or excision biopsy) were analyzed separately from those with any coexistent risk lesions.

ductal in situ only. One case was upgraded to invasive carcinoma. The overall underestimation rate was 1.3%.[8]

Bacci et al.[9] retrieved from an electronic medical record every patient with a histological diagnosis of RS/CSL through vacuum-assisted biopsy at the Comprehensive Cancer Care Centre - Institut Bergonie (France) over a period of 7 years and 5 months, from May 2008 to October 2015. The mean age was 53.4 years old (range: 25 to 83 years old). Ninety-two

benign biopsies were identified (biopsies showing isolated RS/CSL or RS/CSL associated with other proliferative lesions without atypia), and 48 lesions underwent surgical excision. After surgery, 16 upgraded to atypia (flat epithelial hyperplasia in 16.7% [8], atypical ductal hyperplasia in 12.5% [6], and atypical lobular hyperplasia in 12.5% [6]). Not a single benign biopsy upgraded to carcinoma in situ or to invasive carcinoma. The overall underestimation rate was 33.3%.[9]

Mooney et al.,[10] in a retrospective review spanning 14.5 years in Los Angeles (USA), analyzed 5,750 results of core biopsy (the needle size was not specified): 462 were high-risk lesions and 54 were radial scars. Of the latter cases, 25 (46%) underwent surgical excision. Of the remaining 29 cases, 12 did not undergo surgical excision due to loss to follow-up, and 17 had documentation recommending radiological follow-up for 6 months. Surgical excision revealed 5 atypical lesions (atypical ductal hyperplasia [2], atypical lobular hyperplasia [2], and radial scar with atypia [1]), 3 ductal carcinomas in situ, and 1 invasive lobular carcinoma. The general underestimation rate was 36%, while the invasive lesion underestimation rate was 4%. Of the high-risk lesions analyzed, the radial scars were less associated with malignant lesions after excision than atypical ductal hyperplasia (odds ratio [OR] = 0.29; $p = 0.014$; confidence interval [CI] = 0.11–0.77, in this cited study, the range was not mentioned). In addition, in the benign results, the number of cases with Breast Imaging Reporting and Data System (BIRADS) < 4B, nodules < 1 cm, and absence of calcifications was lower than that in the malignant results after surgical excision.[10]

In Matrai et al.,[11] 77 radial scar lesions were found in core biopsies, which subsequently underwent surgical excision were identified in New York (USA). Three patients (3/77) were upgraded to atypical lesions (atypical ductal hyperplasia [2] and atypical lobular hyperplasia [1]) and 6 to lobular carcinoma in situ. There was no upgrade to ductal carcinoma in situ or to invasive carcinoma. The overall underestimation rate was 11.7%. Older age was a predictor of higher risk of upgrade in this setting (62.0 versus 49.9 years old, $p < 0.001$).[11]

Nassar et al.[12] performed a retrospective chart review of cases of RS/CSL diagnosed by core biopsy from January 1, 1994 to August 31, 2013 in a single institution in Rochester (USA). One hundred RS/CSL were identified, and the mean age of the patients was 50.2 years old. Of the 100 lesions, 38 underwent surgical excision. The median size of the excision was 1.2 cm (69% > 1 cm). The results were the following: 6 atypical lesions (atypical ductal hyperplasia [1] and atypical lobular hyperplasia [5]), 1 lobular carcinoma in situ, 2 ductal carcinomas in situ, and 2 invasive carcinomas, with an overall underestimation rate of 28.9% and an invasive lesion underestimation rate of 5.3%.[12] Of these 11 lesions, all were diagnosed with radial scar: 3 by mammotomy and 8 by core biopsy.

Stefenon et al.[1] reviewed cases from the archives of the Diagnostic Imaging Center and of the Hospital Santa Rita, Vitória, state of Espírito Santo, Brazil, between October 1993 and December 2001. Of the 926 lesions that underwent percutaneous biopsy, 57 were histopathologically diagnosed with RS/CSL. The mean age of the patients was 49 years old (range: 31 to 84 years old). The lesions were palpable in 10 cases. Mammography showed 48 cases of distortion in architecture, 4 of spiculated nodule, 4 of asymmetric density, and 14 of microcalcifications. The diagnosis after surgical excision was 9 atypical lesions (atypical ductal hyperplasia [5] and atypical lobular hyperplasia [4]), 3 ductal carcinomas in situ together with tubular carcinoma (without specification of adjacent or distant location), 2 tubular carcinomas, and 1 invasive carcinoma. The overall underestimation rate was 26.3% and the invasive lesion rate was 1.7%.[1]

Discussion

The behavior of RS/CSL, a benign lesion of the breast, is not well known, owing to its mimicry and possible progression to atypia and cancer.[12] However, complex sclerosing lesion should not be confused with sclerosing adenosis. The latter refers to another type of benign lesion of glandular proliferation.

Many studies have questioned the need for surgical excision since a histopathological diagnosis is also enabled percutaneously. Brenner et al.,[2] in 2002, propounded that percutaneous biopsy should only be complemented by surgical excision when there is associated atypical hyperplasia, a biopsy with < 12 fragments, or when mammographic findings are not compatible with the histological diagnosis of RS/CSL.[2] Chou et al.,[13] in 2018, in a follow-up of a mean of 32.3 months, found that in only 1.6% of the patients with a percutaneous diagnosis of RS, the disease had developed into invasive carcinoma. Thus, the RS on percutaneous biopsy could be followed-up with clinical monitoring without the need for an excisional biopsy.[13]

Similarly, Nassar et al.,[12] in 2015, suggested that RS size at image and the biopsy tissue volume sample may be related to the likelihood of underestimation. Of 11 cases upstaged at excision, 8 (73%) of them were not vacuum-assisted. In this study, "upstaging was noted more often in women with RS lesions larger than 1.0cm and in women with worrisome radiologic features." In this data, the 29% overall underestimation rate supported the role of excisional biopsy in the follow-up of patients with RS/CSL on percutaneous biopsy.[12]

Reaching a correct diagnosis is of extreme clinical importance since the postsurgical treatment described in the literature is different for each lesion. The pure RS/CSL requires no additional procedures. In high-risk histological lesions, an association with endocrine therapy is recommended. For these high-risk lesions, the use of tamoxifen (selective estrogen receptor modulator [SERM]) reduces the risk of invasive carcinoma by 49% ($p < 0.00001$) and of carcinoma in situ by 50% ($p < 0.002$). Likewise, the use of aromatase inhibitors demonstrated a 49% decrease in the risk of breast cancer (HR = 0.51; CI = 0.39–0.66; $p < 0.0001$).[14,15] In ductal carcinoma in situ, radiotherapy, after conservative surgery with free margins, reduces the risk of recurrence by up to 59% (HR = 0.41; CI = 0.30–0.57; $p < 0.0001$) and the association with tamoxifen for 5 years also contributes significantly to this reduction (HR = 0.71;

CI = 0.58–0.88; $p = 0.002$).[16,17] Finally, invasive carcinomas may require adjuvant treatment (radiotherapy or systemic treatment), depending on histological type, molecular subtype, and staging.

The present study showed that a significant portion of percutaneous biopsies with a diagnosis of RS/CSL turned out to be atypical and malignant lesions upon examination after surgical excision, with a general underestimation rate ranging from 1.3 to 40% in the review studies. In 5 of the 8 studies analyzed, the diagnosis of invasive carcinoma after excision was made, so that the invasive lesion underestimation rate ranged from 1.3 to 10.5% in the studies.

The small number of published articles and their statistical variation constitute a limitation of the present study. The variance may be explained by a different patient profile at each center. The similarity in the mean age of the patients in the 8 studies is stated, but there is no mention of the comorbidities of the patients and of the period between percutaneous and surgical biopsies. There is much variability of percutaneous biopsy types performed in each study: some of the diagnoses were obtained by vacuum-assisted biopsies and others by core biopsies, and two studies did not specify needle sizes, nor the methods used. Probably, a vacuum-assisted biopsy should have a lower underestimation rate than a core biopsy, because it yields larger tissue samples. Despite these limitations and considering that, of the 442 RS/CSL which underwent surgical excision, 109 upgraded to atypical and malignant lesions, which amounts to a 24.6% rate, the present review presents relevant data and reinforces the assumption that a diagnosis by percutaneous biopsy alone can underestimate atypical and malignant lesions.

The relatively high underestimation rate shows the fundamental role of surgical exeresis in the confirmation of a diagnosis, which is necessary to define an appropriate treatment plan for each patient.

Conclusion

The histopathologic diagnosis of a RS/CSL by percutaneous biopsy is not definitive and may underestimate atypical and malignant lesions, as pointed out in the reviewed studies. In the management of RS/CSL diagnosed by percutaneous biopsy, it is important to consider the volume of tissue evaluated. The high underestimation rate identified in the present study shows the role of surgical excision in the management of the patient.

Conflict of interests

The authors have no conflict of interests to declare.

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The present review is dedicated to the memory of Prof. Nestor de Barros, MD, a model of excellence in breast radiology in Brazil and responsible for the training of many specialists.

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Perinatal Outcomes after Fetal Endoscopic Tracheal Occlusion for Isolated Congenital Diaphragmatic Hernia: Rapid Review

Resultados perinatais após oclusão traqueal endoscópica fetal por hérnia diafragmática congênita isolada: Revisão rápida

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Abstract

Objective To compare the perinatal outcomes of fetuses with isolated congenital diaphragmatic hernia after fetal endoscopic tracheal occlusion (FETO) and antenatal expectant management.

Data sources In this rapid review, searches were conducted in the MEDLINE, PMC, EMBASE and CENTRAL databases between August 10th and September 4th, 2020. Randomized controlled trials (RCTs), quasi-RCTs or cluster-RCTs published in English in the past ten years were included.

Study selection We retrieved 203 publications; 180 studies were screened by abstract. Full-text selection was performed for eight studies, and 1 single center RCT met the inclusion criteria (41 randomized women; 20 in the FETO group, and 21 in the control group).

Data collection Data collection was performed independently, by both authors, in two steps (title and abstract and full-text reading).

Data synthesis There were no cases of maternal mortality. The mean gestational age at delivery was of 35.6 $\pm$ 2.4 weeks in the intervention group, and of 37.4 $\pm$ 1.9 weeks among the controls ($p < 0.01$). Survival until 6 months of age was reported in 50% of the intervention group, and in 5.8% of the controls ($p < 0.01$; relative risk: 10.5; 95% confidence interval [95%CI]: 1.5–74.7). Severe postnatal pulmonary hypertension was found in 50% of the infants in the intervention group, and in 85.7% of controls ($p = 0.02$; relative risk: 0.6; 95%CI: 0.4–0.9). An analysis of the study indicated some concerns of risk of bias. The quality of evidence was considered moderate to low.

Conclusion Current evidence is limited but suggests that FETO may be an effective intervention to improve perinatal outcomes.

Keywords

- congenital diaphragmatic hernias
- ultrasound diagnosis
- prenatal ultrasonography
- prognosis
- systematic review

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Resumo

Objetivo Comparar os resultados perinatais de fetos com hérnia diafragmática congênita após oclusão traqueal endoscópica fetal (OTEF) e conduta expectante pré-natal.

Fontes dos dados Nesta revisão rápida, pesquisas foram conduzidas nas bases de dados MEDLINE, PMC, EMBASE e CENTRAL entre 10 de agosto de 2020 e 4 de setembro de 2020. Ensaios clínicos randomizados (ECRs), quase-ECRs e ECRs em *cluster* publicados em inglês nos últimos dez anos foram incluídos.

Seleção dos estudos Foram recuperadas 203 publicações; 180 destas foram triadas pelo resumo. Fez-se a leitura do texto completo de 8 estudos, e 1 ECR cumpriu os critérios de inclusão (41 mulheres aleatorizadas; 20 no grupo OTEF e 21 no grupo de controle).

Coleta de dados A coleta de dados realizada independentemente pelos dois autores, em duas etapas (título e resumo, e leitura do texto completo).

Síntese dos dados Não houve casos de morte materna. A idade gestacional média no parto foi de 35,6 ± 2,4 semanas no grupo de intervenção, e de 37,4 ± 1,9 semanas entre os controles ($p < 0{,}01$). A sobrevida até 6 meses de idade foi relatada em 50% do grupo de intervenção, e em 5,8% dos controles ($p < 0{,}01$; risco relativo: 10,5; intervalo de confiança de 95% [IC95%]: 1,5–74,7). Hipertensão pulmonar grave ocorreu em 50% dos lactentes do grupo de intervenção, e em 85,7% dos controles ($p = 0.02$; risco relativo: 0,6; IC95%: 0,4–0,9). Uma análise do estudo indicou algumas preocupações quanto ao risco de viés. A qualidade da evidência foi considerada de moderada a baixa.

Conclusão As evidências atuais são limitadas, mas sugerem que a OTEF pode ser uma intervenção eficaz para melhorar resultados perinatais.

Palavras-chave

- hérnias diafragmáticas congênitas
- ultrassonografia
- ultrassonografia pré-natal
- prognóstico
- revisão sistemática

Introduction

Congenital diaphragmatic hernia (CDH) is the failure in the closure of the pleuroperitoneal folds, which usually occurs between the fourth and tenth weeks of gestation.[1–5] This leads to herniation of abdominal organs to the thorax, which impairs bronchial ramification, reduces lung volume and the production of surfactant, and induces anatomic and functional adaptations in the pulmonary vasculature. Furthermore, herniated structures may result in mediastinal shift and associated hypoplasia of the cardiac structures ipsilateral to the hernia.[1,5]

The estimated prevalence of CDH is of 1 to 4 cases in every 10 thousand live births,[1,2] but it may be higher if stillbirths and pregnancy terminations are considered, because many cases are associated with potentially-lethal syndromes.

The diagnosis is usually suspected prenatally, in the second trimester scan, which evidences abdominal organs inside the fetal thorax.[1,3,5] The sensitivity depends on the presence of associated anomalies, the size of the defect, the gestational age, and the sonologist's experience.[1] When other anomalies are detected, an association with genetic or chromosomic syndromes, such as trisomy 18, Pallister-Killian and Fryns syndromes, is possible.[5] The condition is then classified regarding prognosis using the lung-to-head ratio (LHR), defined as the relationship between the contralateral lung area and fetal head circumference (lower ratios indicate more serious cases), the observed/expected LHR (o/e LHR) and liver herniation.[5,6] In addition, serial scans may detect other characteristics of poor prognosis, such as fetal growth restriction and abnormalities in the amniotic fluid index.[1–3]

For severe cases, the fetal endoscopic tracheal occlusion (FETO) procedure aims to prevent pulmonary hypoplasia and enable lung growth, which could reduce perinatal morbidity and mortality.[5] The FETO is a percutaneous procedure involving the placement of a balloon inside the fetal trachea, which retains lung fluid, elevating intrapulmonary pressure and enlarging the volume of the fetal lung. Traditionally, this intervention is performed in severe cases between 26 and 28 weeks of gestation and reversed around 34 weeks of gestation. Pregnancy continuation until term is expected to enable maturation of type-II pneumocytes and the production of surfactant.[1] There is recent evidence[5,7] indicating that this procedure could improve perinatal morbidity and mortality. Thus, the present study aimed to review and describe the quality of the evidence regarding perinatal outcomes after FETO, and compare it with the expectant management, for fetuses with isolated CDH.

Methods

Study Design

This rapid review was conducted according to the Cochrane Rapid Reviews Methods.[8] The risk of bias was assessed with the Risk of Bias 2(RoB 2) tool (Cochrane, London, UK).[9] The quality of the evidence was assessed using the Grading of Recommendation, Assessment, Development and

Evaluation (GRADE) guidelines.[10–14] The final report was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] The study protocol is registered with PROSPERO CRD42020186509, which is available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020186509.

Search Strategy

The objective of the present study was to identify randomized controlled trials (RCTs), quasi-RCTs and cluster-RCTs comparing perinatal and maternal morbidities and mortality of pregnant women whose fetuses with isolated CDH underwent FETO or no intrauterine intervention. Searches were conducted on the MEDLINE, PMC, EMBASE and CENTRAL databases, using the terms related to CDH and fetoscopy, by an information specialist and the authors between August 10th and September 4th, 2020. Articles published in English in the past ten years were included for further selection. Unpublished studies and other types of publication were not sought. The searches were rerun prior to the final analysis.

MEDLINE Search Strategy

The search strategy on the MEDLINE database was as follows: (((Hernias, Diaphragmatic, Congenital[MeSH Terms]) OR ("Hernias, Diaphragmatic, Congenital"[Title/Abstract] OR "Unilateral Agenesis of Diaphragm"[Title/Abstract] OR "Diaphragm Unilateral Ageneses"[Title/Abstract] OR "Diaphragm Unilateral Agenesis"[Title/Abstract] OR "Congenital Diaphragmatic Hernias"[Title/Abstract] OR "Congenital Diaphragmatic Hernia"[Title/Abstract] OR "Diaphragmatic Hernia, Congenital"[Title/Abstract] OR "Diaphragmatic Hernias, Congenital"[Title/Abstract] OR "Hernia, Congenital Diaphragmatic"[Title/Abstract] OR "Hernias, Congenital Diaphragmatic"[Title/Abstract] OR "Agenesis of Hemidiaphragm"[Title/Abstract] OR "Hemidiaphragm Ageneses"[Title/Abstract] OR "Hemidiaphragm Agenesis"[Title/Abstract] OR "Congenital Diaphragmatic Defect"[Title/Abstract] OR "Congenital Diaphragmatic Defects"[Title/Abstract] OR "Defect, Congenital Diaphragmatic"[Title/Abstract] OR "Defects, Congenital Diaphragmatic"[Title/Abstract] OR "Diaphragmatic Defect, Congenital"[Title/Abstract] OR "Diaphragmatic Defects, Congenital"[Title/Abstract] OR "Bochdalek Hernias" OR"Hernias, Bochdalek"[Title/Abstract] OR "Morgagni Hernias"[Title/Abstract] OR "Hernias, Morgagni"[Title/Abstract] OR "Morgagni's Hernias"[Title/Abstract] OR "Hernias, Morgagni's"[Title/Abstract] OR "Morgagnis Hernias"[Title/Abstract])) OR ((Hernia, Diaphragmatic[MeSH Terms]) OR ("Hernia, Diaphragmatic"[Title/Abstract] OR "Diaphragmatic Hernias"[Title/Abstract] OR "Hernias, Diaphragmatic"[Title/Abstract] OR "Diaphragmatic Hernia"[Title/Abstract]))) AND ((Fetoscopy[MeSH Terms]) OR (Fetoscopy[Title/Abstract] OR Fetoscopies[Title/Abstract] OR Amnioscopy[Title/Abstract] OR Amnioscopies[Title/Abstract] OR "Fetoscopic Surgical Procedures"[Title/Abstract] OR "Fetoscopic Surgical Procedure"[Title/Abstract] OR "Procedure, Fetoscopic Surgical"[Title/Abstract] OR "Procedures, Fetoscopic Surgical"[Title/Abstract] OR "Surgical Procedure, Fetoscopic"[Title/Abstract] OR "Surgery, Fetoscopic"[Title/Abstract] OR "Surgical Procedures, Fetoscopic"[Title/Abstract] OR "Fetoscopic Surgery"[Title/Abstract] OR "Fetoscopic Surgeries"[Title/Abstract] OR "Surgeries, Fetoscopic"[Title/Abstract] OR Embryoscopy[Title/Abstract] OR Embryoscopies[Title/Abstract] OR "Amnioscopic Surgical Procedures"[Title/Abstract] OR "Amnioscopic Surgical Procedure"[Title/Abstract] OR "Procedure, Amnioscopic Surgical"[Title/Abstract] OR "Procedures, Amnioscopic Surgical"[Title/Abstract] OR "Surgical Procedure, Amnioscopic"[Title/Abstract] OR "Surgery, Amnioscopic"[Title/Abstract] OR "Surgical Procedures, Amnioscopic"[Title/Abstract] OR "Amnioscopic Surgery"[Title/Abstract] OR "Amnioscopic Surgeries"[Title/Abstract] OR "Surgeries, Amnioscopic"[Title/Abstract] OR "Embryoscopic Surgical Procedures"[Title/Abstract] OR "Embryoscopic Surgical Procedure"[Title/Abstract] OR "Procedure, Embryoscopic Surgical"[Title/Abstract] OR "Procedures, Embryoscopic Surgical"[Title/Abstract] OR "Surgical Procedure, Embryoscopic"[Title/Abstract] OR "Surgery, Embryoscopic"[Title/Abstract] OR "Surgical Procedures, Embryoscopic"[Title/Abstract] OR "Embryoscopic Surgery"[Title/Abstract] OR "Embryoscopic Surgeries"[Title/Abstract] OR "Surgeries, Embryoscopic"[Title/Abstract])). Filters: in the past 10 years, English.

Study Selection

The search results of each database were gathered using the Rayyan online software (Rayyan Systems Inc., Cambridge, MA, US).[16] After the exclusion of duplicates, the publications were independently screened by title and abstract by J.C.S. and J.R.B. regarding the eligibility criteria. After both authors finished screening the search results, the study selection was compared, and disagreements were resolved by consensus. The remaining studies were further independently screened by full-text reading by J.C.S. and J.R.B., and those that met the eligibility criteria were assessed for data extraction. The exclusion criteria weere wrong type of publication, wrong population, studies with animal models, or experimental studies.

Data Extraction

Data were extracted using an online data extraction form specifically designed for this review and piloted prior to the data collection. J.C.S. performed data extraction, and all information was checked in a second data extraction performed by J.C.S and J.R.B. The form included: study design, total of participants, number of patients randomized per group, number of patients excluded after randomization, maternal age, parity (nulliparous/parous), side of the lesion (left/right), liver herniation, LHR, o/e LHR, gestational age (GA) at FETO, GA at balloon removal, maternal death, perinatal death, infant death until 6 months of age, maternal admission to intensive care unit (ICU), maternal blood transfusion, chorioamnionitis, birth before 37 weeks, preterm premature rupture of membranes (PPROM), total of days of stay in the neonatal ICU, oxygen use at infant discharge, and pulmonary hypertension (as defined by the included studies).

Risk of Bias

The assessment of the risk of bias was performed for every reported outcome and for individual studies using the Cochrane RoB 2 tool.[9,17] Both reviewers performed the risk of bias assessment, and any disagreement was resolved by consensus. This tool consists of five domains: 1) risk of bias arising from the randomization process; 2) risk of bias due to deviations from the intended interventions (effect of assignment to intervention); 3) missing outcome data; 4) risk of bias in the measurement of the outcome; and 5) risk of bias in the selection of the reported result. Every domain consists of questions approaching aspects of the publication which could indicate bias. The answers to these questions characterize the domains as "low risk of bias," "high risk of bias" or "some concerns." Finally, the study receives an overall classification of risk of bias.

Measures of Effect

When applicable, continuous outcomes were measured by mean differences and 95% confidence intervals (95%CIs); dichotomous outcomes were measured by risk ratio/relative risk (RR) and 95%CIs.

Data Synthesis

Elements of the Patient, Intervention, Comparison, Outcomes (PICO) strategy, study design features of the included publications and numerical data were described in tables. Data were summarized in a summary of findings table. The GRADE approach was used to assess the quality of the evidence for all outcomes: a "high certainty" label is given when there is confidence that the true effect is close to that of the estimate of the effect; a "moderate certainty" label is given when the true effect is probably close to the estimate of the effect, but it is possible that it is substantially different; a "low certainty" label is given when the true effect may be very different from the estimate of the effect; and a "very low certainty" label is given when the true effect is probably substantially different from the estimate of the effect.[10–14]

Results

Study Selection

Through the searches in the MEDLINE, PMC, EMBASE and CENTRAL databases, we retrieved 203 publications which were exported to the Rayyan software. Duplicates (23 studies) were excluded prior to the first step of screening. Initially, both authors independently screened all the 180 publications by title and abstract. There were 19 discrepant evaluations between the authors, which were resolved by consensus, and a final list of eight potentially-eligible studies was developed. The reasons for exclusion were studies with animal models or experimental studies, wrong type of publication, wrong study design, or wrong population. The next step in the study selection was reading the full texts of the remaining articles. They were independently screened by full text by both authors, and one study[18] that met the eligibility criteria was identified, and is described in the next sections. The publications excluded in the first step comprised 5 systematic reviews and/or metanalyses, 17 retrospective studies, 18 non-randomized clinical trials, 16 case reports or series, 16 experimental studies or animal model studies, 6 studies exclusively approaching the postnatal period, and 93 miscellaneous studies, which were mostly narrative reviews. ►**Fig. 1** shows the PRISMA flowchart of the selection of studies.

Study Characteristics

One study[18] met the inclusion criteria for the present review. This single-center study evaluated pregnant women whose fetuses presented isolated CDH (no other malformation apart from CDH), normal karyotype, LHR < 1.0, and at least one third of the liver herniated into the thoracic cavity as estimated by ultrasound. After applying the inclusion criteria and obtaining informed consent, the authors randomized 41 women into 2 groups (expectant management and FETO) with a computer-generated randomization scheme at a 1:1 ratio. After randomization, 20 women were assigned to the FETO group (also referred to as the intervention group), and 21, to the expectant management group (also referred to as the control group or controls). One patient in the FETO group and two in the expectant management group declined the assigned intervention after randomization, and were excluded from the study. **Chart 1** highlights the main aspects of the study.[18] At 26 to 30 weeks of gestational age, FETO was performed, and the authors planned elective balloon removal by ex utero intrapartum treatment (EXIT) at 38 weeks, which was not performed in all cases due to PPROM or preterm labor. The newborns of both groups underwent the same perinatal management, and were followed up until 6 months of age. The authors performed intention-to-treat and received-treatment analyses.

Study Results

In the study,[18] the mean maternal age was 29.5 ± 6.6 years in the FETO group, and 30.3 ± 6.4 years in the control group ($p = 0.85$). In the FETO group, 60% of the women were nulliparous; in the control group, 57.1% were nulliparous ($p = 0.76$). Parous women constituted 40% of the intervention group and 42.9% of the expectant management group ($p = 0.76$).

In the intention-to-treat analysis, the groups did not differ in terms of the side of the diaphragmatic defect (left-sided CDH in 75% of the intervention group and in 71.4% of the control group; $p = 0.99$), LHR (0.8 ± 0.11 in the FETO group and 0.79 ± 0.10 in the expectant management group), o/e LHR (0.18 ± 0.02 in the FETO group and 0.17 ± 0.06 in the control group), neither regarding other characteristics. Fetal endoscopic tracheal occlusion was successfully performed in all cases between 26 and 30 weeks of gestation.

The obstetric outcomes were detailed, and they included mean gestational age at delivery, preterm delivery (before 37 weeks of age), and PPROM. The mean gestational age at delivery was of 35.6 ± 2.4 weeks in the intervention group (range: 31 to 38 weeks), and of 37.4 ± 1.9 weeks in the expectant management group (range: 33 to 40 weeks), with $p < 0.01$. Preterm premature rupture of membranes

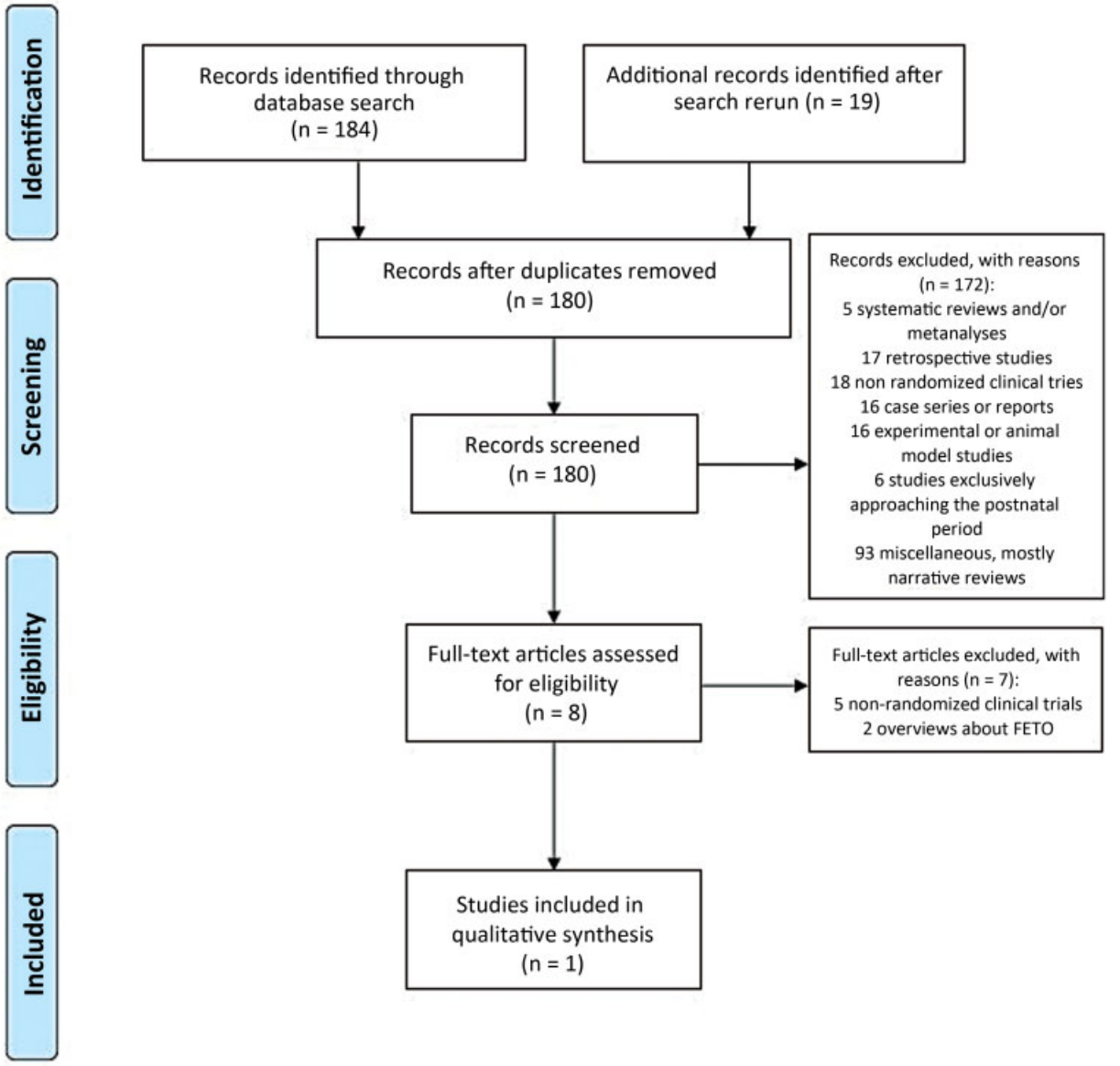

Fig. 1 Flowchart of the screening and selection process of the rapid review. The reasons for the exclusion of studies are listed in the boxes. **Source:** Moher et al.[15]

Chart 1 Characteristics of the study reviewed

	Ruano et al.[18] (2012)
Study design	Randomized controlled trial
PICO: patient	Pregnant women whose fetuses presented isolated Congenital diaphragmatic hernia (with no other malformation), normal karyotype, lung-to-head ratio < 1.0, and at least one third of the liver herniated into the thoracic cavity as estimated by ultrasound.
PICO: intervention	Fetal endoscopic tracheal occlusion at 26 to 30 weeks of gestational age and programmed balloon removal at 38 weeks
PICO: comparison	Antenatal expectant management
PICO: outcomes	Primary outcome: survival until 6 months of age. Additional outcomes: maternal complications, severe postnatal pulmonary hypertension and length of time until surgical repair of the diaphragmatic defect.[a]

Note: [a]This outcome was not included in this review.

occurred in 35.5% of the cases in the FETO group, and in 23.8% of the controls ($p = 0.51$).

Maternal morbidity and mortality were reported for both groups: there were no cases of maternal death or maternal blood transfusion in the study, and there was 1 (5%) case of chorioamnionitis in the intervention group, which was diagnosed after PPROM. There were no cases of chorioamnionitis among the controls.

Neonatal and infant outcomes were presented as intention-to-treat and received-treatment analyses. In the intention-to-treat analysis, 50% of the newborns who had undergone FETO and 5.8% of those in the control group survived until 6 months of age ($p < 0.01$; RR: 10.5; 95%CI: 1.5–74.7). Severe postnatal pulmonary hypertension was defined as a pre- to postductal saturation difference of more than 10% associated with echocardiography confirmation, and was found in 50% of the newborns in the intervention group and in 85.7% of the controls ($p = 0.02$; RR: 0.6; 95% CI: 0.4–0.9).

Ruano et al.[18] did not report maternal admission to ICU, neonatal ICU length of stay, perinatal mortality, and oxygen use at discharge.

All reported outcomes and their respective RRs and 95% CIs are detailed in **Chart 2**.

Explanations

a. **Chart 2** shows outcomes that were reported in at least one of the groups. Chorioamnionitis was only reported in the intervention group, so the RR cannot be estimated. We intended to analyze maternal admission to ICU, neonatal ICU length of stay, perinatal mortality, and oxygen use at discharge, but these outcomes were not included in the study by Ruano et al.[18]
b. The range of the 95%CI is wide, leading to imprecision.

One patient in the FETO group presented chorioamnionitis, and the authors report this happened after PPROM. Although PPROM was measured in both groups, there is no description of the diagnostic procedures used, and if these procedures were standardized between groups. Furthermore, it is not clear whether chorioamnionitis was clinical and/or histopathological, nor if this affected patient had preterm delivery, which could be a confounding factor if chorioamnionitis was limited to the histological findings. This could lead to information bias.

Risk of Bias

The evaluation of the risk of bias was performed by both reviewers using the RoB2 tool for outcomes that were present in both groups (newborn survival until 6 months of age, severe postnatal pulmonary hypertension, PPROM, delivery before 37 weeks of gestation) and for an overall assessment of the study[18] in question. The sources used for this evaluation were the published article[18] and the information available at Clinical Trials' webpage.[19]

Preterm delivery was at a low risk of bias; PPROM, newborn survival until 6 months of age and severe postnatal pulmonary hypertension raised some concerns; PPROM, because there was no description of how this diagnosis was established, which could lead to detection bias, and newborn survival until 6 months of age and severe postnatal pulmonary hypertension, due to possible reporting bias, as neither of these were intended to be described in the Clinical Trials protocol. Therefore, an analysis of the study indicated some concerns of bias. ►**Figure 2** shows the overall evaluation using the Cochrane risk-of-bias visualization (robvis) tool.[17]

Quality of Evidence

The quality of the evidence was assessed according to GRADE definitions. Moderate certainty was considered for preterm

Chart 2 Summary of findings: Ruano et al.[18] (2012)

Outcomes[a]	Number of participants (studies)	Certainty of the evidence (GRADE)	*Risk ratio (95% confidence interval)	Anticipated absolute effects	
				Risk with no intrauterine intervention	Difference in risk with fetal endoscopic tracheal occlusion
Infant survival until 6 months	41 (1 randomized controlled trial)	Moderate[b]	10.50 (1.47–74.71)	48 per 1,000	452 more per 1,000 (22 more to 3,510 more)
Severe postnatal pulmonary hypertension	41 (1 randomized controlled trial)	Moderate	0.58 (0.36–0.93)	857 per 1,000	360 fewer per 1,000 (549 fewer to 60 fewer)
Chorioamnionitis	41 (1 randomized controlled trial)	Low[c]	Not estimable	0 per 1,000	0 per 1,000
Preterm birth	41 (1 randomized controlled trial)	Moderate	1.75 (0.78–3.91)	286 per 1,000	214 more per 1,000 (63 fewer to 831 more)
Preterm premature rupture of membranes	41 (1 randomized controlled trial)	Low[c]	1.47 (0.55–3.88)	238 per 1,000	112 more per 1,000 (107 fewer to 686 more)

Abbreviation: GRADE, Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guidelines.
Source: Ruano et al.[18]
Note: *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% confidence interval).

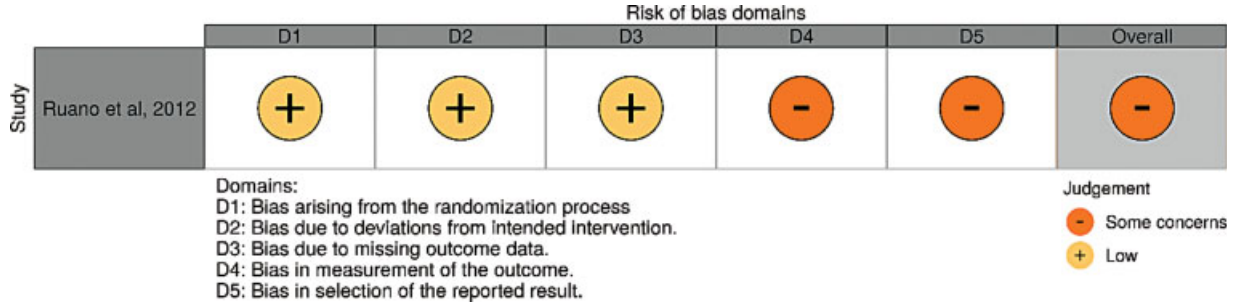

Fig. 2 Risk of bias of each individual RoB 2 domain and overall evaluation. Due to some concerns about domains 4 and 5, the overall evaluation of the study is some concerns of risk of bias. **Source:** Ruano et al.[18]

birth, newborn survival until 6 months and severe postnatal pulmonary hypertension. The reasons for this classification were broad 95%CIs, single study, and small sample. Chorioamnionitis and PPROM were considered of low certainty because there was no description of the diagnostic tests used to identify the cases of PPROM or chorioamnionitis, which could lead to information bias. Moreover, it is not clear whether chorioamnionitis followed a preterm delivery and this is another possible limitation.

Discussion

Summary of the Main Results

The collected evidence suggests that FETO may be an effective intervention to reduce severe postnatal pulmonary hypertension and to enhance survival rates until 6 months of age. It is not possible to make assumptions about the role of FETO in the maternal or obstetric outcomes. This uncertainty is explained by the small sample of the only study[18] that met the inclusion criteria. Moreover, in the included study,[18] some of the outcomes we planned to analyze were not described.

Quality of Evidence

The analyzed evidence was evaluated as of moderate to low certainty according to GRADE definitions, which means that, in the best-case scenario, the estimate of the effect is probably close to the true effect of the intervention, although it is possible that the true effect may be substantially different. The small sample of the only RCT[18] that met the inclusion criteria for the present review might clarify why some of the outcomes were not observed in both groups. Additionally, the high RR and broad 95%CIs suggest that future research might revise these estimates.

Implications for Practice and Research

Fetal endoscopic tracheal occlusion was introduced in the clinical practice as a percutaneous procedure in 2004.[5] Ever since, various attempts to improve the technique have been made, and currently there is a better understanding of the pathophysiology of the disease before and after FETO.[20–33]

Although CDH has been extensively studied, there are many gaps in the current knowledge, especially regarding perinatal outcomes. The clinical implications of these are challenges during patient counselling and suitable antenatal management,[34] which can only be resolved when large and well-conducted RCTs are available. Meanwhile, some authors[4,34–36] advocate that FETO should preferably be considered in the setting of clinical trials. In our opinion, even though the evidence is limited, the potential improvements in postnatal survival and reduction in pulmonary hypertension may justify performing FETO in the clinical practice.

Strengths and Limitations

The reliability of this rapid review is endorsed by the strict adherence to the proposed methods: registration of the protocol prior to conducting the searches, thorough use of the Cochrane Rapid Reviews Methods,[8] evaluation of the risk of bias with a recommended tool (RoB 2),[9,17] assessment of the quality of the evidence with worldwide accepted guidelines (GRADE),[13–17] and development of the final report according to the PRISMA statement.[15] Every measured outcome is clinically relevant, although the evidence is limited. Some limitations for the present study are expected. Congenital diaphragmatic hernia is a rare condition, which restricts the availability of data. Assuming that the searches were conducted in the main databases of the medical literature, it is unlikely that RCTs meeting our inclusion criteria were missed due to the requirements of a rapid review. The present review could not provide strong evidence for any outcome or subgroup analyses due to the small sample of the study[18] reviewed – these important issues of medical research might be overcome by future publications.

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

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FEBRASGO POSITION STATEMENT

Use of androgens at different stages of life: climacterium

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The National Specialty Commission on Gynecology Endocrinology of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) endorses to this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key points

- Female sexual dysfunction (FSD) includes hypoactive sexual desire disorders (HSDD) and sexual arousal, orgasm disorders and genito pelvic pain disorder, and vaginal penetration disorders.
- Female sexual dysfunction affects around 45% of women, most of them postmenopausal.
- The genitourinary menopause syndrome (GMS) includes signs and symptoms related to atrophy of the genital tract and predisposes to vaginal and/or urinary infections, in addition to interfering with the woman's sexual performance.
- There is a decline in cognitive function in postmenopausal women, and estrogens and androgens appear to independently influence cognitive activity.
- The characterization of postmenopausal androgen deficiency and the prescription of androgen therapy is still a controversial topic.

Recommendations

- It is not recommended to establish a diagnosis of androgen insufficiency based on low concentrations of serum androgens.
- Androgens are indicated for the treatment of FSD, although until now no specific androgen therapy is approved by the Food and Drug Administration (FDA). Data are insufficient to ensure long-term efficacy and safety.
- Patients should be counseled on the scarcity of long-term safety studies. In the short term, the most reported adverse events are greater hair growth at the application site and acne.
- Physiological doses of transdermal testosterone associated or not with estrogen therapy are effective for the treatment of HSDD in postmenopausal women, but there are no formulations available in Brazil so far.
- Testosterone gel formulated in compounding pharmacies can be considered a therapeutic option for HSDD in postmenopausal women, as it is the only form of drug treatment with natural testosterone available to date.
- It is recommended to dose testosterone before starting treatment and after three to six weeks of use in order to avoid supraphysiological levels, in addition to monitoring the appearance of potential effects of excess androgens.
- If there is no satisfactory improvement in HSDD within six months of testosterone use, treatment should be discontinued. Data on the safety of treatment after two years of use are unavailable.
- Vaginal dehydroepiandrosterone (DHEA) was recently approved by the FDA [prasterone (Intrarosa®)] for the treatment of genitourinary menopause syndrome, but it is unavailable in Brazil to date. It has shown effectiveness in the treatment of dyspareunia due to atrophy of the vaginal mucosa.
- There is no evidence to recommend the use of androgens to delay cognitive decline.
- Given the paucity of more consistent studies, treatment with androgens to improve postmenopausal bone mass is not recommended.

Background

Female sexual disfunction encompasses hypoactive sexual desire disorder (HSDD), defined as the recurrent absence or lack of fantasies and desire to have sex, associated with marked suffering or interpersonal difficulties, not explained by another mental or physical disorder, medical condition or asexuality, and female sexual arousal disorder, currently considered a single category according to the DSM-5 (5th edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders).[1] Dyspareunia and vaginismus, currently included in the genito pelvic pain and disorders of vaginal penetration category, are also part of the FSD.[1] Considering that most studies evaluating the use of testosterone in FSD have been conducted in women with HSDD, the new diagnostic categories have not been validated in clinical studies nor are uniformly accepted by experts in the field.[1] Thus, evidences that the female sexual function (SF) is associated with androgenic action are based, above all, on studies that observed an improvement in HSDD in postmenopausal women treated with testosterone.[2-5]

What is the evidence for the different forms of androgen therapy in the treatment of FSD?

There is a consensus that FSD is multifactorial and influenced by numerous clinical, surgical, interrelational and psychosocial conditions, including hormonal changes resulting from ovarian failure during the climacteric period.[6,7] The decline in androgen production coincides with the reduction of sexual fantasies and motivation in postmenopausal women, suggesting a correlation with dysfunctional sexual behavior.[7] Although the use of testosterone in the treatment of hypoactive sexual desire is supported by the Endocrine Society[6] and the American College of Obstetricians and Gynecologists,[8] there is no FDA-approved specific androgen therapy for the treatment of FSD to date.

Transdermal testosterone - patches

Transdermal testosterone has been the most studied. Evidence with a high degree of recommendation has shown that the use of 150 to 300 mcg of transdermal testosterone for the treatment of HSDD in women with natural or surgical menopause, with or without estrogen therapy, improves sexual desire, sexual satisfaction and the frequency of intercourse and orgasms.[2-5,9,10] However, evidence regarding long-term safety and efficacy is limited. In most studies, the usage time was not longer than six months. The patch, the most studied transdermal form in the literature, is not available in Brazil. In addition, the FDA has disapproved of the continued use of testosterone patches for lack of long-term safety evidence.

Transdermal testosterone - gel or creams

There are no testosterone gel preparations in suitable doses for climacteric women for the treatment of FSD approved by the FDA or regulatory agencies in other countries. Australia is the only exception, where a 1% testosterone in cream is available in doses that maintain plasma levels of testosterone in the physiological limits of pre-menopause (Androfeme® 1, 0.5 g/day), and the effects of excess androgens are rare. Testosterone gel 1% (Libigel®) was tested in the US, but showed no improvement in FSD during phase 3 of a large clinical trial and was discontinued by the FDA.[1] Testosterone approved for the treatment of male hypogonadism, including injections, subcutaneous implants and gels is strongly disapproved for use in climacteric women. As testosterone levels in women represent approximately 10% of male levels, there is a significant risk of supraphysiological doses of testosterone with adverse effects, some of which are irreversible.[6] As an alternative, 1% testosterone in high absorption cream or gel prepared in compounding pharmacies for transdermal use with systemic effect has been prescribed. The recommended dose is 0.5 g of gel or cream per day, equivalent to 5 mg of testosterone per day. It should be applied on the inner thigh, buttocks or lower abdomen, and not on the arms or trunk, avoiding the lymphatic system in the breast region. Hand washing after application is recommended to prevent transfer of the product to other people. As there is no approval by the FDA or regulatory bodies in Brazil, it is difficult to assess and prove the pharmacokinetic and pharmacodynamic properties of manipulated drugs. Thus, the plasma levels of the active substance may vary between batches of the product.[11] In addition, other variables can interfere with the absorption of manipulated preparations not securely standardized, such as the use of various active substance release vehicles (creams, gels, alcoholic medium), the body location and body surface area where the medication is applied.[11] Thus, the efficacy and adverse effects of manipulated preparations cannot be fully anticipated. Another relevant aspect is that the production and consumption of manipulated hormones are not subject to systematic pharmacovigilance and notification of adverse effects, which creates the mistaken interpretation that manipulated hormones are safer. Despite restrictions on safety, testosterone manipulated in gel or cream may be considered for the treatment of HSDD, as it is the only form of natural testosterone available for transdermal use.

Some recommendations for prescribing and monitoring the treatment with manipulated testosterone:[1,6,12]

- Indication for postmenopausal women with an accurate diagnosis of HSDD without contraindications to the use of hormonal therapy associated or not with estroprogestative therapy.
- Prescribe 1% testosterone formulated in a high absorption gel (eg Pentravan) for transdermal use at a dose of 0.5 g of gel per day for three to six months. As a suggestion for prescription, testosterone 5 mg per mL in a measuring bottle containing 30 mL with a release of 1 mL per day is recommended. This dose can be individualized with a variation between 1 and 5 mg. If there is improvement, reinforce to the patient that there is no evidence of efficacy and safety in use for a period longer than 24 months.
- Dose the testosterone before starting, after three to six weeks of use and while the treatment lasts to avoid supraphysiological plasma levels, and monitor the appearance of clinical signs of hyperandrogenism, because the clinical response does not always correlate with plasma levels of testosterone.[1,12]
- In the presence of a satisfactory therapeutic result, maintain the clinical and laboratory evaluation described above every three to six months.
- Discontinue treatment when no improvement in FSD is observed after six months of use.

Subdermal testosterone implants

Subdermal testosterone implants should be avoided because of the potential for adverse effects from prolonged exposure to high doses of testosterone, especially in biodegradable implants that cannot be removed from the application site.[13] These are not available in Brazil, unless in manipulation laboratories, nor are approved by regulatory agencies.[14]

Oral testosterone

Oral testosterone (eg, methyltestosterone) is not recommended because of its high biological potency, potential risk of adverse effects and hepatotoxicity.[1,8]

Intramuscular testosterone

Intramuscular administration of testosterone is not recommended because the plasma levels are often supraphysiological and there are important side effects, some of which irreversible.[8]

Vaginal testosterone

The use of vaginal testosterone was evaluated in studies with a small sample and few weeks of follow-up without proven effectiveness and safety yet.[8] Phase 2 clinical trials have evaluated new presentations of testosterone alone or associated with other drugs, such as oral testosterone associated with buspirone or sildenafil and nasal application testosterone, although with few promising results.[1]

DHEA

The systemic use of DHEA for the treatment of HSDD in postmenopausal women has no proven efficacy.[15] In addition, the endocrinology societies do not recommend its use due to the lack of evidence of long-term safety.[16] Dehydroepiandrosterone replacement is recommended for women with adrenal insufficiency with FSD and low plasma levels of DHEA, with starting doses between 25 and 50 mg per day for a period of three to six months and dose adjustments according to circulating levels of DHEA and clinical symptoms. In the absence of a satisfactory therapeutic result or the presence of adverse effects, therapy should be suspended.[6] Dehydroepiandrosterone (25 to 50 mg per day) is marketed in the US as a dietary supplement, even though high doses can induce androgenic effects such as hirsutism and acne. As supplements typically receive minimal regulatory surveillance, available presentations may vary in quality, purity, and concentrations.[17]

What are the side effects associated with the use of transdermal testosterone at a physiological dose?

The main adverse effects associated with the use of transdermal testosterone in postmenopausal women at physiological doses, are mild acne and hirsutism and rarely alopecia, voice thickening or clitoromegaly.[12] At physiological doses, it has not been associated with significant effects in the lipid profile and the levels of blood pressure, blood glucose and glycated hemoglobin. A trend towards a higher risk for deep vein thrombosis has been observed, although the effect of estrogen therapy, usually associated with hormonal therapy regimens, cannot be excluded. Data to assess the effects of testosterone therapy on the risk of coronary heart disease are insufficient.[18] Endometrial abnormalities were not found after 12 months of transdermal testosterone patch use. In patients who bled during treatment, histopathology revealed atrophic endometrium.[9] The transdermal testosterone patch at physiological doses for a period not exceeding six months was not associated with higher mammographic breast density or risk of breast cancer. Current data are insufficient to ensure the absence of long-term risk. The use of testosterone in women with breast cancer with hormone receptors is not recommended.[18]

Is there an indication for the use of androgens in GMS?

Estrogen replacement was the main form of treatment and considered the gold standard for treating GMS.[19,20] Estrogen and androgen receptors and androgen-depen-

dent proteins are distributed in the female genitourinary tract and exert a trophic effect.[20] The progressive reduction in androgen production is an additional factor in the onset of signs and symptoms of GMS.[15,16,20]

The use of intravaginal testosterone at a dose of 300 mcg of testosterone daily for four weeks was effective in restoring the vaginal epithelium, reducing symptoms of vaginal atrophy and dyspareunia and improving libido, without increasing serum levels nor clinical signs of hyperandrogenism.[21,22] However, to date, there is no proven safety and efficacy for the recommendation of intravaginal testosterone in postmenopausal GMS. Dehydroepiandrosterone (6.5 mg) in the form of vaginal eggs was recently approved by the FDA [prasterone (Intrarosa®)] for the treatment of GMS, although it is still unavailable in Brazil.[1] Although the DHEA is converted into estrogen and testosterone by the vaginal cells,[17] plasma levels of estradiol, DHEA, testosterone or androstenedione possibly do not change after vaginal administration of DHEA, and laboratory monitoring is not necessary.[23] The effects of vaginal DHEA application have not been studied in women with a history of breast cancer, nor in other estrogen-dependent neoplasms. It is not indicated for the treatment of HSDD or other domains of sexual dysfunctions.[24] In conclusion, androgens seem to independently contribute to the maintenance of the structure and function of the genitourinary tissue. The effects of androgens on cell proliferation, collagen turnover, higher perfusion and neurotransmitter synthesis may complement the estrogenic action.[16]

Is androgen therapy indicated to improve cognitive function?

Postmenopausal women using injectable testosterone and estrogen showed improvement in verbal memory, suggesting that estrogen and testosterone independent effects would be neuroprotective.[25] In addition to its neuroprotective action, a positive endothelial action of testosterone has also been demonstrated, promoting arterial vasodilation.[26] However, in another clinical trial using oral testosterone undecanoate, a negative response for immediate verbal memory was obtained.[27] The use of estrogen plus methyltestosterone resulted in better memory building performance compared to the use of estrogen alone.[28] However, the divergent results between studies do not allow definitive conclusions. Dehydroepiandrosterone sulfate (SDHEA) has also shown neuroprotective effects. Women aged 21 to 77 years who had higher serum levels of SDHEA demonstrated better performance in executive functions, especially those with more than 12 years of education and high scores on simple concentration tests as well as on memory tests.[29] However, other studies with SDHEA have not shown positive results.[30] Assessments of cognitive function with androgen therapy in postmenopausal women have inconsistent results, usually in small population samples for a short period of time and using doses that are expressed in supraphysiological androgenic plasma levels. Thus, there is insufficient evidence to support the use of androgens in order to delay the decline in postmenopausal cognitive action.

Is there evidence to indicate androgen therapy in this period of life, considering its effects on the musculoskeletal system?

Estrogen deficiency represents an important risk factor for osteoporosis. Previous studies show that androgens play an enhancing role in the formation of bone mass.[31] However, the role of testosterone in preserving bone mass in postmenopausal women is not fully recognized. A study of late postmenopausal women showed a correlation between circulating androgens and trabecular and cortical bone mineral density.[32] Investigations on the effect of androgens on the bone system are not frequent and when available, include the use of small hormonal doses for a short time. Few studies have evaluated the influence of androgens on the frequency of postmenopausal fractures. In premature ovarian insufficiency, the inclusion of androgens in estrogen replacement therapy did not show a significant increase in bone mass compared to estrogen therapy alone.[33] In surgical menopause, the use of methyltestosterone 2.5 mg daily associated with estrogens showed a significant increase in bone mass in the hip and lumbar spine.[34] The androgenic effects (T and DHEA) on the musculoskeletal system are undefined, because studies are scarce and have methodological limitations. Thus, the available studies are insufficient to indicate androgen therapy in postmenopausal musculoskeletal disorders.

Final considerations

The use of androgens in postmenopausal women is limited and the evidence supports their use for the treatment of hypoactive desire. Evidence to support other indications is lacking.

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- **Contributions:** according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit must be based on three conditions met in full: 1. Substantial contributions to conception and design, data collection or analysis, and interpretation of data; 2. Writing of the article or critical review of the intellectual content; and 3. Final approval of the version to be published.

Manuscript

Instructions to Authors

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

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

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

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

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

Editorial, only at the publisher's invitation.

Title

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

Abstract

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

Informational abstract of structured type of original articles

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

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

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

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

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

Informational abstract of structured type of systematic review articles

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

Objective: Declare the main purpose of the article.

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

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

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

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

Conclusions: Indicate the main conclusions and their clinical usefulness.

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

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

Keywords

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

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

Introduction

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

Methods

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

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

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

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

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

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

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

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

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

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

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

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

Script for statistical review of original scientific papers

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

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

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

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

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

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

Abstract: Does the abstract contain the proper article synthesis?

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

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

IMPORTANT!

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

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

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

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

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

Results

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

ATTENTION!

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

Discussion

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

Conclusion

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

References

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

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

Please check the Vancouver Citation Style to format your references.

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

Submission of papers

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

There is no fee for submission and review articles.

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