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Presidency and Executive Staff

Avenida das Américas, 8445 – sala 711
Barra da Tijuca – Rio de Janeiro – RJ
CEP: 22793-081 Brazil
Phone.: (+55 21) 2487-6336
Fax: (+55 21) 2429-5133
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Editorial

Controversies in the Use and Periodicity of Mammography as a Screening Method for Breast Cancer

Controvérsias no uso e periodicidade de mamografia para diagnóstico de câncer de mama

Rogério Bonassi Machado[1,*]

[1] Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil

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Mammography[Q4] has been used as a preparatory method for breast cancer screening, considering different protocols for specific age groups, which suggest the periodicity of its undertaking. The exam is considered necessary, both by physicians and the public, in population strategies to reduce mortality caused by breast cancer. However, studies have questioned the benefit of the periodic mammographic screening. In Canada, an analysis of women between 40 and 59 years old submitted to an annual mammography test for 5 consecutive years showed that there was no significant reduction in mortality rates associated with breast cancer.[1] In the United Kingdom, annual mammographic screening in women between 39 and 41 years old for 7 years resulted in a nonsignificant advantage.[2] These studies indicate that mammographic screening does not seem to offer benefits to prevent breast cancer in low- or medium-risk women.

From an epidemiological perspective, screening assumes the use of mammography in healthy women to detect suspected cancer, which will subsequently be submitted to specific diagnostic tests to confirm the disease and guide the treatment. A better mammographic screening approach would effectively reduce death rates in women who undergo this type of exam. Any case of cancer detected through screening should be treated and followed-up over a long period of time for professionals to verify its impact on mortality rates. When mortality rates associated with breast cancer are compared, it is necessary to separate the cases which were detected, treated and followed-up in screening programs from those in which the diagnosis was performed without screening mammography, according to the disease stage indicated by the diagnosis.

In this scenario, which confronts recent studies and the traditional epidemiological concept, it is important to stress the fact that the detection of a breast cancer case through mammographic screening does not guarantee that the death risk by the disease is reduced. Consequently, part of the controversy results from the confusion about what is known as early detection versus method efficacy. It is believed that a few biases are responsible for the questioning of mammographic screening, such as execution time, selection bias, and especially overdiagnosis.[3] The latter consists of diagnosing a disease that will lead to neither symptoms nor death. The Canadian study previously mentioned detected 26% of overdiagnosis, and the number can reach up to 50% if cases of ductal carcinoma in situ are included, as revealed by a 25-year follow-up.[1] In the oncology field, overdiagnosis is defined as the detection of cancer that would not have evolved to be clinically detectable. The type of cancer most frequently detected through mammographic screening is ductal carcinoma in situ, and studies have not shown significant effects of this tumor on women's survival after 20 years of follow-up post- diagnosis.[4]

Previous investigations demonstrated that the probability of a woman who had a cancer diagnosis receiving an overdiagnosis is 19%.[5–7] Applying this value to the recent cumulative incidence of breast cancer in the United Kingdom (invasive and in situ) means that 1 out of 77 women screened from 55 to 70 years would have an overdiagnosed breast cancer. Authors also claim that the consequences of overdiagnosis are unnecessary surgeries, radiotherapy, and chemotherapy. Nevertheless, they conclude that it is impossible to distinguish between life-threatening carcinomas and overdiagnoses initially, and that

* *President of the Brazilian Commission for Contraception at FEBRASGO, Brazil.*

Address for correspondence Rogério Bonassi Machado, President of the Brazilian Commission for Contraception at FEBRASGO, Brazil, Faculdade de Medicina de Jundiaí, R. Francisco Teles, 250 - Vila Arens II, Jundiaí, SP, 13202-550, Brazil (e-mail: rogeriobonassi@terra.com.br).

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further studies assessing accurate overdiagnosis rates are fundamental. There are other issues associated with mammographic screening, although they are more infrequent. Around 4% of women submitted to the test are called to repeat the exam and possibly undergo a biopsy.[8] Among them, 20% will have cancer, 70% will need further imaging studies, and 30% will require biopsy, procedures that cause psychological damage and anxiety.[8]

The main question concerning the implementation of screening programs relates to the disease mortality though. The first conclusions regarding breast cancer mortality are based on a Cochrane systematic review.[9] The global relative risk, comparing screened and non-screened women, is 0.80 (confidence interval of 95%, 0.73–0.89), that is, the reduction in relative risk of breast cancer mortality in screened women is 20%.[9]

In terms of absolute gain, women screened from 50 to 70 years will experience no benefit in the first 5 years of screening, but mortality reduction will last for 10 years after the last exam. Regarding the direct impact on deaths provoked by breast cancer, 1 death will be prevented in a group of 235 screened women.[9]

Despite the data from studies performed in developed countries, reflections are necessary when the Brazilian reality is evaluated. In our country, 40% of 50- to 69-year-old women do not undertake mammograms.[10] Consequently, our context still needs improvement in the potential of basic screening for the disease. Taking into account that the Brazilian female population between 50 and 69 years is around 15 million,[11] and that 60% of these women are effectively screened through mammography, there would be 40 thousand breast cancer-related deaths prevented.

There is a striking contrast between developed and developing countries when it comes to unmet needs. In the former, mammographic screening is questioned and efforts are made toward breast cancer therapy, which is undeniably the main factor associated with decreased mortality rates. Developing countries still have a great challenge to increase effective screening rates. The Brazilian reality seems not to allow the dismissal of mammography in breast cancer screening. However, faced with current evidence, women must be informed about the benefits and potential risks of overdiagnosis, so their decision on participating in a screening program is as clarified as possible.

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Tocolysis among Women with Preterm Birth: Associated Factors and Outcomes from a Multicenter Study in Brazil

Tocólise entre mulheres com parto prematuro: fatores associados e desfechos de um estudo multicêntrico no Brasil

Tabata Zumpano Dias[1] Mariana Lacerda Fava[1] Renato Passini Júnior[1] Jose Guilherme Cecatti[1] Ricardo Porto Tedesco[2] Giuliane Jesus Lajos[1] Patricia Moretti Rehder[1] Marcelo Luis Nomura[1] Paulo Fanti Oliveira[2] Maria Laura Costa[1]

[1] Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil
[2] Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil

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Address for correspondence Tabata Zumpano Dias, Universidade Estadual de Campinas (UNICAMP), Cidade Universitária Zeferino Vaz, 13083-970, Barão Geraldo, Campinas, SP, Brazil (e-mail: tabatazumpano@gmail.com).

Abstract

Objective To evaluate the use of tocolysis in cases of preterm birth due to spontaneous preterm labor in a Brazilian sample.

Methods A sample of 1,491 women with preterm birth due to spontaneous preterm labor were assessed, considering treatment with tocolysis or expectant management, according to gestational age at birth ($<$ 34 weeks and 34 to 36 $+$ 6 weeks) and drugs prescribed. The study took place in 20 Brazilian hospitals from April 2011 to July 2012. Bivariate analyses were conducted to evaluate associations with sociodemographic and obstetric characteristics and odds ratios with their respective 95% confidence intervals were estimated for maternal and neonatal outcomes.

Results A total of 1,491 cases of preterm birth were considered. Tocolysis was performed in 342 cases (23%), 233 of which (68.1%) were delivered before 34 weeks. Within the expectant management group, 73% was late preterm and with more advanced labor at the time of admission. The most used drugs were calcium channel blockers (62.3%), followed by betamimetics (33%). Among the subjects in the tocolysis group, there were more neonatal and maternal complications (majority non-severe) and an occurrence of corticosteroid use that was 29 higher than in the expectant management group.

Conclusion Tocolysis is favored in cases of earlier labor and also among those with less than 34 weeks of gestation, using preferably calcium channel blockers, with success in achieving increased corticosteroid use. Tocolysis, in general, was related to higher maternal and neonatal complication rates, which may be due to the baseline difference between cases at admission. However, these results should raise awareness to tocolysis use.

Keywords
- preterm birth
- prematurity
- preterm labor
- tocolysis
- neonatal outcomes
- maternal outcomes

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Resumo

Objetivo: Avaliar o uso da tocólise em partos prematuros decorrentes de trabalho de parto espontâneo numa amostra brasileira.

Métodos Um total de 1.491 mulheres com parto prematuro decorrente de trabalho de parto espontâneo foram avaliadas, considerando a realização de tocólise ou conduta expectante, de acordo com a idade gestacional ao nascimento ($<$ 34 semanas e 34 a 36 + 6 semanas) e com as drogas prescritas. O estudo ocorreu em 20 hospitais brasileiros, de abril de 2011a julho de 2012. Análises bivariadas foram realizadas para avaliar associações com características sociodemográficas e obstétricas. Foram calculadas as relações de probabilidade com seus respectivos intervalos de confiança (95%) para os desfechos neonatais e maternos.

Resultados Um total de 1.491 casos de partos prematuros foram considerados, e a tocólise foi realizada em 342 (23%) casos, dos quais 233 (68,1%) tiveram partos antes das 34 semanas. No grupo da conduta expectante, 73% foram pré-termos tardios e com trabalho de parto mais avançado à admissão. As drogas mais utilizadas foram os bloqueadores do canal de cálcio (62.3%), seguidos pelos betamiméticos (33%). No grupo da tocólise houve mais complicações neonatais e maternas (maioria não grave) e um uso de corticosteroides 29 vezes mais frequente que nos casos de conduta expectante.

Conclusão A tocólise foi mais favorável nos casos de trabalho de parto inicial e nos partos realizados antes de 34 semanas de gestação, usando preferencialmente bloqueadores do canal de cálcio, com sucesso em realizar altas taxas de corticoterapia. A tocólise esteve associada a maiores taxas de complicações maternas e neonatais, o que pode ser explicado pela diferença basal dos casos à admissão. Entretanto, esses resultados devem acender um alerta em relação ao uso de tocolíticos.

Palavras-chave

- parto prematuro
- prematuridade
- trabalho de parto prematuro
- tocólise
- desfechos neonatais
- desfechos maternos

Introduction

Despite recognized advances in obstetrical care in the last decades, preterm birth (PTB), defined as delivery before 37 weeks, continues to be one of the most significant burdens worldwide, with increasing numbers in most high and middle-income countries, including Brazil.[1–3] Preterm newborns represented $\sim$ 10% of live births in Brazil in the last decade.[4] The impact of prematurity is relevant not only for neonatal health but also for infant health, with major long-term consequences, such as neurologic handicap, deafness, blindness and chronic respiratory disease.[5] Furthermore, prematurity is the main cause of neonatal deaths.[6] Around 75% of PTBs follow spontaneous prematurity (preterm labor [PTL] and preterm premature rupture of membranes), while the remaining 25% are provider-initiated PTBs due to fetal or maternal complications.[7,8]

The pathogenesis of spontaneous PTBs is most likely multifactorial, which makes it very difficult to prevent or predict this condition. The main identified causes are related to intrauterine infection, bleeding and uterine overdistension, among others.[3]

Tocolysis is an available resource in the care of these women, aiming to prolong pregnancies.[9] The use of tocolytic medications is not clearly associated with a reduction in perinatal or neonatal mortality; however, the potential benefits are related to inhibition of uterine contractions, allowing the administration of antenatal glucocorticoids.[10] The antenatal corticosteroid administration is shown to reduce the risk of fetal complications related to prematurity, such as respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis. Another relevant goal of tocolysis is to allow the maternal transfer, in a timely manner, to a center with neonatal intensive care unit.[9,11]

Tocolytic drugs should be considered only in the absence of contraindications, such as non-reassuring fetal status, severe fetal growth restriction, intra-amniotic infection, lethal fetal anomalies, and complicated maternal comorbidity. There are many groups of tocolytic drugs, and the decision as to which agent should be used for an individual woman should be based on multiple factors, including gestational age, medical conditions, cost, personal experience, and commercial availability.[12]

Calcium channel blockers (CCB), such as nifedipine, cause the inhibition of calcium reuptake by myometrial cell, leading to smooth muscle relaxation. Nifedipine is usually well tolerated and the main described mild side effects are nausea, flushing, headache, and palpitations. However rare, more severe side effects can also present, such as pulmonary edema, atrial fibrillation, and hypotension. The fetal side effects are related to maternal hypotension and placental

hypoperfusion. A significant reduction in neonatal morbidity is shown with CCB use in comparison with other tocolytic drugs.[13]

Betamimetics (terbutaline) are β-adrenergic agonists that stimulate the enzyme adenyl cyclase in the smooth muscle cell. By doing so, they decrease the availability of intracellular calcium and suppress myometrial contractility. The most common maternal side effects are tachycardia, pulmonary edema, and hyperglycemia. For that reason, the woman should be constantly monitored. Furthermore, this class of medication is contraindicated in women with poorly controlled baseline diseases, such as diabetes or heart disease, and it should be discontinued if maternal heart rate reaches over 120 beats/minute or if the woman experiences chest pain or dyspnea. Terbutaline can cause fetal side effects, especially hypoglycemia and tachycardia. The use of betamimetics presented no benefits in comparison with placebo in cases of respiratory distress syndrome as well as in cases that resulted in perinatal or neonatal deaths.[14]

Prostaglandin inhibitors, such as indomethacin, constrain the cyclooxygenase enzyme, which synthesizes prostaglandins from arachidonic acid. The most common side effects are nausea, vomiting, gastritis, and platelet dysfunction. Indomethacin is contraindicated over 32 weeks of gestation because of the risk of premature closure of ductus arteriosus and oligohydramnios. No clear benefits were shown over placebo or any other tocolytics; however, a 2012 systematic review concluded that prostaglandin inhibitors and CCB had the highest probability of delaying delivery and improving neonatal and maternal outcomes.[9,15]

Oxytocin receptor antagonists (ORA), represented by atosiban, act on the uterine myometrial cell and can cause fewer side effects (like nausea, vomiting, and headache) than treatment with the CCB or betamimetics. Oxytocin receptor antagonists did not demonstrate superiority as a tocolytic compared with placebo, betamimetics or CCB for pregnancy prolongation or neonatal outcomes.[16] Currently, this medication is not easily available in public hospitals in Brazil due to its high cost.

Magnesium sulfate reduces calcium in the intracellular and extracellular levels, which decreases myometrial contractility. The administration should be monitored regularly due to the risk of lethargy, nausea, hyporeflexia and respiratory depression. A Cochrane systematic review (2002)[17] concluded that magnesium sulfate is ineffective at delaying birth and its use is associated with an increased mortality for the infant.

The long-term use of tocolysis has not shown effectiveness; therefore, tocolytics should not be continued once uterine contractions have been suppressed.[13] The benefit of using associations of tocolytics are also not clear in the literature.[18]

Given the scarce data on the actual clinical practice on tocolysis in our setting, and the great variances among available protocols, this study aims to evaluate women with PTB due to PTL in 20 institutions of different regions of Brazil, regarding the prevalence of tocolytic drugs used, factors associated with this use, the most prescribed drugs, and the maternal and perinatal outcomes, according to the drug and gestational age considered.

Methods

This is a cross-sectional multicenter study called Brazilian Multicenter Study on Preterm Birth (*Estudo Multicêntrico de Investigação de Prematuridade* [EMIP, in the Portuguese acronym]), which assessed PTB in 20 obstetric reference hospitals in three regions of Brazil from April 2011 to July 2012. The research protocol and main results have already been published previously elsewhere.[7,19]

For the current analysis, we focused on cases of PTB (gestational age at birth up to 36 + 6 weeks) due to PTL only. Among those, we analyzed the frequency of tocolysis and split all cases into two groups: women who underwent tocolysis, and those in which tocolysis was not performed (expectant group). Specific analyses were performed also considering only births before 34 weeks. Afterwards, a bivariate analysis was conducted to estimate the odds ratios (ORs) with their respective 95% confidence intervals (CIs) for perinatal results. Finally, a comparison of maternal complications and neonatal outcomes between the two most prevalent classes of tocolytics, CCB and betamimetics, was considered. For statistical analysis, the Statistical Analysis System (SAS) for Windows version 9.4 (SAS Institute, Cary, NC, USA) was used. The Mann-Whitney test was performed to compare the numeric variables, and the Chi-square and Fisher Exact tests were used to evaluate the categorical variables.

This study followed all ethical principles of the Helsinki Declaration. It abides by the guidelines and rules of the Resolution 196/96 of the National Health Council on research involving human beings, current at the time of data collection. The study was approved by the National Council for Ethics in Research and by the Institutional Review Board of each participating institution. An Informed Consent Form was developed, and each subject was enrolled in the study only after the understanding and accepting the conditions on the form. Confidentiality of the data and medical care of these women were assured.

Results

From April 2011 to July 2012, 1,491 women with PTBs due to PTL were enrolled. Tocolysis was performed in 342 women, 23% of all PTBs. Out of these, 233 (68.1%) delivered before 34 weeks, and 109 (31.9%) delivered between 34 and 36 + 6 weeks. Among women with expectant management, the majority was late preterm (73%), as shown in ►**Fig. 1**.

►**Tables 1** and **2** present the sociodemographic characteristics, obstetric history and characteristics of the current pregnancy in the studied population. Among the women who underwent tocolysis, there were significantly more nulliparous, more cases with a history of vaginal bleeding during pregnancy, cervical insufficiency, women without comorbidities, the integrity of membrane at admission, more cases of antenatal corticosteroids prescribed and

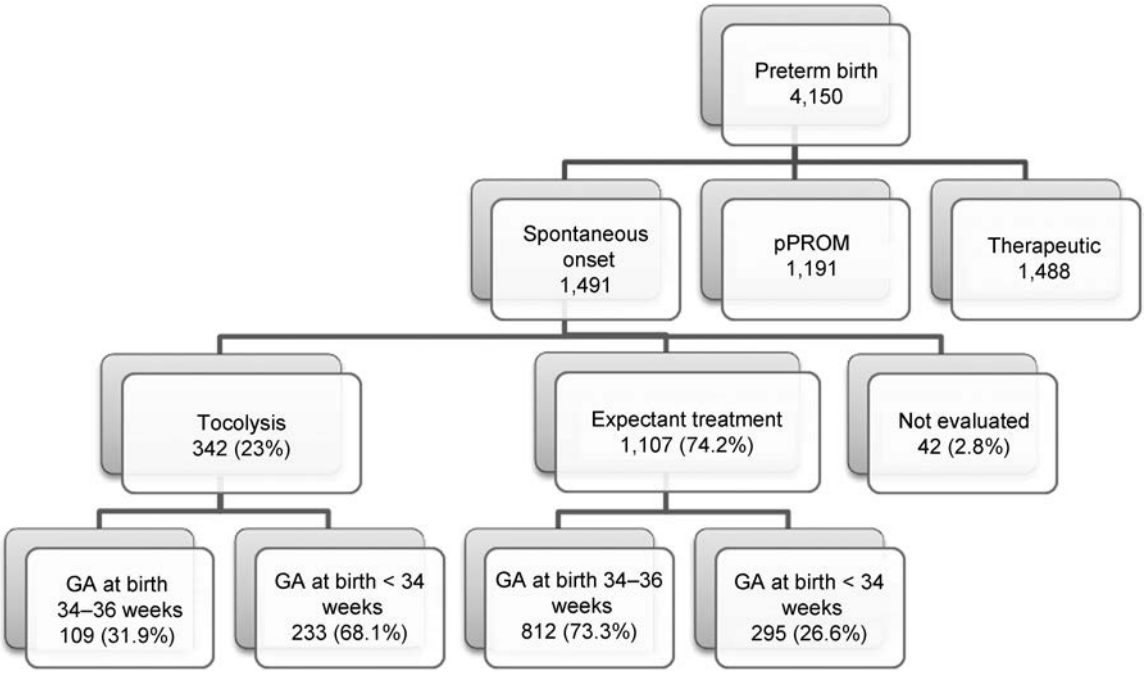

Fig. 1 Flowchart of subjects and gestational age at birth in the Brazilian Multicenter Study on Preterm Birth (EMIP, in the Portuguese acronym). Abbreviation: GA, gestational age.

more maternal complications. They were: 23 cases of genital hemorrhage (1.6%), 57 chorioamnionitis (3.9%), only one maternal sepsis (0.1%), 6 cases of treatment interruption due to adverse effects, only 1 cardiac decompensation (0.1%), 14 oligoamnios (1.0%), 34 other complications (2.3%) and 10 associations of answers (0.6%). The majority of cases related no maternal complications (1,292 or 88.3%).

The cases of expectant management were clearly of more advanced labor at admission (significantly more contractions in 10 minutes and increased cervical dilation); the mean dilation at admission for expectant management was overall 5.3 cm and 6.5 cm under 34 weeks of gestation. Furthermore, cases submitted to tocolysis were more preterm (mean gestational age at birth of $\sim$ 31 weeks versus 33 weeks for expectant management) and more likely to have neonatal intensive care unit (NICU) admission (►**Table 2**).

The most used class of tocolytic drug was the CCB (62.3%), followed by betamimetics (33%) and prostaglandin inhibitors (1.5%) (►**Fig. 2**). There was a therapeutic failure in 11.3% of the attempted inhibitions, leading to change in the medication. Again, we considered only cases that progressed to PTB.

►**Table 3** compares betamimetics and CCB concerning neonatal and maternal outcomes. The Cesarean section rate as well as the need for newborn admission to NICU were significantly higher in women who used betamimetics compared with those who used CCB.

Considering the clinically most relevant group for tocolysis, cases under 34 weeks of gestational age and comparing those submitted to tocolysis to those with expectant management, again it is clear that the cases of expectant management had more advanced labor at admission

Table 1 Comparison of sociodemographic characteristics, obstetric history, and current pregnancy conditions between women who were treated with tocolytic drugs and women who were treated expectantly (Chi-square test) (n = 1,449)

Condition	Tocolysis	Expectant	*p* Value
	n (%)	n (%)	
Maternal Age			
≤ 19	114 (33.3)	313 (28.2)	
20–34	203 (59.3)	689 (62.2)	0.1354
≥ 35	25 (7.3)	105 (9.4)	
Skin Color			
White	150 (43.8)	483 (43.6)	0.9407
Other	192 (56.1)	624 (56.3)	
Schooling (years)[a]			
≤ 8	150 (44.3)	478 (43.8)	
09–12	171 (50.5)	546 (50.0)	0.7804
≥ 13	17 (5.0)	66 (6.0)	
Parity			
Nulliparous	167 (48.8)	438 (39.5)	
1–2 deliveries	116 (33.9)	431 (38.9)	0.0090
≥ 3 deliveries	59 (17.2)	238 (21.5)	
Previous cesarean section[b]			
Yes	54 (15.8)	191 (17.2)	0.5414
Previous preterm birth[c]			
Yes	18 (5.2)	69 (6.3)	0.4966

Table 1 (*Continued*)

Condition	Tocolysis	Expectant	*p* Value
	n (%)	n (%)	
Previous preterm labor[d]			
Yes	39 (11.4)	113 (10.2)	0.5164
Previous pPROM[e]			
Yes	23 (6.7)	98 (8.8)	0.2126
Previous cerclage[f]			
Yes	9 (2.6)	14 (1.2)	0.0750
Prenatal care[g]			
Yes	319 (93.8)	1053 (95.2)	0.3110
Use of alcohol[h]			
Yes	42 (12.3)	183 (16.6)	0.0556
Smoking			
Yes	45 (13.1)	192 (17.3)	0.0673
Antenatal substance abuse			
Yes or before pregnancy	19 (5.5)	73 (6.5)	0.4911
No	323 (94.4)	1034 (93.4)	
Vulvovaginitis[i]			
Yes	65 (32.5)	194 (29.6)	0.4376
Urinary tract infection[j]			
Yes	86 (33.4)	313 (36.6)	0.3440
Vaginal bleeding during pregnancy[k]			
Yes	119 (35.0)	282 (25.5)	0.0007
Anemia[l]			
Yes	96 (29.0)	314 (29.0)	0.9878
Cervical insufficiency (clinical or US) [m]			
Yes	12 (11.0)	20 (4.2)	0.0059
Cerclage[n]			
Yes	10 (3.1)	19 (1.9)	0.1708
Maternal comorbidity			
Yes	79 (23.1)	336 (30.3)	0.0095
Membrane integrity[o]			
Yes	320 (94.9)	853 (81.1)	< 0.0001
Antenatal corticosteroids[p]			
Yes	274 (80.8)	138 (12.6)	< 0.0001
Maternal Complication[q]			
Yes	67 (19.7)	94 (8.6)	< 0.0001

Abbreviations: pPROM, pre-labor premature rupture of membranes; US, ultrasonography;
Note: Missing information for – a: 21; b: 1; c: 14; d: 5; e: 5; f: 3; g: 3; h: 7; i: 594; j: 39; K: 5; l: 38; m: 874; n: 163; o: 61; p: 19; q: 19.

Table 2 Characteristics at admission and perinatal outcomes comparing women who were treated with tocolytic drugs and women who were treated expectantly ($n = 1{,}449$)

Variables	Tocolysis n (%)	Expectant n (%)	*p* Value
Adequacy of number of prenatal care visits[a]			< 0.0001
Adequate (≥ 6)	101 (35.5)	507 (52.7)	
Inadequate (< 6)	183 (64.4)	455 (47.3)	
Number of contractions in 10-minute at admission[b]			0.0006
♥	132 (57.3)	288 (44.3)	
≥ 3	98 (42.6)	362 (55.6)	
Cervical dilatation ≥ 5 cm in the current hospitalization[c]			< 0.0001
Yes (≥ 5)	116 (35.6)	606 (58.6)	
Cervical effacement ≥ 50% in the current hospitalization[d]			0.9174
Yes (≥ 50%)	187 (87.7)	526 (87.5)	
Birthweight			< 0.0001
≤ 1,500 g	120 (35.2)	161 (14.6)	
1,501 to 2,500 g	181 (53.2)	535 (48.5)	
> 2,500 g	39 (11.4)	406 (36.8)	
Gestational age at birth (weeks)			< 0.0001
< 32	151 (44.1)	171 (15.4)	
32–33	82 (23.9)	124 (11.2)	
34–36	109 (31.8)	812 (73.3)	

Notes: Chi square test. Missing information for: a: 203; b: 569; c: 91; d: 635.

(significantly more contractions, cervical dilation, and effacement) (►**Table 4**).

On the multiple analysis, cases undergoing tocolysis presented 29 times more risk of receiving corticosteroids, 18 times considering only cases under 34 weeks. The rate of maternal complications was 55% higher for the cases under 34 weeks, in which labor inhibition was attempted (►**Tables 5** and **6**).

Discussion

Here we present the results of the EMIP for tocolysis in cases of PTB due to PTL. Among the cases that delivered preterm (< 37weeks), we studied and compared the tocolysis and the expectant management groups. The main results show that tocolysis is favored in cases of earlier labor at admission and also among those with less than 34 weeks of gestation, using preferably CCB, with success in achieving increased corticosteroid use, in spite of higher maternal and perinatal complication rates.

The use of antenatal corticosteroids and tocolysis have been previously analyzed in the World Health Organization (WHO) Multicountry Survey on Maternal and Newborn Health, with data from 29 different countries, including

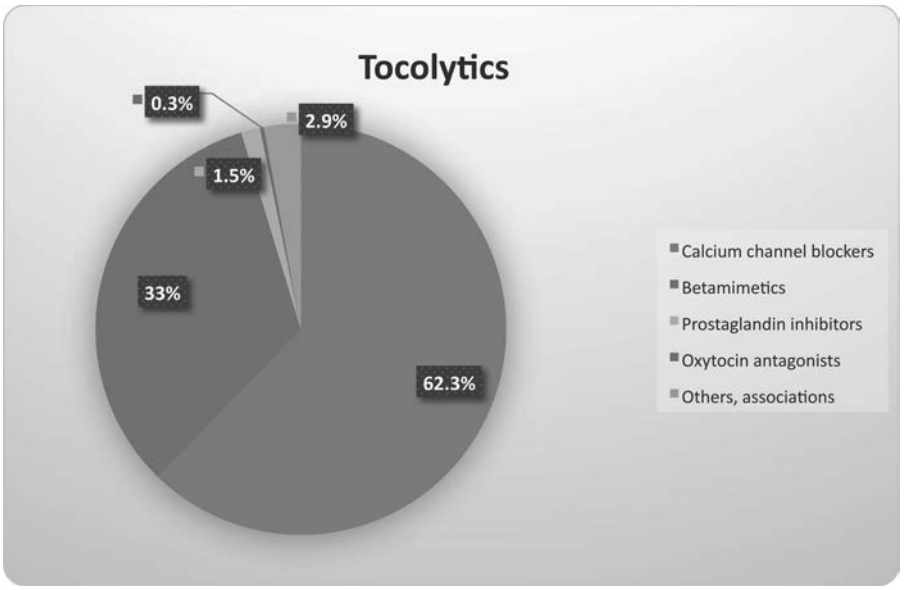

Fig. 2 The proportion of different tocolytic drugs used in the Brazilian Multicenter Study on Preterm Birth (EMIP, in the Portuguese acronym) among spontaneous preterm birth submitted to tocolysis.

Brazil, with overall 6% of PTB and among women who delivered at 26–34 weeks of gestation, 52% received antenatal corticosteroids.[20] In the WHO-multicountry study, the specific data on Brazil presented a low number of subjects (288 women), with 30% coverage of corticosteroids in the considered gestational age interval and 13% of tocolysis and antenatal corticosteroids (only 14 women). We do not have a population-based study and need to highlight that most of the 20 considered facilities in our study (EMIP) were tertiary care centers, which might explain the difference in our findings, with overall 12% of preterm deliveries, 23.6% of tocolysis among PTB due to PTL and 80% of combined corticosteroids and tocolysis. In the current study, we only considered PTL; however, the analysis on the provider-initiated PTBs on the same database has also shown over 70% use of corticosteroids between 28–31weeks of gestation.[8]

Tocolysis is still a very controversial topic; Nonetheless, most clinical protocols consider it plausible to attempt inhibition aiming the complete course of corticosteroids.[9]

Table 3 Acute tocolysis: betamimetics compared with calcium channel blockers ($n = 342$)

Variables	Betamimetics n (%)	Calcium channel blockers n (%)	*p* Value
Therapeutic failure[a]	17 (15.4)	21 (10.1)	0.1611
Antenatal corticosteroids[b]	85 (75.2)	177 (83.8)	0.0588
Maternal complications[c]	21 (18.5)	43 (20.3)	0.6989
Neonatal morbidity[d]	86 (78.1)	179 (86.4)	0.0577
Delivery[e*]			
Vaginal	73 (66.9)	161 (78.5)	
Forceps	1 (0.9)	3 (1.4)	0.0493
C-section	35 (32.1)	41 (20.0)	
	(mean SD)		
Duration of use in hours[f**]	18.94 (20.1)	28.38 (28.3)	0.0533
Gestational age at birth in weeks[g**]	31.25 (3.5)	31.17 (3.4)	0.7252
Newborn birthweight (g)[h**]	1741.0 (651.6)	1753.4 (661.4)	0.6995
Neonatal intensive care unit (days)[i**]	21.04 (24.9)	14.99 (20.9)	0.0264

Abbreviation: SD, standard deviation.
Notes: Categorical variables: Chi square test; *Fisher exact test; numeric variables; **Mann-Whitney test. Missing information for: a- 24; b- 18; c- 18; d- 25; e- 28; f: 40; g: 16; h: 18; i: 45.

Table 4 Comparison of characteristics at admission and birth outcomes in spontaneous preterm birth < 34 weeks between women who were treated with tocolytic drugs and women who were treated expectantly (Chi-square test) ($n = 528$)

Variables	Tocolysis n (%)	Expectant n (%)	*p* Value
Vaginal bleeding in the current hospitalization[a]			0.8340
Yes	51 (23.2)	61 (24.1)	
Contractions in 10 minutes (< 3)[b]			0.0106
Yes	97 (62.1)	73 (47.7)	
Cervical dilatation ≥ 5 cm in the current hospitalization[c]			< 0.0001
Yes	87 (39.5)	203 (74.0)	
Cervical effacement ≥ 50% in the current hospitalization[d]			0.0334
Yes	127 (87.5)	141 (94.6)	
Birth weight[e]			0.9717
≤ 1,500 g	120 (51.7)	147 (50.6)	
1,501 to 2,500 g	104 (44.8)	133 (45.8)	
> 2,500 g	8 (3.4)	10 (3.4)	
Gestational age at birth (weeks)			0.1096
< 32	151 (64.8)	171 (57.9)	
32–33	82 (35.1)	124 (42.0)	

Note: Missing information: a - 56; b - 219; c - 34; d - 234; e - 6.

The use of antenatal corticosteroids, though, is key in improving the outcomes in preterm babies with 31% reduction in neonatal deaths and a significant reduction in morbidity as well, including a recently published additional benefit in late preterm with a reduction in the rate of neonatal respiratory complications.[11] In the current study, it was estimated that women who underwent tocolysis had 29 times more chance of receiving corticosteroids than the ones who did not and the chances were 18 times higher among those under 34 weeks.

In the EMIP, the mean dilation at admission for expectant management was 5.3 cm and 6.5 cm under 34 weeks of gestation. Cervical dilation over 5 cm at diagnosis of PTL has been shown to progress to delivery in less than 24 hours in 50% of cases, and the chance of delivery before 24 hours increases to 89% when dilation is over 6 cm at diagnosis, according to a 2009 study.[21] Again, we have to emphasize that our study only considered cases that progressed to PTB, which justifies the findings on dilation and effacement at admission.

As pointed previously, it is very difficult to predict PTBs; however, known risk factors and early recognition of the signs and symptoms of PTL should always be considered.[3] We did find that among the tocolysis group, there were significantly more cases with a history of bleeding during gestation and with cervical insufficiency, which shows that risk factors were assessed.

An important finding in our study was that tocolytic drugs, in general, were related to higher neonatal complication rates. We cannot ascertain causality, and this might be a consequence of the difference in baseline gestational age at admission and not necessarily due to tocolysis. The cases submitted to tocolysis were more preterm (mean gestational age at birth of ~ 31 weeks versus 33 weeks in the expectant management group) and therefore more likely to have NICU admission. Unfortunately, we do not have specific data on latency from the time of the initiated use of tocolytic drugs to delivery, but we do have the information on the time of use of medications and, in average, for all considered drugs, it was less than 30 hours (~ 19 hours for betamimetics and 28 hours for CCB). Given the strong association between tocolysis and corticosteroid use, another factor to be considered for the presented worse neonatal outcomes is the lack of optimal time for corticosteroids action in many cases. The best effect of antenatal corticosteroids is seen after 48 hours of the initiation of treatment.[22]

Tocolytic drugs, in general, were also related to higher maternal complications rates. It is noteworthy that detailed clinical assessment, and an infection screening at admission and during all the in-hospital period is paramount to early diagnose possible infection and other complications. The increase in complications must be addressed in future studies considering all cases of tocolysis and not only those that progressed to PTB.

The most used drug in our study was CCB (mainly Nifedipine), currently considered first-line therapy in many

Table 5 Variables independently associated with tocolysis: multiple analyses by nonconditional logistic regression

Variables	n	*p* Value	OR	CI 95%
Maternal complications	1,430	< 0.0001	2.613	1.85–3.67[a]
Neonatal morbidity	1,380	< 0.0001	2.742	2.01–3.72[b]
Neonatal respiratory distress	914	< 0.0001	2.567	1.73–3.79[c]
Newborn intubation	1,386	< 0.0001	2.372	1.77–3.17[d]
Necrotizing enterocolitis	897	0.0022	4.024	1.64–9.82[e]
Antenatal corticosteroids	1,430	< 0.0001	29.105	21.05–40.24[f]

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: Missing information: a - 19; b - 69; c - 535; d - 63; e - 552; f - 19.

Table 6 Variables independently associated with tocolysis in women who delivered before 34 weeks: multiple analyses by nonconditional logistic regression

Variables	n	*p* Value	OR	CI 95%
Maternal complications	517	0.0487	1.551	1.003–2.40[a]
Neonatal morbidity	482	0.3690	1.364	0.69–2.68[b]
Neonatal respiratory distress	439	0.0753	1.810	0.94–3.48[c]
Newborn intubation	483	0.1624	1.295	0.90–1.86[d]
Necrotizing enterocolitis	424	0.1926	1.822	0.73–4.49[e]
Antenatal corticosteroids	520	< 0.0001	18.521	11.60–29.55[f]

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: Missing information: a - 11; b - 46; c - 89; d - 45; e - 104; f - 8.

countries due to how simple it is to administer, to the low rate of severe side effects and low cost. According to the last Cochrane Systematic review, CCB is better than betamimetics in terms of increased prolongation of pregnancy, decreased maternal side effects and neonatal outcomes.[23] In our sample, there was a significant difference between these drugs, with increased NICU stay and increased cesarean rates among users of betamimetics. Although known to be less safe than CCB, the prescription rate of betamimetics was high, including one third of the sample.

Since many important institutions worldwide have protocols that consider the restricted or no use of tocolysis, the results of this study can also be considered as an alert and incentive to review regional protocols and raise awareness toward the careful use of tocolysis.[24–26]

Brazil is in the tenth position among the countries with the highest absolute number of PTBs, according to the report "Born too soon," published by the World Health Organization in 2013.[1] Therefore, EMIP was a study with great clinical and epidemiological relevance due to the focus on prematurity and its risk factors and management in the most populated areas of the country.[7]

Conclusion

The original study was not designed to evaluate the efficiency of tocolysis, and we only have the outcomes of cases that did deliver preterm. However, our findings present a very interesting picture of management on prematurity. The EMIP was an innovative study that enabled a broad and detailed assessment of PTL in Brazil.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Contributors

Dias T. Z., Fava M. L., Passini Júnior R., Cecatti J. G., Tedesco R. P., Lajos G. J., Rehder P. M., Nomura M. L., Oliveira P. F. and Costa M. L. contributed with the project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

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Effectiveness of Metformin in the Prevention of Gestational Diabetes Mellitus in Obese Pregnant Women

Efetividade da metformina na prevenção do diabetes mellitus gestacional em gestantes obesas

Willian Barbosa Sales[1] Iramar Baptistella do Nascimento[1] Guilherme Dienstmann[1] Matheus Leite Ramos de Souza[2] Grazielle Dutra da Silva[2] Jean Carl Silva[1]

[1] Universidade da Região de Joinville, Jonville, SC, Brazil
[2] Department of Medicine, Universidade da Região de Joinville, Jonville, SC, Brazil

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Address for correspondence Willian Barbosa Sales, Universidade da Região de Joinville, Rua Paulo Malschitzki, 10, Zona Industrial Norte, Joinville, SC, 89219-710, Brazil (e-mail: willianbarbosasales@gmail.com).

Abstract

Objective To assess the effectiveness of metformin in the incidence of gestational diabetes mellitus (GDM) in obese pregnant women attending a public maternity hospital in Joinville, Santa Catarina, Brazil.

Methods Randomized clinical trial including obese pregnant women with a body mass index (BMI) $\geq$ 30 kg/m^2, divided into two groups (control and metformin). Both groups received guidance regarding diet and physical exercise. The participants were assessed at two moments, the first at enrollment (gestational age $\leq$ 20) and the second at gestational weeks 24–28. The outcomes assessed were BMI and gestational diabetes mellitus (GDM) diagnosis. The data distribution was assessed with the Friedman test. For all the analytical models, the *p*-values were considered significant when lower than 0.05. The absolute risk reduction was also estimated.

Results Overall, 164 pregnant women were assessed and further divided into 82 participants per group. No significant difference was observed in BMI variation between the control and metformin groups (0.9 $\pm$ 1.2 versus 1.0 $\pm$ 0.9, respectively, $p = 0.63$). Gestational diabetes mellitus was diagnosed in 15.9% ($n = 13$) of the patients allocated to the metformin group and 19.5% ($n = 16$) of those in the control group ($p = 0.683$). The absolute risk reduction was 3.6 (95% confidence interval 8.0–15.32) in the group treated with metformin, which was not significant.

Conclusion Metformin was not effective in reducing BMI and preventing GDM in obese pregnant women.

Keywords
- obesity
- gestation
- gestational diabetes mellitus
- metformin

Resumo

Objetivo Avaliar a efetividade da metformina na incidência de diabetes mellitus gestacional (DMG) em gestantes obesas de uma maternidade pública de Joinville, Santa Catarina, Brasil.

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Métodos Ensaio clínico randomizado desenvolvido com gestantes obesas com índice de massa corporal (IMC) $\geq 30\ kg/m^2$, divididas em dois grupos (controle e metformina). Ambos os grupos receberam orientação sobre dieta e exercício físico. As participantes foram avaliadas em dois momentos, o primeiro na inclusão (com idade gestacional $\leq$ 20 semanas) e o segundo entre 24 e 28 semanas de gestação. Os desfechos avaliados foram IMC e diagnóstico de diabetes mellitus gestacional (DMG). A distribuição dos dados foi avaliada com o teste de Friedman. Para todos os modelos analíticos, foram considerados significativos os valores de p inferiores a 0,05. Foi estimada também a redução absoluta de risco.

Resultados Foram avaliadas 164 gestantes, divididas em 82 participantes em cada grupo. Não houve diferença significativa na variação do IMC entre os grupos controle e metformina (0,9 $\pm$ 1,2 versus 1,0 $\pm$ 0,9, respectivamente, $p = 0{,}63$). O DMG foi diagnosticado em 15,9% ($n = 13$) das pacientes alocadas para o grupo metformina e 19,5% ($n = 16$) das incluídas no grupo controle ($p = 0{,}683$). A redução absoluta de risco foi de 3,6 (intervalo de confiança de 95% 8,0–15,32) no grupo metformina, o que não foi significativo.

Conclusão A metformina não foi eficaz em reduzir o IMC e prevenir o DMG em gestantes obesas.

Palavras-chave
- obesidade
- gestação
- diabetes mellitus gestacional
- metformina

Introduction

Obesity is one of the major epidemics of this millennium and is considered a public health problem by the World Health Organization (WHO).[1] In Brazil, cases of obesity have grown over the last decades; specifically among women, 1.9 million cases were registered in 1975 compared with 18 million in 2014.[2] This public health problem affects a great number of women, particularly those in reproductive age.[3]

Maternal obesity during pregnancy is associated with the development of gestational diabetes mellitus (GDM).[4] Gestational diabetes mellitus is the most common metabolic disorder during gestation, affecting 3–25% of all pregnancies, depending on the diagnostic criteria applied and on the population and ethnic groups studied. Between 24–28 weeks of gestation, all pregnant women without a previous diagnosis of diabetes undergo screening for GDM with the oral glucose tolerance test (OGTT) after 8 hours of fasting. The Brazilian Society of Diabetes (Sociedade Brasileira de Diabetes [SBD, in the Portuguese acronym]) recommends that pregnant women should be classified as having GDM when presenting a blood glucose level between 92 and 125 mg/dL at fasting, $\geq$ 180 mg/dL at 1 hour, or 153–199 mg/dL at 2 hours; an abnormal result at one of the time points of the test characterizes GDM.[5]

Prevention of hyperglycemia during pregnancy may reduce immediate adverse pregnancy outcomes, childbirth risks, and, consequently, costs to the public health care system directed to GDM treatment.[6] Strategies for GDM prevention among women at risk of developing the disease may include changes in lifestyle, reduction of obesity, nutritional intervention, physical activity, and pharmacological measures.[7]

Women who develop GDM during one of the gestational trimesters require attention during prenatal care to stabilize blood glucose levels to values similar to those of pregnant women without GDM.[6,8] Nutritional therapy is the first step in GDM management, but when it fails to achieve glycemic control, it is associated with drug therapy.[8] The standard pharmacological treatment of GDM is insulin therapy; however, oral hypoglycemic agents, like metformin, have also been used for glycemic control of overweight and obese women with GDM.[9]

In obese pregnant women, nutritional intervention and lifestyle changes may reduce many of the problems caused by GDM, achieving reduced blood glucose levels and BMI, as well as controlled blood pressure; however, low adherence by the patients fails to lead to a significant decrease in GDM incidence.[10,11]

The use of drugs like metformin has a preventive effect, especially in the control of obesity, which is one of the major causes of GDM. In the past, the use of hypoglycemic agents was contraindicated during pregnancy due to a risk of teratogenicity; however, this concept has changed over the past years. Metformin is no longer considered teratogenic; it is now considered a safe drug during pregnancy, with a low incidence of side effects, in addition to being helpful in controlling blood glucose levels and reducing BMI and levels of total cholesterol and fractions.[12,13] When associated with lifestyle changes, metformin is also a potentially effective and safe approach to obesity and GDM control.[13–15]

Based on these considerations, this study aimed at evaluating the effectiveness of metformin in the incidence of GDM in obese pregnant women attending a public maternity hospital in Joinville (Santa Catarina, Brazil).

Methods

The present study was a randomized clinical trial analyzing the use of metformin in obese pregnant women, who were randomized into two groups (control group and metformin

group). Both groups received counseling regarding diet and physical activity. All pregnant women received care by a multidisciplinary team comprising a nutritionist, nurse, physical therapist, and an obstetrician in a reference maternity hospital in the city of Joinville (Santa Catarina, Brazil).

Considering that GDM has a 2-fold higher risk in obese women and an incidence of 18% in the general population, and with the objective of obtaining a 50% decreased incidence with the drug, with a confidence level of 80%, we found that a sample size of 94 subjects in each group would be adequate. Considering a 10% rate of loss to follow-up, we selected 208 pregnant women to participate in the study, 104 of whom were allocated to the control group and 104 to the metformin group.[5]

The data were collected at Maternidade Darcy Vargas (MDV, in the Portuguese acronym) from October 31, 2014 to October 1, 2016. The study was initiated after approval by the Research Ethics Committee at Universidade da Região de Joinville (Univille), with the Certificate of Presentation for Appreciation (CAAE, in the Portuguese acronym) approval number 34863514.1.0000.5366, and was made possible by the Research Ethics Committee of Hospital Regional Hans Dieter Schmidt/Sesc/SC, with the CAAE approval number 34863514.1.3001.5363. This study is registered with the Brazilian Registry of Clinical Trials with the code RBR-9rpqdn and identification number U1111–1162–6908. This report follows the recommendations of the Consolidated Standards Reporting Trial (CONSORT).[16]

Pregnant women with gestational age (GA) $\leq$ 20 weeks and obesity (body mass index [BMI] $\geq$ 30 kg/m^2) were referred by primary health care units to the gestational obesity outpatient clinic at the MDV. The patients were invited to participate during lectures held at the MDV auditorium about gestational obesity and the effectiveness of metformin in the prevention of GDM, during which the study objectives, as well as its risks and benefits, were explained. The women who agreed to participate in the study signed two copies of a free and informed consent form, one of which was given to the participant and the other was maintained by the principal investigator. The lectures took place on Thursdays at 7:30 AM in the MDV auditorium during the period of the study.

The study included pregnant women with a diagnosis of obesity according to the WHO criteria (BMI $\geq$ 30 kg/m^2); age $\geq$ 18 years; negative GDM screening in early pregnancy (GA $\leq$ 20 weeks); no history of diabetes before pregnancy; no allergy to metformin; no history or presence of liver, renal, or gastrointestinal disease, or other condition that could interfere with the absorption, distribution, excretion, or metabolism of the drug. We excluded women who interrupted the follow-up, had intolerance or allergic reaction to the drug, or refused to continue participating in the study.

The participants received prenatal care according to the primary protocol recommended by the Brazilian Ministry of Health. Screening for GDM was performed between 24–28 weeks with the OGTT (75 g of glucose diluted at 25%). According to the SBD, a diagnosis of GDM should be established in pregnant women presenting a glucose level between 92 and 125 mg/dL at fasting, $\geq$ 180 mg/dL at 1 hour, or 153 to 199 mg/dL at 2 hours; an abnormal result at one of the time points of the test characterizes GDM.[5]

All participants were referred for nutritional care, in which they received dietary guidance with small reductions in their caloric intake of 24 kcal/kg/day, a fractionated diet with five to six daily meals, a daily caloric composition comprising 40–50% of fiber-rich complex carbohydrates, 20% of protein, and 30–40% of unsaturated fats. Daily calories were distributed as 10–20% at breakfast, 20–30% at lunch, 20–30% at dinner, and up to 30% as snacks, including a snack before bedtime to avoid nocturnal hypoglycemia. The participants were referred to physical therapy and received recommendations for physical activity, with a regular walking program of 20 minutes per day.[17]

Participants in the metformin group received a metformin dose of 1,000 mg twice daily (500 mg at breakfast and 500 mg at dinnertime), as prescribed by the obstetrician. If a diagnosis of GDM was established, metformin was not discontinued, since it was offered free of charge by the Brazilian Unified Health System (SUS, in the Portuguese acronym). Laboratory tests were performed at Laboratório Gimenez Ltda., which is located adjacent to the MDV. All tests performed in the study are part of the clinical and laboratory routine of obese pregnant women seen at MDV.

During the first visit to the gestational obesity outpatient clinic, the participants were randomized with a computerized algorithm using the software Microsoft Excel (Microsoft, Redmond, WA, USA), which generated a random allocation order list in a non-fixed proportion, divided into two groups: a study group, which was treated with metformin and received guidance on diet and physical activity, and a control group, which received only diet and physical activity counseling. The participants received a coded seal on their prenatal follow-up record, which identified them as participants of the multidisciplinary research team during outpatient visits throughout the study.

All patients were identified using a specific research form containing the participant's name; date of birth; age; marital status; occupation; educational level; ethnicity; BMI; GA; allergy to metformin; number of pregnancies; age at birth of first child; interval between deliveries; abortion; type of delivery; use of medication during pregnancy; diagnosis of liver, renal, or gastrointestinal disease; diagnosis of GDM in previous pregnancies; and diagnosis of polycystic ovary disease. The results of the laboratory tests, fasting blood glucose levels, and OGTT throughout the prenatal period were recorded during appointments at the obesity outpatient clinic. The tests were ordered at baseline (GA $\leq$ 20 weeks) and at 24–28 gestational weeks.

For the statistical analysis, the collected data were entered into a Microsoft Excel version 2016 spreadsheet and were later analyzed using the statistical software IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). The quantitative variables are presented as mean and standard deviation, while the qualitative variables are represented as absolute and relative frequencies. Once the normal distribution of the studied characteristics was confirmed, the Student t-test

was applied to analyze quantitative variables and the chi-square test for qualitative ones. To verify the distribution of fasting blood glucose values before and after treatment, boxplot graphs were built, and the Friedman test was used to compare the distribution of the data. For all analytical models, p values below 0.05 were considered significant, and the absolute risk reduction was estimated.

Results

Obese pregnant women with a BMI $\geq$ 30 kg/m^2, classified as having high-risk pregnancies, were referred by the primary health care units to the gestational obesity outpatient clinic at the MDV maternity, as shown in ►**Fig. 1**.

Among the pregnant women referred to the clinic, 116 failed to meet the study's inclusion criteria. Out of 253 eligible obese pregnant women, 89 declined to participate in the study, yielding 164 participants for randomization, of whom 82 were enrolled in the metformin group and 82 in the control group. The main demographic characteristics analyzed in the study were maternal age, marital status, occupation, education level, ethnicity, number of pregnancies, and GA at the first visit. Assessments included the anthropometric characteristic BMI and the metabolic parameter fasting blood glucose level (in mg/dL) ►**Table 1**.

When comparing BMI values in the control and metformin groups prior to metformin treatment, at GA $\leq$ 20 weeks, and after treatment, at 24–28 gestational weeks, no influence of the drug was observed on BMI increase in the control and metformin groups (0.9 $\pm$ 1.2 versus 1.0 $\pm$ 0.9, respectively, $p = 0.63$) ►**Table 2**).

Blood glucose levels during the OGTT were comparable among participants allocated to the metformin and control groups: fasting 77.5 (9.0) mg/dL and 78.9 (12.1) mg/dL, respectively ($p = 0.66$), 1 hour 129.3 (27.5) mg/dL and 134.0 (33.9) mg/dL, respectively ($p = 0.50$), 2 hours 110.6 (28.1) mg/dL and 111.7 (30.6) mg/dL, respectively ($p = 0.99$) ►**Fig. 2**.

The diagnosis of GDM was established in 13 (15.9%) patients in the metformin group and 16 (19.5%) of those in the control group ($p = 0.683$). The absolute risk reduction in the metformin group was 3.6 (95% confidence interval -8.0 to 15.32), which was not significant. The magnitude of the risk of GDM development in the metformin group was equivalent to 80% of that in the control group, that is, the metformin group had a 20% reduction in the risk of GDM development compared with the control group, as shown in ►**Table 3**.

Discussion

The present study demonstrated that none of the groups (control or metformin) influenced the BMI increase between gestational weeks $\leq$ 20 and 24–28, and that the efficacy of metformin in preventing the development of GDM in obese pregnant women was not significant. The general characteristics of the participants in each group showed no significant differences, except for GA at the first visit. Similar findings have been observed regarding maternal characteristics and obstetric history in a clinical trial with 202 obese pregnant women treated with metformin.[11] Another study with 43 pregnant women, which assessed the glycemic control with metformin during pregnancy in GDM, also found no significant differences in demographic characteristics among the groups.[18]

The relationship between the pharmacodynamics and pharmacokinetic mechanisms of metformin has not been well elucidated in the scientific literature yet, especially concerning the effect of these mechanisms on obese pregnant

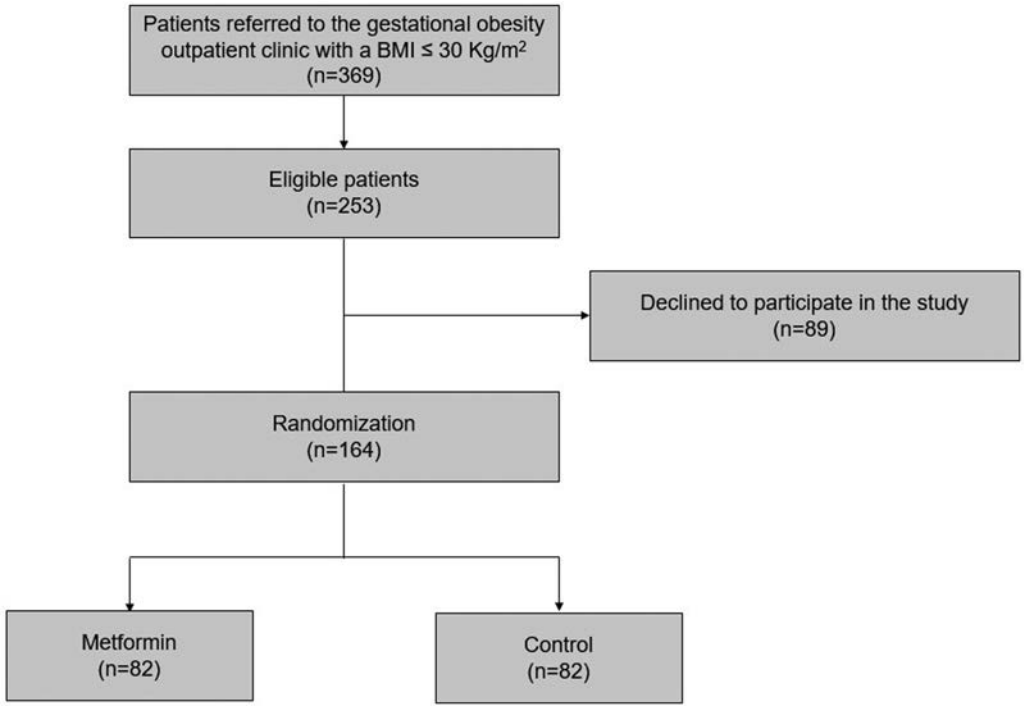

Fig. 1 Flowchart of the participants at each stage of the study.

Table 1 Characteristics of obese pregnant women at ≤ 20 weeks of gestation

	Metformin ($n = 82$)	Control ($n = 82$)	p value
Age (years)			
Mean (SD)	28.8 (6.0)	29.7 (6.3)	0.36†
Range	18.0–40.0	19.0–44.0	
Marital status			
Married	63 (76.8)	66 (80.5)	0.56‡
Single	19 (23.2)	16 (19.5)	
Occupation			
Working	82 (100)	82 (100)	–
Not working	0 (0.0)	0 (0.0)	
Education level			
Elementary school	27 (32.9)	25 (30.5)	0.89‡
High school	42 (51.2)	45 (54.9)	
Higher education	13 (15.9)	12 (14.6)	
Ethnicity			
White	67 (81.7)	65 (79.3)	0.86‡
Black	8 (9.8)	8 (9.8)	
Others	7 (8.5)	9 (11.0)	
Number of pregnancies			
Mean (SD)	2.3 (1.3)	2.6 (1.5)	0.09†
Range	1.0–6.0	1.0–8.0	
GA (first visit)			
Mean (SD)	15.1 (4.2)	17.1 (4.6)	< 0.01†
Range	5.0–24.0	6.0–26.0	
Fasting glucose (mg/dL)			
Mean (SD)	79.3 (9.5)	80.4 (10.2)	0.47†
Range	52.0–99.0	63.0–120.0	
BMI (kg/m^2)			
Mean (SD)	37.5 (4.7)	37.5 (5.0)	0.99†
Range	25.3–50.8	25.3–49.5	

Abbreviations: BMI, body mass index; GA, gestational age; SD, standard deviation.
†Student t test.
‡Chi-square test.

women. However, studies have demonstrated the ability of metformin to activate the AMP-activated protein kinase (AMPK), a protein involved in the control of body energy and a metabolic substrate, helping to reduce the BMI.[13–19] Several studies have shown fewer BMI changes among obese women with GDM treated with this drug.[20–22]

The results of the present study identified that participants in both control and metformin groups showed no significant increase in BMI between gestational weeks ≤ 20 and 24–28. The combination of metformin with lifestyle changes represents a potentially effective and safe approach to obesity control.[14] According to Fattah et al,[15] metformin limits the weight gain throughout pregnancy. A similar finding has been reported in a clinical trial by Syngelaki et al,[11] in which obese women without GDM taking prophylactic metformin for 12–18 weeks until delivery achieved lower weight gain during pregnancy, in contrast to the findings of the present study.

Of note, both groups received diet and physical activity counseling in the present study. According to the literature, adherence to these preventive practices by women before, during, and after pregnancy is effective in controlling BMI and blood glucose, and reducing the incidence of GDM.[23,24] Promising results in GDM prevention have been observed among obese women adhering to nutritional counseling recommendations.[25,26]

Physical activity performed early in pregnancy has a beneficial effect in reducing the risk of GDM in obese women.[27,28] Among the participants performing physical activity in the present study, GDM developed in 15.9% of those in the metformin group and 19.5% of those in the control group. Depending on the diagnostic criteria applied, GDM has an incidence between 3 and 25%, according to the Brazilian Society of Diabetes.[5] A multicenter, prospective study performed in nine European countries compared different approaches to prevent GDM among obese women; the study found that 14% of the women developed GDM between 24 and 28 weeks of gestation, regardless of the interventions used.[29] These findings are similar to those in the present study.

Women presenting with increased BMI, elevated fasting blood glucose level, and glucose intolerance have an increased short- and long-term risk of developing diabetes mellitus. However, according to the results of a study assessing the impact of lifestyle and metformin interventions over 10 years in women with a history of GDM in 27 clinical centers,[30] this risk can be substantially reduced with lifestyle changes and use

Table 2 Body mass index at ≤ 20 weeks and 24–28 weeks of gestation in obese pregnant women in the control and metformin groups

	Control Group ($n = 82$)			Metformin Group ($n = 82$)			Δ Metformin versus Δ Control (p)
	≤ 20	24–28	Δ	≤ 20	24–28	Δ	
BMI kg/m^2 (mean ± SD)	37.5 ± 4.7*	38.4 ± 4.9*	0.9 ± 1.2	37.5 ± 5.0*	38.5 ± 5.1*	1.0 ± 0.9	0.63**

Abbreviations: Δ, Variation; BMI, body mass index, SD, standard deviation. *Student t-test. **Chi-square test.

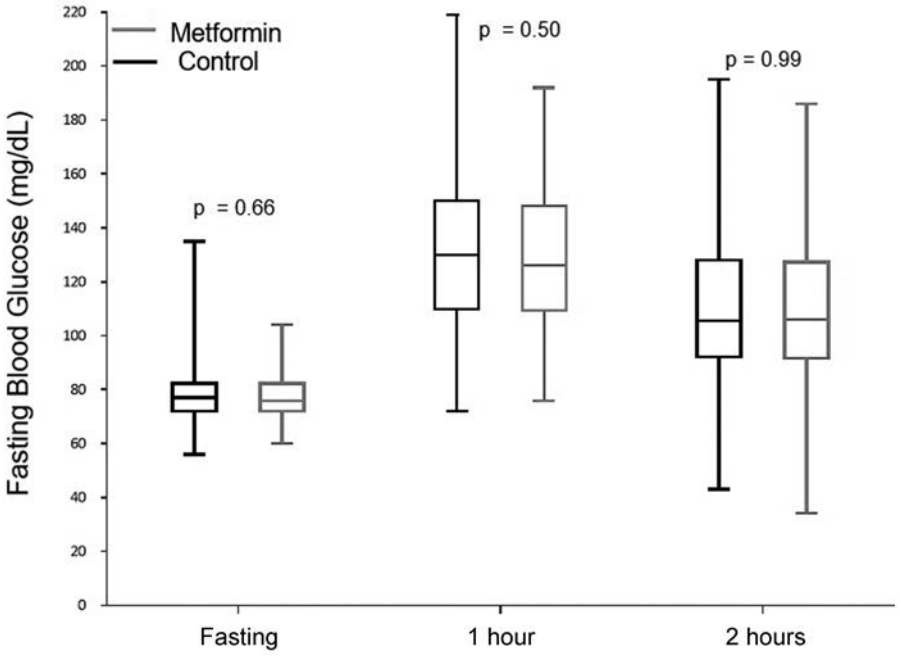

Fig. 2 Oral glucose tolerance test (OGTT) at 24–28 gestational weeks in obese pregnant women allocated to the metformin and control groups

of metformin. In the present study, 15.9% of the participants treated with metformin along with diet and physical activity developed GDM. Of note, lifestyle changes must take place during pregnancy to reduce the risk of GDM occurring before the 15th week of gestation in women with obesity.[27,31]

The differences in the results of the OGTT, performed in both control and metformin groups, were not significant. However, other studies with GDM women support the treatment of GDM with metformin, without an increased risk of maternal hypoglycemia.[13,32–35] In the present study, metformin was administered at a dosage of 1,000 mg twice daily. This dose of 1,000 mg is different from the one used in another study with 104 pregnant women treated with 500 to 2,500 mg of metformin, in which the drug was effective in controlling blood glucose levels during pregnancy.[18] A clinical trial with 132 pregnant women also treated with metformin 500–2,500 mg also obtained blood glucose control at 28 weeks of gestation.[6] In contrast, a clinical trial with 100 pregnant women treated with metformin 500–1,500 mg found no significant difference in glycemic control.[15]

Table 3 Absolute risk reduction in the incidence of gestational diabetes mellitus with metformin in obese pregnant women

	Group	N (%)	*P* value
Gestational diabetes mellitus	Metformin	13 (15.9)	0.683
	Control	16 (19.5)	
	Absolute risk reduction (95%CI)		**NNT**
	3.6% (-0.08–0.15)		25

Abbreviation: NNT, number needed to treat; 95%CI, 95% confidence interval.

Studies performed with pregnant women with polycystic ovary syndrome (PCOS) who underwent lifestyle changes combined with treatment with metformin have shown a relationship between lower BMI increase and improvements in metabolic rate and glycemic control. Of note, metformin has been used for some time in patients with PCOS with promising results when treatment is initiated before pregnancy.[35]

This study offers a new perspective in GDM prevention in obese women and is aligned with recommendations by other authors describing that prevention, detection, control, and early access to therapy are fundamental and necessary interventions to reduce the occurrence of GDM.[36]

Conclusion

Limitations of this study include the reduced number of pregnant women randomized to each group and the effectiveness of dietary intervention and physical activity. The study lacks high-quality evidence to offer significant conclusions regarding the benefits of the use of metformin in relation to diet and physical activity since a group without intervention was not used. Further studies are suggested to confirm the efficacy of metformin in a larger number of obese pregnant women in several centers throughout the country and with a metformin dose similar to that used in international clinical trials.

Contributors
Sales W. B., Nascimento I. B., Dienstmann G., Souza M. L. R. and Silva G. D. have contributed with the project conception, analysis, and interpretation of data. Sales WB, Silva JC. Contributed with final approval of the version to be

published: Sales W. B., Nascimento I. B., Dienstmann G., Souza M. L. R., Silva G. D., Silva J. C. have contributed with critical review of the intellectual content.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Association between Insulin Resistance and Cardiovascular Risk Factors in Polycystic Ovary Syndrome Patients

Associação entre resistência à insulina e fatores de risco cardiovascular em pacientes com síndrome dos ovários policísticos

Miriam da Silva Wanderley[1] Lara Cristina Ribeiro Pereira[1] Carla Borges Santos[1] Vinícius Santos da Cunha[1] Mariam Viviane Jovino Neves[1]

[1] Gynecology and Obstetrics, Faculty of Medicine, Hospital Universitário de Brasília, Universidade de Brasília, Brasília, DF, Brazil

Address for correspondence Miriam da Silva Wanderley, Universidade de Brasília, Campus Universitário Darcy Ribeiro, Asa Norte, Brasília, DF, 70210-900, Brazil (e-mail: miriamsw@unb.br).

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Abstract

Objective To analyze the association between the indirect methods of evaluating insulin resistance (IR) and blood pressure, anthropometric and biochemical parameters in a population of polycystic ovary syndrome (PCOS) patients.

Methods Cross-sectional study performed at the Hospital Universitário de Brasília (HUB, in the Portuguese acronym) involving PCOS patients diagnosed from January 2011 to January 2013. Four indirect methods, namely, fasting blood insulin level, fasting glucose/insulin ratio (G/I), homeostatic model-assessment-insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI), were used to obtain the IR diagnosis. The data were analyzed using the test of proportions, the Chi-square test, and Fisher exact test, when indicated.

Results Out of the 83 patients assessed, aged 28.79 $\pm$ 5.85, IR was found in 51.81–66.2% of them using the G/I ratio and the QUICKI, respectively. The test of proportions did not show a significant difference between the methods analyzed. The proportion of IR diagnoses was statistically higher in obese women than in women with normal body mass index (BMI). We observed a statistically significant association between all the methods for diagnosing IR and BMI, waist circumference (WC) and lipid accumulation product (LAP). With regards to arterial hypertension (AH), we observed a significant association according to three methods, with the exception of the ratio G/I.

Conclusion Insulin resistance prevalence varied according to the diagnostic method employed, with no statistical difference between them. The proportion of IR diagnoses was statistically higher in obese women than in women with normal BMI. We observed a significant association between IR and WC, BMI, LAP, as well as dyslipidemia and AH in a high proportion of patients.

Keywords
- polycystic ovary syndrome
- insulin resistance
- body mass index
- waist circumference
- lipid accumulation product

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Resumo

Objetivo Analisar a associação entre os métodos indiretos de avaliação de resistência à insulina (RI) e parâmetros pressóricos, antropométricos e bioquímicos em uma população de pacientes com síndrome dos ovários policísticos (SOP).

Métodos Estudo transversal realizado no Hospital Universitário de Brasília (HUB), envolvendo pacientes que apresentaram o diagnóstico de SOP no período de janeiro de 2011 a janeiro de 2013. O diagnóstico de RI foi obtido por meio de quatro métodos indiretos: insulinemia de jejum, relação glicemia de jejum/insulinemia de jejum (G/I), avaliação da resistência à insulina através do modelo homeostático (HOMA-IR) e índice quantitativo de sensibilidade à insulina (QUICKI). Os dados foram analisados utilizando o teste de proporções, o teste do Qui-quadrado e o teste exato de Fisher, quando indicado.

Resultados Foram avaliadas 83 pacientes com idade média de 28,79 $\pm$ 5,85 anos. A RI foi diagnosticada em 51,81–66,27% dos casos pela relação G/I e QUICKI, respectivamente, e o teste de proporções não evidenciou diferença significativa entre os métodos analisados. A proporção de diagnósticos de RI foi estatisticamente maior em mulheres obesas em comparação à proporção de mulheres com índice de massa corporal (IMC) normal. Foi observada uma associação estatisticamente significativa entre todos os métodos diagnósticos de RI e IMC, circunferência da cintura (CC) e produto de acumulação lipídica (LAP). Quanto à hipertensão arterial (HA), foi observada associação significativa de acordo com três métodos, com exceção da relação G/I.

Conclusão A prevalência de RI variou conforme o método diagnóstico utilizado, mas não houve diferença estatística entre eles. A proporção de diagnósticos de IR foi maior nas mulheres obesas do que naquelas com peso normal. Foi observada associação significativa entre RI e CC, IMC e LAP, assim como com dislipidemia e HA em uma proporção elevada de pacientes.

Palavras-Chave

- síndrome de ovários policísticos
- resistência à insulina
- índice de massa corporal
- circunferência da cintura
- produto de acumulação lipídica

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women in childbearing age. It is a heterogeneous disorder whose pathogenesis is not well understood despite evidence of complex interaction with genetic, behavioral and environmental factors that contribute to its occurrence.[1]

Three distinct diagnostic criteria have been used, namely, the National Institutes of Health (NIH), the Rotterdam consensus, and the Androgen Excess and PCOS Society (AE-PCOS) criteria. The previous exclusion of pathologies presenting a similar clinical picture is important for all three diagnostic criteria.[1]

In addition to being an ovulatory disorder, PCOS can also be considered a metabolic disorder, since insulin resistance (IR) and consequent compensatory hyperinsulinemia, which are closely related to its pathogenicity and comorbidities, can be exacerbated by the coexistence of obesity, which affects $\sim$ 50% of PCOS women.[2]

However, IR is not part of the diagnostics criteria, partly and probably because of the absence of an accurate validated method for use in clinical practice, since the hyperinsulinemic-euglycemic clamp, the gold standard for diagnosing IR, is expensive and difficult to perform.[3]

It has been observed that, in addition to IR, PCOS patients are at a higher risk of developing glucose intolerance, Type 2 *Diabetes Mellitus*, dyslipidemia, and metabolic syndrome (MS),[1,2] all of which are traditional risk factors for the development of cardiovascular diseases (CVDs).

Nevertheless, there remain uncertainties regarding the clinical outcomes and mortality due to CVD.[4] Furthermore, the fact that these patients are predominantly young and often show normal lipid profile could be contributing to delays in their evaluation and in the adequate establishment of their clinical management.[1,5]

The purpose of this paper is to analyze the association between the indirect methods of evaluating IR and the blood pressure, anthropometric and biochemical parameters in a population of PCOS patients.

Methods

A cross-sectional study was performed at the Hospital Universitário de Brasília (HUB, in the Portuguese acronym) using information obtained from the records of patients diagnosed with PCOS from January 2011 to January 2013.

The population of the study included women 18 years of age or older with a PCOS diagnosis according to the Rotterdam criteria.[5] Cases of thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, glucose intolerance, diabetes, ovarian or adrenal tumors, premature ovarian failure, patients who had used any hormonal or non-

hormonal medication that could interfere with the results during the 6 months prior to the study, patients under 18 years of age, and records lacking any of the information required were excluded from the study.

In addition to demographic data, such as marital status, parity and age, the analysis included menstrual patterns, the existence of hyperandrogenism, acne, and acanthosis nigricans. Menstrual cycles were considered anovulatory when longer than 35 and shorter than 90 days, and amenorrheic in the absence of menstruation for at least 3 months,[6] while hirsutism was defined as a Ferriman and Gallwey[7] score of eight or more. Total blood testosterone was obtained using the chemiluminescence method, with values exceeding 80 ng/dL considered altered.

The analysis of the anthropometric measurements included the body mass index (BMI) and the waist circumference (WC). The BMI was obtained using the Quetelet[8] index, namely, the ratio of weight over height in square meters, and the results were subdivided into normal (18.5–24.9), overweight (25–29.9) and obese ($\geq$ 30). The WC was the smallest circumference between the last rib and the iliac crest,[8] with a cutting point at 88 cm.[9]

Blood pressure (BP) and biochemical evaluation, through the analysis of the concentration of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), lipoproteins excluding HDL cholesterol (non-HDL-c), and fasting glucose were also evaluated. The parameters of normality, as well as the diagnostic criteria of MS were defined.[9] In addition, the lipid accumulation product (LAP),[10] which uses an anthropometric measurement (waist circumference) and a biochemical measurement (triglycerides), was also calculated and considered normal when lower than 34.5.[11]

Insulin Resistance was diagnosed using four indirect methods, namely, fasting blood insulin in excess of 12 µIU/mL,[12] the fasting blood glucose over fasting blood insulin ratio lower than 6.4,[12] homeostatic model assessment-insulin resistance(HOMA-IR), calculated using the Mathews formula,[13] higher than 2.71,[14] and quantitative insulin sensitivity check index(QUICKI) lower than 0.333.[12]

The Chi-square test (X^2) or the Fisher exact test (where recommended) were used to evaluate the association between the four indirect methods of evaluating IR and the blood pressure, anthropometric and biochemical parameters. Contingency tables were performed with IR diagnostic method and the BMI classified into groups (normal, overweight and obesity), and the test for equality of proportions was used to identify which groups were different from one another in terms of IR. The test of proportions was also used to evaluate the differences between the frequencies among the four IR diagnostic methods. The SAS 9.3 statistical software package (SAS Institute, Cary, NC, USA) was used and considered statistically significant when p 0.05.

The study was approved by the Committee of Ethics in Research in Human Beings of the Faculdade de Ciências da Saúde da Universidade de Brasília (CAAE 14168613.3.0000.0030).

Results

After applying the inclusion and exclusion criteria, 83 PCOS patients were included in the study. Age varied from 18 to 42 years-old, 44.57% of patients being single and 51.8% nulliparous. In the clinical evaluation, 96.39% of the patients reported oligomenorrhea or amenorrhea, 73.49%, hirsutism (Ferriman-Gallwey index), 48.19%, acanthosis nigricans, 43.37%, acne and one patient reported androgenic alopecia. Total testosterone exceeded 80 ng/dL in 18.29% of the patients, and 70 ng/dL in 50.60% of them. The clinical, anthropometric, blood pressure, and biochemical results are shown in ►**Table 1**.

Insulin resistance was diagnosed in 66.27% of the cases using the QUICKI; in 60.24% by the fasting blood insulin; in 59.04% by the HOMA-IR; and in 51.81% by the fasting glucose/insulin (G/I) ratio. With regards to the frequency of IR, there was no significant difference among the methods analyzed according to the test of proportions ($p = 0.304$). As shown in ►**Table 2**, there was a statistically significant association between BMI and all the IR diagnostic methods, as well as between IR and WC. Regarding high blood pressure, no significant association was found for the G/I.

Obesity and overweight were diagnosed in 56.62% and 24.09% of the patients, respectively. Comparing the BMI groups two by two, the prevalence of IR was higher among

Table 1 Anthropometric, blood pressure and biochemical characteristics of the 83 patients with polycystic ovary syndrome

Parameters	Mean ± Standard Deviation	Reference
Age (years)	28.79 ± 5.85	
Weight (Kg)	76.43 ± 13.91	
Height (cm)	160.12 ± 6.63	
Ferriman-Gallwey score	11.83 ± 2.94	< 8
Body mass index	29.9 ± 5.28	18–25 kg/m^2
Waist circumference	92.15 ± 10.72	< 88 cm
Systolic blood pressure	123.15 ± 18.38	< 130 mm Hg
Diastolic blood pressure	79.13 ± 11.00	< 85 mm Hg
Total cholesterol	183.07 ± 34.88	≤ 200 mg/dL
High-density lipoprotein	49.47 ± 12.91	≥ 50 mg/dL
Low-density lipoprotein	117.16 ± 32.74	< 100 mg/dL
Non-HDL lipoproteins	133.41 ± 35.17	< 130 mg/dL
Triglycerides	110.6 ± 59.09	< 150 mg/dL
Fasting blood glucose	87.74 ± 6.52	< 100 mg/dL

Table 2 Association between insulin resistance and the anthropometric and blood pressure parameters in 83 patients with polycystic ovary syndrome

Method	BMI	WC	SBP	DBP	AH
Fasting insulinemia	$< 0.0001^{*}$	$< 0.0001^{*}$	0.0019^{*}	0.0099^{*}	0.0118^{*}
G/I	0.0014^{*}	$< 0.0001^{*}$	0.1225	0.2308	0.2866
HOMA-IR	0.0002^{*}	$< 0.0001^{*}$	0.0051^{*}	0.0252^{*}	0.0253^{*}
QUICKI	0.0001^{*}	$< 0.0001^{*}$	0.0057^{*}	0.0591	0.0348^{*}

Abbreviations: AH, arterial hypertension; BMI, body mass index; DBP, diastolic blood pressure; G/I, fasting blood glucose/fasting blood insulin ratio; HOMA-IR, homeostatic model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; WC, waist circumference.
*Chi-square test. Significant association ($p < 0.05$).
(Full data are available in the supplemental file).

the obese patients regardless of the indirect method used, varying from 68.09–82.98% using the G/I and the QUICKI, respectively. In overweight women, IR varied from 50–55%, while in normal BMI women, the highest IR value was 25%, according to the QUICKI, and the lowest value was 18.75%, as per the other three methods.

►**Table 3** shows that the proportion of IR diagnoses was statistically higher in obese women when compared with the proportion of normal BMI patients in all methods of assessment. There was no difference in proportions of IR among normal weight and overweight women.

Table 3 Test of proportions for the body mass index groups as related to the insulin resistance diagnostic methods

Method	Normal/ Overweight	Normal/ Obesity	Overweight/ Obesity
Fasting insulinemia	0.1117	$< 0.0001^{*}$	0.0395^{*}
G/I	0.3119	0.0017^{*}	0.0611
HOMA-IR	0.1117	0.0001^{*}	0.0629
QUICKI	0.0779	$< 0.0001^{*}$	0.0881

Abbreviations: G/I, fasting blood glucose/fasting blood insulin ratio; HOMA-IR, homeostatic model assessment- insulin resistance; QUICKI, quantitative insulin sensitivity check index.
(Full data are available in the supplemental file).
*Test of proportions; Significant difference between the proportions ($p < 0.05$).

With regards to the biochemical parameters, the association between IR and the non-HDL-c level was statistically significant according to the QUICKI, while in the case of the triglycerides a statistical significance was found in the fasting blood insulin and the QUICKI (►**Table 4**). ►**Table 4** also shows a statistically significant association among all the IR diagnostic methods and the LAP.

An analysis of the isolated parameters showed that 22.89% of the patients presented at least three diagnostic criteria for MS. And the X^2 test showed a statistically significant association between those cases and all the IR diagnostic methods with $p = 0.0005$ for fasting insulin, $p = 0.0070$ for the G/I, $p = 0.0021$ for the HOMA-IR, and $p = 0.0004$ for the QUICKI.

Discussion

Polycystic ovary syndrome is one of the most common endocrine pathologies of women of bearing-age. Although its prevalence could be even higher when the Rotterdam diagnostic criteria[5] are followed, a large percentage of the cases might not be diagnosed at the primary health service level.[1,15] Also, these patients might not receive due attention from the metabolic and cardiovascular points of view,

Table 4 Association between insulin resistance diagnostic methods and the lipid accumulation product and biochemical variables in polycystic ovary syndrome patients

Method	LAP	Total Cholesterol	HDL-c	LDL-c	Non-HDL-c	TG
Fasting Insulinemia	0.0001^{*}	0.4863	0.1149	0.6782	0.0941	$0.0099^{*\#}$
G/I	0.0001^{*}	0.1148	0.2689	0.6922	0.0816	0.1579 #
HOMA-IR	0.0001^{*}	0.4107	0.1786	0.5686	0.1448	0.0750 #
QUICKI	0.0001^{*}	0.2657	0.1623	0.9134	0.0190^{*}	$0.0252^{*\#}$

Abbreviations: G/I, fasting blood glucose/fasting blood insulin ratio; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; LAP, lipid accumulation product; LDL-c, low-density lipoprotein cholesterol; Non-HDL-c, non–HDL cholesterol; QUICKI, quantitative insulin sensitivity check index; TG, triglycerides.
(Full data are available in the supplemental file).
*Chi-square test. Significant association ($p < 0.05$).
*#Fisher exact test. Significant association ($p < 0.05$).

because their management tends to focus on their aesthetic and reproductive problems.[1]

Although its physiopathology is not quite understood, there is no doubt that IR plays an important role, since it leads to compensatory hyperinsulinemia with complex effects on the regulation of lipid metabolism, protein synthesis and modulation of androgen production,[16] whose mechanism results from a defect in the insulin receptor characterized by increased serine phosphorylation.[3]

Nevertheless, the prevalence of IR has been an object of discussion. In our study, IR was found in 51.81–66.27% of the patients, depending on the diagnostic method employed, but it has been diagnosed in 50–80% of PCOS patients.[1,12,16] Such great variability may result from the diagnostic criteria used in PCOS, different PCOS phenotypes, ethnic differences in insulin action, or even environmental factors such as diet, as well as the method used to identify IR.[3]

Because the complexity and cost of the hyperinsulinemic-euglycemic clamp for IR diagnosis make its use impractical for routine use in clinical practice,[3] other measures have been employed, such as HOMA-IR, QUICKI and the G/I,[3,12] which appear effective in diagnosing IR.[12] However, despite the statement that the HOMA-IR and QUICKI would be more sensitive in detecting IR,[12] we have not observed a statistically significant difference among the four methods used in our study.

Insulin resistance may be found in PCOS patients with normal weight, but its frequency and magnitude increase in the presence of obesity.[1,2,17] The average frequency of IR was 20.31% among normal weight patients, 50% among overweight patients and 76.59% among obese patients in our study. We also observed a significantly higher proportion of IR among the obese patients when compared with normal weight patients. These findings are similar to those of Reyes-Muñoz et al[18] using HOMA. In addition, Moran et al[17] observed a strong positive correlation between the magnitude of IR, measured using the G/I, and the women's BMI.

Obesity is an independent risk factor of developing CD and it has been suggested that, independently from the BMI, PCOS women tend to accumulate fat in the visceral abdominal region, which confers them a metabolic risk.[1]

In our study, there was a statistically significant association between both anthropometric factors— BMI and WC— and all the IR diagnostic methods. An extensive review published recently[19] observed that the greatest health implications for PCOS patients are associated with excess weight and abdominal circumference, since visceral abdominal fat is associated with increasing IR.[19]

It has been observed that IR could promote CD directly and/or, indirectly, through changes in fibrinolysis, compromising lipolysis suppression and inducing arterial hypertension (AH).[4]

A Swedish study found that, even in the absence of a true hypertensive state, PCOS women had higher average blood pressure than the controls, even after adjusting for the BMI and body fat distribution[20] and a Brazilian study observed the prevalence of AH two times higher in PCOS women than in non-PCOS women.[21] In our study, we observed a statistically significant association between AH and IR with three of the four diagnostic methods employed.

It has also been suggested that IR could contribute to the dyslipidemia frequently observed in PCOS patients through various mechanisms. While Slowińska-Srzednicka et al[22] observed a positive correlation between total triglycerides and fasting insulin and a negative correlation between apolipoprotein A-I and fasting insulin in PCOS women, our study showed a significant association between the triglyceride levels and IR diagnosed using the QUICKI and the fasting blood insulin level. Furthermore, the frequent finding of high non-HDL-c in PCOS patients, seen in 53.01% of the cases in our study, also reflects another cardiovascular risk factor in these women.[19]

Although dyslipidemia can occur independently of obesity,[23] BMI is believed to be the main determining factor for high triglyceride levels and reduced HDL levels, frequently found in PCOS.[24]

However, the LDL-c in PCOS seems less dependent on body weight and could be partially related to the hyperandrogenism frequently observed in these women.[1,19] In our study, 73.49% of the patients showed hirsutism and in 18.29% of them total plasma testosterone exceeded 80 ng/dL. Nevertheless, although the high LDL-c levels could be associated with hyperandrogenism, it is not clear whether there is a causal relation between them.[1] Furthermore, the androgens could also contribute to IR by means of a direct effect on skeletal muscle and action on adipose tissue.[3]

It has also been reported that the menstrual pattern of these patients could contribute to the IR finding. Brower et al[25] observed that, in PCOS women, when the menstrual cycle exceeded 35 days, HOMA-IR levels were higher than those of the controls or of PCOS women with regular cycles. In our study, 55.43% of the patients showed such menstrual cycle pattern and 40.96% were amenorrheic. Acanthosis nigricans, observed in 48.19% of the patients, cannot be forgotten, since a substantial percentage of PCOS patients suffer from this condition and its severity correlates with the degree of IR.[26]

Besides that, the metabolic abnormalities in PCOS patients can coincide with the diagnostic components of the MS,[9] in which IR and compensatory hyperinsulinemia also play a crucial role in the physiopathology of the MS.[27] Nevertheless, the prevalence of this syndrome can vary depending on the ethnicity, age, BMI, country, as well as the criteria used in defining both PCOS and the MS.[28] Despite having excluded the analysis the patients' charts with fasting glucose higher than 100 mg/dL, 22.89% of the patients in our study had at least three parameters altered the normalcy standards, which would comply with the MS diagnostic criteria,[9] reinforcing the higher cardiovascular risk in PCOS women.

In addition, we observed a statistically significant association between all the indirect methods of diagnosing IR and the presence of at least three diagnostic parameters for MS. The most prevalent association involved high WC (68.67%) and low HDL (50%). These findings are similar to those of Madani et al,[28] who also observed a higher prevalence of

those two criteria, although decreased HDL was the most frequently observed alteration in their study.

The LAP index, combining the WC measurement and the triglyceride levels, was initially tested in 2005. The results suggested that it could become a predictor of CD incidence.[10]

The LAP has been shown to be more accurate than HOMA-IR in the diagnosis of IR.[29] While Macut et al[30] observed an association between HOMA-IR and LAP, we observed a statistically significant association between LAP and all the methods of diagnosing IR. So that LAP could be an indicator of IR and other possible comorbidities related to this metabolic disorder, including CD in PCOS patients, in agreement with the previously observed findings.[11] Nascimento et al[31] corroborated this statement in a study of PCOS patients in which the researchers found an association between LAP and various cardiovascular risk parameters.

Some limitations in our study should be mentioned, particularly concerning the diagnosis of PCOS and MS. In regard to MS, we used internationally accepted criteria,[9] and although we did not use the five classic measures for MS diagnosis, since fasting blood glucose level was excluded from the statistical analysis, we did use the other four to demonstrate the important metabolic disorders occurring in these patients and the significant association with IR.

Although the new PCOS guidelines suggest modifications in one of the diagnostic criteria by increasing the number of follicles to 25 because of new technologies for ultrasonography examination, the ovary size was not influenced by this innovation and 10 cm^3 is still the cut-off point between a normal and an increased ovary.[32] Thus, we based our diagnoses on the size of the ovary alone, rather than in the number of follicles. In addition, the guidelines of the Endocrine Society issued in 2013 suggested the use of the Rotterdam criteria for the diagnosis of PCOS.[33]

The gold standard in the diagnosis of IR is the hyperinsulinemic-euglycemic clamp. Nevertheless, this method is too expensive and elaborate for use in clinical practice. The diagnosis was established using four indirect methods, and it has been shown the mathematical methods, such as HOMA-IR and QUICKI, have a good correlation with the clamp.[12,34] Furthermore, they are sensitive enough to detect IR in PCOS.[12] In addition, no statistical differences were found among the four methods, which could facilitate the initial identification of the patients suffering from IR at the primary health care level. Thus, more complex calculations would be avoided, and the patients referred to other specific clinical evaluations much sooner.

It is also important to mention that this study evaluated an institutional rather than a population-based sample, so the real prevalence of IR and cardiovascular risk factors in PCOS women could not be determined. Also, even though we have observed various associations between IR and these factors, like others in the literature,[11,18,28,30] the cross-sectional design cannot infer causal relationships between IR, obesity, dyslipidemia and PCOS.

Another limitation, albeit unrelated to the study per se, results from the possible repercussions of the findings. The average age of the patients was 28.79 years, similarly to that of other studies in the literature.[15,28,30,31] It could be assumed, therefore, that the existence of high metabolic risk in the young PCOS patients could predispose them to CD as they grow older.[19]

However, the actual incidence of CD and mortality is still under dispute. While a 21-year follow-up study of a cohort of Swedish PCOS patients did not find increased myocardial infarct, stroke or mortality, despite the higher prevalence of AH and dyslipidemia in these women,[35] a prospective Iranian study with a 12-year follow-up of PCOS patients and controls did not find any significant difference in the cardiac-metabolic risk factors between the two groups.[4] Besides that, it was also found that the difference in insulin levels and IR, initially higher in the PCOS group, diminished along time.[4] Nevertheless, a recent meta-analysis observed a significant association between PCOS and coronary heart disease, although no association was found between PCOS and myocardial infarction.[36]

It is possible that the heterogeneous nature of the PCOS, the lack of knowledge about its physiopathology and the existence of exogenous factors and other confounding elements, such as obesity, make it difficult to evaluate with any degree of precision the extension of the long-term complications of the syndrome.[19] In addition, changes in metabolic regulation and ovarian function could also modify the expression of the disease and act over its morbidity.[19]

Nevertheless, despite the controversies about the future of these patients, we cannot ignore the findings of our study: a series of independent and associated factors of cardiovascular risk, such as the existence of IR and its significant association with WC, BMI, LAP, as well as dyslipidemia and AH in a high proportion of patients.

Early detection of those metabolic and cardiovascular risk factors by the primary health care services through the use of simple measures, such as the anthropometric evaluation of the patients and LAP, would lead to appropriate counseling regarding the patients' lifestyle or to the prescription of medications that could improve their quality of life and reduce the risk of PCOS' long term complications, which increase considerably the costs of the health care provided.

Conclusion

Insulin resistance was found in 51.81–66.2% of the patients, with no significant difference between the four methods analyzed. The proportion of IR diagnoses was statistically higher in obese women than in women with normal BMI. A statistically significant association was observed between IR and WC, BMI, LAP, as well as dyslipidemia and AH in a high proportion of patients.

Contributors

Wanderley M. S., Pereira L. C. R., Santos C. B., Cunha V. S. and Neves M. V. J. contributed with project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

Conflicts of Interest

The authors have no conflict of interest to disclaim.

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Association between Hormonal Contraception and Injuries Induced by Human Papillomavirus in the Uterine Cervix

Associação entre a contracepção hormonal e lesões induzidas pelo vírus do papiloma humano no colo uterino

Lia Karina Volpato[1] Isabela Ribeiro Siqueira[1] Rodrigo Dias Nunes[1] Anna Paula Piovezan[1]

[1] Post-Graduation Program in Health Sciences, Universidade do Sul de Santa Catarina, Palhoça, SC, Brazil

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Address for correspondence Lia Karina Volpato, Postgraduate Program in Health Sciences, Universidade do Sul de Santa Catarina (UNISUL), Campus Grande Florianópolis, Av. Pedra Branca, 25, Palhoça, SC, 88137-270, Brazil (e-mail: liakarina@hotmail.com).

Abstract

Objective To evaluate the association between hormonal contraception and the appearance of human papillomavirus HPV-induced lesions in the uterine cervix of patients assisted at a school outpatient clinic - ObGyn outpatient service of the Universidade do Sul de Santa Catarina.

Methods A case-control study, with women in fertile age, performed between 2012 and 2015. A total of 101 patients with cervical lesions secondary to HPV were included in the case group, and 101 patients with normal oncotic colpocytology, in the control group. The data were analyzed through the Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, US) software, version 24.0, using the 95% confidence interval. To test the homogeneity of the proportions, the chi-square (χ^2) test was used for the qualitative variables, and the Student t-test, for the quantitative variables.

Results When comparing the occurrence of HPV lesions in users and non-users of combined oral contraceptives (COCs), the association with doses of 0.03 mg or higher of ethinylestradiol (EE) was observed. Thus, a higher probability of developing cervical lesions induced by HPV was identified (odds ratio [OR]: 1.9 $p = 0.039$); and when these cases were separated by the degree of the lesion, the probability of these patients presenting with low-grade squamous intraepithelial lesion was 2.1 times higher ($p = 0.036$), but with no impact on high-grade squamous intraepithelial lesions and the occurrence of invasive cancer. No significant differences were found in the other variables analyzed.

Conclusion Although the results found in the present study suggest a higher probability of the users of combined hormonal contraceptives with a concentration higher than 0.03 mg of EE to develop low-grade intraepithelial lesions, more studies are needed to conclude causality.

Keywords
- hormonal contraception
- human papillomavirus
- HPV
- ethinylestradiol

Resumo

Objetivo Avaliar a associação entre a contracepção hormonal e a presença de lesões induzidas pelo vírus do papiloma humano (HPV) no colo uterino de pacientes do serviço

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Métodos Estudo observacional do tipo caso-controle, com mulheres no menacme, no período compreendido entre 2012 e 2015. Foram incluídas 101 pacientes com lesões cervicais secundárias ao HPV, no grupo caso, e 101 pacientes com colpocitologia oncótica normal, no grupo controle. Os dados foram analisados por meio do programa SPSS 24.0, utilizando-se o intervalo de confiança de 95%. Para testar a homogeneidade de proporções foram utilizados o teste do qui-quadrado (χ^2) para as variáveis qualitativas e o teste t de Student para as variáveis quantitativas.

Resultados Ao comparar-se a ocorrência das lesões pelo HPV em usuárias de contraceptivos orais combinados (COCs) com a em não usuárias, observou-se a associação com doses de 0.03 mg ou superiores de etinilestradiol (EE), na qual se identificou 1.9 vezes mais probabilidade destas desenvolverem lesões cervicais induzidas pelo HPV ($p = 0.039$); ao separar-se esses casos pelo grau da lesão, a probabilidade destas pacientes apresentarem lesão cervical de baixo grau foi 2.1 vezes maior ($p = 0.036$), porém sem impacto nas lesões cervicais de alto grau e na ocorrência de câncer invasor. Não foram encontradas diferenças significativas nas outras variáveis analisadas.

Conclusão Embora os resultados encontrados no presente estudo sugiram maior probabilidade das usuárias de contraceptivo hormonal combinado, com concentração superior a 0.03 mg de EE, desenvolverem lesão cervical de baixo grau, mais estudos são necessários para concluir causalidade.

Palavras-chave
- contracepção hormonal
- vírus do papiloma humano
- HPV
- etinilestradiol

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted disease (STD), affecting ~ 50% of the world's population.[1] It is estimated that between 75 and 80% of sexually-active individuals will acquire some subtype of HPV throughout life.[2] In Brazil, the prevalence rate of HPV varies from 13.7 to 54.3%, according to the population and region studied.[3,4]

Most genital infections are asymptomatic, but clinical forms are usually associated with low-risk oncogenic HPV and tend to be benign, whereas subclinical forms may include benign and/or malignant lesions and are usually caused by high-risk oncogenic HPV.[5]

Among the factors associated with the increase of HPV infection are the number of sexual partners, STD, multiparity, age of onset of sexual activity[6,7] and smoking.[2,8–11] There is no consensus in the literature on the association of hormonal contraceptives with the prevalence and/or persistence of cervical lesions induced by HPV. Numerous hypotheses attempt to justify the connection between the use of hormonal contraceptives and these aspects, such as the possibility of exogenous steroids acting on the HPV genome, causing mutations and the onset of cervical cancer, and the fact that progesterone increases the transcription of certain types of HPV, including HPV-16, through mediation by glucocorticoid-responsive elements that regulate virus transcription.[12] Furthermore, immune responses in the female genital tract are regulated by endogenous and exogenous sex hormones, and antigen presentation, cytokine production, immunoglobulin production and transport, and induction of tolerance have all been shown to be influenced by variations in the levels of sex hormones.[13] Users of combined oral contraceptives (COCs) have a decrease in immunoglobulin A (IgA) and immunoglobulin G (IgG) levels during the pause period in the cyclic schemes, thus providing a favorable environment for the appearance of HPV lesions.[11,14–17]

Due to the many divergences found in the literature, it is extremely important to try to clarify if there is a relationship between these factors, in order to enable physicians to provide better guidance and information to the users of this class of drugs so they may choose the best contraceptive option. Thus, this study aims to evaluate the association between hormonal contraception and the appearance of HPV-induced lesions in the uterine cervix of patients assisted at a school outpatient clinic at the Gynecology and Obstetrics Service of the Medical Ambulatory of Specialties of Universidade do Sul de Santa Catarina (AME,/USNISUL in the Portuguese acronym).

Methods

This study was based on the ethical principles of Resolution 466/12 of the Brazilian National Health Council and the Code of Ethics of the Declaration of Helsinki, and it was approved by the Research Ethics Committee of Universidade do Sul de Santa Catarina (UNISUL, in the Portuguese acronym), under the CAAE no. 17596313.9.0000.5369.

A case-control study was performed with women in fertile age at the Gynecology and Obstetrics Service of the Medical Ambulatory of Specialties (AME, in the Portuguese acronym) of UNISUL, located in the municipality of Palhoça, state of Santa Catarina, in the period between 2012 and 2015.

Patients were selected according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) on an electronic file. For the case group, the ICD-10 was used for cervical lesions (N87) and, for the control group, it was used for a gynecological revision (Z01.4). The choice of medical records was made using a systematic technique that will be explained subsequently.

In the case group, patients aged 18 to 45 years, who were submitted to cervical biopsy for alterations suggestive of HPV lesion, confirmed by anatomopathological examination, were included in the study. These patients were classified, according to the Bethesda classification, as having low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and invasive cancer.[18] In the control group, patients within the same age range as the case group, who underwent routine gynecological evaluation, and whose oncotic colpocytology was normal, were included. In both groups, the medical records of immunocompromised patients, smokers or patients whose diagnosis of injury occurred during pregnancy, and the medical records that did not contain all the necessary information for the study, were excluded.

The sample size was calculated in the OpenEpi 2.3.1 software (Open Source Epidemiologic Statistics for Public Health, Atlanta, Georgia, EUA) using the formula for case-control studies with the following parameters: 95% confidence interval (95%CI), 80% test power, 60% exposed proportion between cases, 1:1 ratio of controls for cases and odds ratio (OR) of 2.2 for a unicaudal test. The last two parameters were used according to the article by Ajah et al, who investigated a similar outcome in a multicenter study.[19] The procedure resulted in a final sample of 104 patients per group.

The extracted data was recorded in a data collection instrument specially developed for the present study. Afterwards, it was inserted in an electronic database of the Microsoft Excel (Microsoft, Redmond, WA, US) software, and exported to the Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, US) software, version 24.0, in which it was analyzed.

Qualitative variables were described by absolute and relative frequencies, while quantitative variables were described as medians, means and standard deviations for a subsequent bivariate analysis. To test the homogeneity of the proportions, the chi-square ($\chi 2$) test was used for the qualitative variables, and the Student t-test, for the quantitative variables.

Results

A total of 202 medical records were included and divided into 101 cases and 101 controls. The average age of the patients with HPV cervical lesion was of 29.7 $\pm$ 8.8 years, while, among those without lesions, it was of 32.7 $\pm$ 10.5 years. This result ($p = 0.687$), which is similar to what was observed for the other sociodemographic characteristics evaluated in the study (ethnicity, marital status and level of schooling), did not differ statistically between the two groups.

Regarding the prevalence of hormonal contraceptive use in the study population, 101 patients (50%) did not use it, while 101 patients (50%) did. The proportion of use between groups was of 55.4% and 44.6% respectively, in the case and control groups ($p = 0.157$). The most commonly used route of administration for hormonal contraceptives in the studied population was the oral route (90.1%), while the route of administration of 9.9% of the women was intramuscular ($p = 0.283$). There was no report of contraceptive use by the transdermal, vaginal, subcutaneous or intrauterine routes.

The average time of use of hormonal contraceptives was 5 years. There was no association between this time of use and the occurrence of cervical lesion by HPV, even when other time stratifications were evaluated. When analyzing the characteristics of time of use, route of administration (►**Table 1**) and formulation of hormonal contraceptives (►**Table 2**), compared to non-users, there was no difference between the two groups studied.

When considering the types of progesterone used and the degree of HPV lesions, 70 (69.3%) women in the case group and 45 (44.6%) patients in the control group used some type of progesterone, but there was no difference between users and non-users, regardless of the type of progesterone (►**Table 3**).

When evaluating the dose of ethinylestradiol (EE) present in the COCs, users of 0.03 mg EE had a 1.9-fold increased risk of developing cervical lesions induced by HPV when compared with non-users of contraceptives ($p = 0.039$) (►**Table 4**); in these cases, the risk of developing LSIL was 2.1 times higher, but with no impact on HSIL and on the occurrence of invasive cancer (►**Table 5**).

Discussion

The present study demonstrated, for the first time in the Brazilian population, the association between the use of oral

Table 1 Association between contraceptive route of administration and HPV lesions compared to non-users in the study patients

Route of Administration	Case n (%)	Control n (%)	Total n (%)	*p*-value	OR (95%CI)
Non-user	45 (44.5)	56 (55.4)	101 (50.0)	–	1
User					
Oral	51 (50.5)	40 (86.9)	91 (45.0)	0.283	0.6443 (0.3648–1.1378)
Intramuscular	5 (5.0)	5 (5.0)	10 (5.0)	0.715	0.8214 (0.2240–3.0126)

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

Table 2 Association between contraceptive composition and HPV lesions compared to non-users in the study patients

Composition	Case n (%)	Control n (%)	Total n (%)	*p*-value	OR (95%CI)
Non-user	45 (44.5)	56 (55.4)	101 (50.0)	–	1
User					
EE + associations	48 (47.6)	39 (39.6)	86 (43.1)	0.147	1.5316 (0.8604–2.7263)
E2 + associations	6 (5.9)	4 (4)	10 (4.9)	0.355	1.8667 (0.4964–7.0201)
DMPA	1 (1.0)	–	1 (0.5)	0.615	0.2743 (0.0109–6.8944)
DSG	1 (1.0)	2 (2.0)	3 (1.5)	0.452	2.4643 (0.2479–24.4951)

Abbreviations: 95%CI, 95% confidence interval; DSG, desogestrel; DMPA, depot medroxyprogesterone acetate; EE, ethynilestradiol; E2, estradiol; OR, odds ratio.

Table 3 Association between the type of progesterone present in hormonal contraceptives and the degree of HPV lesions compared to non-users in the study patients

Progesterone	Case n (%)	Control n (%)	Total n (%)	*p*-value	OR (95%CI)
LSIL ($n = 70/98$)					
Non-user	31 (31.6)	56 (57.1)	87 (51.8)	–	1
User					
CPA	6 (8.6)	7 (7.1)	15 (8.9)	0.466	1.5484 (0.4780–5.0160)
DSG	22 (31.4)	19 (19.4)	41 (24.4)	0.055	2.0917 (0.9836–4.4482)
DHPA	2 (2.9)	1 (1.0)	3 (1.8)	0.302	3.6129 (0.3148–41.4622)
DMPA	1 (1.4)	–	1 (0.6)	0.307	5.3810 (0.2128–136.0563)
DRSP	3 (4.3)	1 (1.0)	4 (2.4)	0.150	5.4194 (0.5404–54.3438)
GST	3 (4.3)	10 (10.2)	13 (7.7)	0.378	0.5419 (0.1387–2.1174)
LNG	1 (1.4)	4 (4.1)	5 (3.0)	0.485	0.4516 (0.0483–4.2203)
NET-EN	1 (1.4)	–	1 (0.6)	0.307	5.3810 (0.2128–136.0563)
HSIL ($n = 28/98$)					
Non-user	12 (42.8)	56 (57.1)	68 (54.0)	–	1
User					
CPA	6 (21.4)	7 (7.1)	15 (11.9)	0.070	3.3333 (0.9029–12.3056)
DSG	4 (14.3)	19 (19.4)	23 (18.2)	0.977	0.9825 (0.2827–3.4138)
DHPA	–	1 (1.0)	1 (0.8)	0.805	1.5067 (0.0579–39.1998)
DRSP	1 (3.6)	1 (1.0)	2 (1.6)	0.287	4.6667 (0.2723–79.9627)
GST	1 (3.6)	10 (10.2)	11 (8.7)	0.486	0.4667 (0.0545–3.9988)
LNG	1 (3.6)	4 (4.1)	5 (4.0)	0.894	1.1667 (0.1195–11.3870)
NET-EN	3 (10.7)	–	3 (2.4)	0.776	0.6457 (0.0313–13.3099)
Invasive cancer ($n = 3/98$)					
Non-user	2 (66.7)	56 (57.1)	58 (57.4)	–	1
User					
CPA	–	7 (7.1)	7 (6.9)	0.797	1.5067 (0.0658–34.4808)
DSG	1 (33.3)	19 (19.4)	20 (19.8)	0.757	1.4737 (0.1264–17.1847)
DHPA	–	1 (1.0)	1 (1.0)	0.250	7.5333 (0.2410–235.4646)
DRSP	–	1 (1.0)	1 (1.0)	0.250	7.5333 (0.2410–235.4646)
GST	–	10 (10.2)	10 (9.9)	0.963	1.0762 (0.0481–24.0580)
LNG	–	4 (4.1)	4 (4.0)	0.570	2.5111 (0.1039–60.6610)

Abbreviations: 95%CI, 95% confidence interval; CPA, cyproterone acetate; DHPA, dihydroxyprogesterone acetate; DMPA, depot medroxyprogesterone acetate; DRSP, drospirenone; DSG, desogestrel; GST, gestodene; HSIL, high-grade squamous intraepithelial lesion; LNG, levonorgestrel; LSIL, low-grade squamous intraepithelial lesion; NET-EN, norethisterone enantate; OR, odds ratio.

Table 4 Association between doses of ethinylestradiol present in oral combined hormonal contraceptives and HPV lesions compared to non-users in the study patients

EE Dose (mg)	Case n = 93	Control n = 95	Total n = 188	*p*-value	OR (95%CI)
Non-user	45 (48.0%)	56 (58.9%)	101 (53.7%)		1
User					
≥ 0.03 mg	38 (40.8%)	24 (25.3%)	62 (33.0%)	0.039	1.9704 (1.0345–3.7529)
≤ 0.02 mg	10 (10.7%)	15 (15.8%)	25 (13.3%)	0.681	0.8296 (0.4829–2.0265)

Abbreviation: 95%CI, 95% confidence interval; EE, ethinylestradiol; OR, odds ratio.

Table 5 Association between doses of ethinylestradiol present in oral combined hormonal contraceptives and the degree of HPV lesions compared to non-users in the study patients

EE Dose (mg)	Case n (%)	Control n (%)	Total n (%)	*p*-value	OR (95%CI)
LSIL (n = 70/95)					
Non-user	31 (44.3)	56 (58.9)	87 (52.7)	–	1
User					
≥ 0.03	28 (40.0)	24 (25.3)	52 (31.5)	0.036	2.1075 (1.0467–4.2434)
≤ 0.02	11(15.7)	15 (15.8)	26 (15.3)	0.537	1.3247 (0.5423–3.2363)
HSIL (n = 28/95)					
Non-user	12 (42.9)	56 (58.9)	68 (55.3)	–	1
User					
≥ 0.03	10 (35.7)	24 (25.3)	34 (27.6)	0.177	1.9444 (0.7401–5.1083)
≤ 0.02	6 (21.4)	15 (15.8)	21 (17.1)	0.280	1.8667 (0.6008–5.7995)
Invasive cancer (n = 3/95)					
Non-user	2 (66.7)	56 (58.9)	58 (59.2)	–	1
User	–	–	–	–	–
≥ 0.03	–	24 (25.3)	24 (24.5)	0.621	0.46120 (0.0213–9.9676)
≤ 0.02	1 (33.4)	15 (15.8)	16 (13.3)	0.620	1.8667 (0.1583–22.0070)

Abbreviations: 95%CI, 95% confidence interval; EE, ethinylestradiol; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio.

hormonal contraceptives based on EE at the dose of 0.03 mg and the appearance of HPV-induced LSIL in the uterine cervix.

When analyzing the sociodemographic variables of the patients in the present study, no characteristic was considered significant either for the development or non-development of the lesions. These findings were similar to those described in 2016 by Abouzeid and El-Agwany,[10] who recorded, in a case-control study with 250 women, that there was no significant statistical difference in age, marital status or parity.

Other studies evaluated the association of cervical lesions with sociodemographic variables not investigated in the present study. Among the women younger than 35 years of age, women who lived in rural areas, and women with no fixed partners, women with a lower educational level and multiparous women, a greater probability of developing cervical neoplasm was observed.[20] Another study aimed at determining the demographic and behavioral factors associated with HPV positivity, a prevalence of 25.3% of HPV lesions was identified in patients aged between 31 and 35 years.[21] In 2010, when investigating the short-term persistence of HPV infection among 2,408 women with low-grade cervical lesions or other cytological abnormalities, Maucort et al found a greater probability of HPV lesion persistence in white women aged between 20 and 29-years.[5]

In addition, there was no difference between the groups when considering the characteristics of the patients observed in the present study, regarding the prevalence of use, route of administration and time of use of hormonal contraceptives. Finally, no association was found between these characteristics of the use of hormonal contraception and the presence of cervical lesions, as well as no significant difference between the case and control groups. These findings are similar to those of Westreich et al[21] in 2014, who analyzed the impact of the use of depot medroxyprogesterone (DMPA), norethisterone enanthate (NET-EN) and COCs separately, on the incidence and progression of cervical lesions, without finding significant differences. Similarly, Binesh et al,[22] in 2013, in a cross-sectional study, found no association between COC consumption and changes in cervical cytology, agreeing with the findings of Sammarco et al,[8]

in 2013, when studying the persistence and clearance of HPV in users of COCs, after evaluating and controlling possible confounding factors.

In contrast, in 2011, Marks et al[23] identified an association between the appearance of new HPV lesions in women using COCs, while Mitchell et al,[20] in 2014, and Jensen et al,[24] in 2013, demonstrated that the use of any hormonal contraceptive increases the probability of the persistence of HPV carcinogenic viruses when compared with non-users, and Maucourt-Bouch et al, in 2010, observed a slight increase in the risk of persistent lesions in injectable contraceptive users.[5]

Regarding the time of use of contraceptives, there was no statistical significance in the present study, a finding similar to those of the studies by Westreich et al,[22] in 2014, and Green et al,[25] in 2003. Watson-Jones et al,[6] in 2013, suggested that the use of hormonal contraceptives, both oral and intramuscular, for less than four years, would serve as a protective factor against HPV lesions when compared to condom use.

On the other hand, Roura et al, in 2016, identified a strong association between the time of COC use and the risk of developing HSIL and invasive cancer.[9] Marks et al,[2] in 2011, identified that current COC use for more than 6 years is associated with an increased risk of developing persistent HPV infections; and Brinton,[26] in 1991, suggested that 10 years of COC use could present an increased risk of developing cervical cancer, which are findings similar to those of other studies with variable research designs that evaluated the long-term use of contraceptives.[19,27]

In the present study, no association was found between HPV lesions and the progesterone types present in the contraceptives, either alone or associated with EE. Abouzeid and El-Agwany[10] reached similar findings in 2016 in a case-control study including 200 users of contraceptives containing progesterone alone and 50 non-hormonal contraceptive users, data corroborated by Darwish et al[28] in 2004. Contradicting these findings, in 1990, Herrero et al[29] demonstrated that women receiving DMPA had a high risk of developing cervical cancer, but this result was significant only in those patients who had used it for more than five years, which was the median time of hormone use in the present study.

When comparing hormonal contraceptive types and associating them with the HPV lesions, a statistical significance was not evidenced, but when comparing only the doses of EE, separated in doses of 0.03 mg and 0.02 mg, there was a significant association. Patients taking higher doses of estrogen are more likely to develop HPV-induced lesions, especially LSIL. This fact could be justified by the stimulation of a cervical ectopy secondary to higher concentrations of estrogen,[30] besides altering the immune system and inducing an increased concentration and activity of pro-inflammatory cytokines,[31] facilitating the development of these lesions.

No studies have been found to systematically assess and compare the dose of EE present in COCs and its association with HPV-induced lesions. In 2012, Aksoy et al,[32] when evaluating the effect of EE 0.30 mg + drospirenone 3 mg on the cervical mucus, observed a statistically significant increase in mucoprotein 2 (MUC2) levels, suggesting that this is related to the efficacy of COCs, and also speculating that the MUC2 increase induced by the hormonal contraceptive may be the mechanism responsible for the cervical carcinogenesis induced by this method, although they consider that large-scale longitudinal studies are necessary to confirm these findings.[32] Mitrani-Rosenbaum et al[33] (1989) and Gadducci et al[34] (2011) have demonstrated that both estrogen and progesterone can affect cervical cells by HPV mRNA transcription and by integrating it into the host DNA. In addition, sex steroids could increase the expression of HPV E6 and E7 genes, leading to apoptosis failure and promoting carcinogenesis. However, Webster et al[35] (2001) failed to demonstrate that estrogen or progesterone could interfere with HPV cellular apoptosis, and Harris et al[36] (2009) found that recent use of concentrations of EE $>$ 0.03 mg for more than 2 years is not associated with high-grade cervical lesions.

The present study had some limitations, which were related but not restricted to the convenience sampling, the number of cases raised, and the design adopted. The evaluation of confounding factors was not possible because the study is retrospective and based on data analysis of medical records. It is possible that the inconsistencies reported in the association between hormonal contraception and cervical lesions caused by HPV may be related in part to these confounding risk factors, including lifestyle, sexual behavior and HPV oncogenic type, which are very difficult to control.

Conclusion

Although the results found in the present study suggest that the users of COCs with concentrations of EE $>$ 0.03 mg could develop LSIL, a cause-effect relationship could not be determined due to the design of the study, and more studies are needed to conclude causality. However, this finding seems even more relevant if we consider the median time of 5 years of use of COCs with concentrations of EE $>$ 0.03 mg, as well as the average age of the users (27.8 $\pm$ 6.4 years), deserving professional attention regarding the orientation and follow-up of these women. The mechanisms involved in the persistence and incidence of HPV lesions are far from being clarified, and new studies are needed to elucidate better approaches regarding the type of contraception, route of administration and hormonal doses that are not associated with HPV-induced lesions.

Contributors

Volpato L. K., Siqueira I. R., Nunes R. D. and Piovezan A. P. contributed with the project and data interpretation, writing of the article, critical review of the intellectual content, and final approval of the version to be published.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Does Knowing Someone with Breast Cancer Influence the Prevalence of Adherence to Breast and Cervical Cancer Screening?

Conhecer alguém com câncer de mama influencia a prevalência da adesão ao rastreamento dos cânceres de mama e colo uterino?

Igor Vilela Brum[1] Tamara Cristina Gomes Ferraz Rodrigues[1] Estela Gelain Junges Laporte[1] Fernando Monteiro Aarestrup[1] Geraldo Sergio Farinazzo Vitral[1] Bruno Eduardo Pereira Laporte[1]

[1] Hospital Universitário, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil

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Address for correspondence Bruno Eduardo Pereira Laporte, MD, MSc, Universidade Federal de Juiz de Fora, Rua José Lourenço Kelmer, s/n, 36036-330, Juiz de Fora, MG, Brazil (e-mail: laportebruno@hotmail.com).

Abstract

Objective To evaluate the prevalence of adherence to screening methods for breast and cervical cancer in patients attended at a university hospital and to investigate whether knowing someone with breast cancer, moreover belonging to the patient's family, affects the adherence to the screening recommendations.

Methods This was a cross-sectional and quantitative study. A structured interview was applied to a sample of 820 women, between 20 and 69 years old, who attended a university hospital in the city of Juiz de for a, MG, Brazil. For the analysis, the chi-square test was used to assess possible associations between the variables, and the significance level was set at p-value ≤ 0.05 for a confidence interval (CI) of 95%.

Results More than 95.0% of the sample performed mammography and cervical cytology exam; 62.9% reported knowing someone who has or had breast cancer, and this group was more likely to perform breast self-examination (64.9%; odds ratio [OR] 1.5; 95% CI 1.12–2.00), clinical breast examination (91.5%; OR 2.11; 95% CI 1.37–3.36), breast ultrasound (32.9%; OR 1.81, 95% CI 1.30–2.51), and to have had an appointment with a breast specialist (28.5%; OR 1.98, 95% CI 1.38–2.82). Women with family history of breast cancer showed higher propensity to perform breast self-examination (71.0%; OR 1.53 95% CI 1.04–2.26).

Conclusion There was high adherence to the recommended screening practices; knowing someone with breast cancer might make women more sensitive to this issue as they were more likely to undergo methods which are not recommended for the screening of the general population, such as breast ultrasound and specialist consultation; family history is possibly an additional cause of concern.

Keywords
- mass screening
- breast neoplasms
- breast self-examination
- uterine cervical neoplasms
- public health

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Resumo

Objetivos Avaliar a prevalência da adesão aos métodos de rastreamento dos cânceres de mama e de colo uterino em pacientes atendidas em um hospital universitário e investigar se conhecer alguém com câncer de mama e, o fato de este pertencer à família, modifica a adesão às recomendações de rastreamento.

Métodos Estudo transversal e quantitativo. Uma entrevista estruturada foi aplicada a uma amostra de 820 pacientes do sexo feminino, entre 20 e 69 anos, usuárias de um hospital universitário na cidade de Juiz de Fora, MG. Para a análise, o Teste Qui-quadrado foi usado para avaliar a possibilidade de associação entre as varáveis, e o valor de significância foi determinado em valor-$p \leq 0,05$ para um intervalo de confiança (IC) de 95%.

Resultados Mais de 95,0% da amostra realizava os exames de mamografia e colpocitologia; 62,9% relataram conhecer alguém que teve ou tem câncer de mama, sendo que este grupo realizou, com maior frequência, autoexame (64,9%; razão de prevalência [RP] 1,5; IC 95% 1,12–2,00), exame clínico (91,5%; RP 2,11; IC 95% 1,37–3,36) e ultrassonografia das mamas (32,9%; RP 1,81, IC 95% 1,30–2,51) e consulta ao mastologista (28,5%; RP 1,98, IC 95% 1,38–2,82). Mulheres com história familiar de câncer de mama realizaram com maior prevalência o autoexame das mamas (71,0%; RP 1,53 IC 95% 1,04–2,26).

Conclusão A amostra apresentou elevada adesão aos métodos de rastreamento preconizados; conhecer alguém com câncer de mama pode tornar as mulheres mais sensíveis a essa questão, aumentando a realização de medidas não recomendadas para o rastreamento da população geral, como ultrassonografia das mamas e consulta com médico especialista; a história familiar possivelmente implica em um fator de preocupação adicional.

Palavras-chave

- programas de rastreamento
- neoplasias da mama
- autoexame de mama
- neoplasias do colo do útero
- saúde pública

Introduction

Breast cancer is the second most common malignant neoplasm among women in Brazil, as well as in the world, being surpassed only by non-melanoma skin cancer.[1,2] In addition to its high prevalence, it is also a source of anxiety and fear for patients, since the primary treatment of this type of cancer is based on the surgical excision of the lesion, sometimes causing mutilations and affecting women's self-image.[3]

After the diagnosis of breast cancer, the patient might face feelings of guilt, anguish, pain, and suffering, as well as doubts about the success of the treatment, and fear of dying. Anxiety, depression, reduced libido, physical discomfort and low self-esteem are some of the situations experienced by patients with cancer, provoking profound changes throughout their lifetime.[4–7]

It is also known that these repercussions go beyond the patient herself, also affecting the women who live around her.[8,9] More than 40% of women know someone with breast cancer, and a study showed that these women had a better knowledge and perception of the disease.[10,11] Women with heightened perceptions of breast cancer risk are more likely to take actions to gain a sense of control over the disease, leading to a higher prevalence of mammography screening, genetic testing, and prophylactic mastectomy.[12,13] Lack of information about cancer, misunderstanding of risk factors or screening guidelines, and inaccurate perception of cancer risk may also affect the individual's behavior toward other types of cancer, such as cervical and colon cancer.[14] Few studies, however, have investigated whether these repercussions instill changes in attitudes and behaviors, leading women, for example, to greater adherence to guidelines for screening of breast and cervical cancer.[15] Determining the factors that influence the adherence to cervical cancer screening measures is also important as it remains the third most prevalent type of cancer among women in Brazil.[1]

The Brazilian Ministry of Health recommends that breast cancer screening for the general female population, meaning women without high risk for such neoplasm, should consist of bi-annual mammography (MMG) between the ages of 50 and 69 years old.[16] It also recommends clinical breast examinations (CBE) as part of the integral care for women's health, and breast self-examination (BSE) as an educational health action, encouraging women to gain knowledge about their own bodies.[16,17] Screening for cervical cancer and its precursor lesions, in turn, consists of a cytological examination, which should begin at the age of 25 for women who have had sexual activity, and it should continue until the age of 64.[16]

This study aims to evaluate the prevalence of adherence to screening methods for breast and cervical cancers in patients attended at a university hospital. Additionally, we sought to investigate whether knowing someone with breast cancer, moreover belonging to the patient's family, would effectively instill a greater adherence to cancer screening recommendations.

Methods

A cross-sectional, quantitative and descriptive field study was performed. The purpose of the study was to assess the possible associations between knowing someone who has had or currently has breast cancer with the adherence to screening measures for breast and cervical cancers.[16]

The sample consisted of 820 female patients, with ages ranging from 20 to 69 years old, attended at a university hospital in the city of Juiz de Fora, MG, Brazil. The minimum sample size was estimated in 820 women, based on a simple random sampling, with a confidence level of 95.0% and a sampling error of 5.0%. Women with a personal history of breast cancer were excluded from this study. A total of 861 patients were invited to respond the questionnaire, 41 of whom refused to participate (refusal rate 4.7%). The data collection was performed during the working hours of the hospital's different outpatient clinics, while the patients were in the waiting room. They were assigned a random number that was electronically generated.

The data was collected through an interview application composed by 43 questions, which were based on the specialized literature about the subject and elaborated by the authors of this research. To cover the points of interest in this study, five questions were asked regarding the socioeconomic profile of the sample, as well as two questions about whether or not someone with breast cancer is known, and six questions regarding adherence to screening measures and other complementary tests.

The study's exposure variables were: 1. knowing someone who has had or currently has breast cancer; 2. if this known individual belonged to the family of the research participant. The outcome variables consisted in the completion or not of the screening measures as recommended by the Brazilian Ministry of Health: 1. BSE; 2. CBE; 3. MMG for women between 50 and 69 years old; 4. cervical cytology, for women between 25 and 64 years of age. In addition to these variables, the following were evaluated: 5. consultation with a breast specialist; 6. to have performed a breast ultrasound (BUS).

Additionally, to carry out the analysis of the association between the variables, the chi-square test of independence (without correction) was applied. The significance level was p-value ≤ 0.05 for a confidence interval of 95.0%. Furthermore, the Statistical Package for The Social Sciences (SPSS) version 15.0 2006 software (SPSS Inc., Chicago, IL, USA) was used to construct the database and the statistical analysis. The approach was done by researchers, the authors of this study, who were previously trained, and the study was approved by the institution's ethics committee under the number 156.162.

Results

The mean age of the patients in the sample was 42.6 years of age (standard deviation [SD]: $\pm$ 12.8), 44.5 years old among the interviewees who knew someone with breast cancer, and 39.4 among those who did not know it ($p < 0.01$). The majority of the sample had completed a secondary/technical or undergraduate education (53.0%), presented monthly family income lower than 2 minimum wages (54.6%), lived in urban areas (92.9%) and were married or in a stable union (55.4%) (►**Table 1**).

Table 1 Distribution of the sociodemographic characteristics of the sample

Variables	n (%)
Age	
20 to 39	356 (43.4)
40 to 44	105 (12.8)
45 to 69	359 (43.8)
Educational level	
Illiterate/incomplete elementary school	9 (1.1)
Completed elementary school/completed high school	376 (45.9)
Completed high school or technical school/incomplete undergraduate education	339 (41.3)
Complete undergraduate education	96 (11.7)
Monthly family income (minimum wages)	
≤ 2	448 (54.6)
> 2 and ≤ 4	307 (37.4)
> 4	65 (8.0)
Living área	
Rural area	762 (92.9)
Urban area	58 (7.1)
Marital status	
Single	242 (28.5)
Married/Stable union	454 (55.4)
Separated/Divorced	78 (9.5)
Widow	46 (5.6)

It is noteworthy to mention that, in the analyzed sampling, a rate of 62.9% reported knowing someone who has had or currently has breast cancer and, among this group of women, 35.5% stated that such patient belonged to their own family.

Statistically, higher rates of the BSE and CBE implementation were observed among those people interviewed who reported having known someone who had or has breast cancer. If we compared them to those women who did not know someone diagnosed with breast cancer, the same fact was not observed in relation to MMG and cervical cytology, which presented a fulfilment rate higher than 94.0% in both researched groups (►**Table 2**).

Additionally, a rate of 28.5% ($n = 147$) of the women who knew someone with breast cancer had already consulted a breast specialist and 32.9% ($n = 170$) had already performed a breast USG. The same fact was observed in 16.8% ($n = 51$, $p < 0.01$, OR = 1.98, 95% CI95% = 1.38–2.82) and 21.4% ($n = 65, p < 0.01$, OR = 1.81, CI95%= 1.30–2.51) of the women who did not report having such knowledge.

Table 2 The correlation between knowing someone with breast cancer or not and adherence to the screening measures

Screening	Do you know someone with breast cancer?			
	Yes n (%)	No n (%)	*p*	OR (CI 95%)
BSE	335 (64.9)	168 (55.3)	0.01	1.50 (1.12–2.00)
CBE	472 (91.5)	254 (83.6)	< 0.01	2.11 (1.37–3.26)
MMG (> 50 years)*	201 (97.6)	65 (95.6)	0.40	1.90 (0.43–7.98)
Colpocytology (25 to 64 years)#	434 (95.4)	245 (94.6)	0.63	1.18 (0.59–2.36)

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination; IC, confidence interval; MMG, mammography; OR, odds ratio. n = 820; * *n* = 274; #n= 714.

A higher prevalence of BSE was observed in patients with a family history of breast cancer in relation to the group of women that knew a person diagnosed with cancer who did not belong to their family. Furthermore, no significant differences were observed regarding the adherence to the other screening measures studied herein (►**Table 3**). It was also observed that in the first group, a rate of 31.1% women ($n = 57$) had already consulted the specialist and 37.2% ($n = 68$) performed a breast USG. The same was observed in 27.0% ($n = 90, p = 0.32$, OR = 1.22, CI = 0.82–1.81) and 30.6% ($n = 102, p = 0.13$, OR = 1.34, CI = 0.92–1.96), respectively, in the second group.

Discussion

The present study described the adherence to screening measures recommended for breast and cervical cancers based on knowing or not knowing someone who was diagnosed with breast cancer, and also, in positive case, if the known individual was a family member. It is noteworthy to mention that more than 60.0% of the sample knew someone who had or currently has breast cancer, and this knowledge implied a higher fulfillment of BSE and CBE, while the first one was performed in an even higher proportion in cases with a family history.

There is an estimation of 58 thousand breast cancer cases each year in Brazil, corresponding to an incidence of 56.2 new cases per 100,000 women.[1] Thus, due to the high prevalence of the disease, it is expected that a considerable proportion of women know patients who had or have such neoplasm. There are few data available about the prevalence of this knowledge among women, ranging from 40 to 63%.[10,18,19] Therefore, the prevalence of women who know someone with breast cancer can be considered elevated in this study. The authors did not find previous Brazilian statistics about it.

It is known that psychological variables make an important contribution to whether an individual seeks cancer screening.[20] Some authors have suggested that a concern of breast cancer is beneficial, since it would lead women to adopt a more proactive attitude toward cancer screening.[21,22] However, others have advocated that such feelings would conduct women to avoid screening for fear of the diagnosis.[23,24] Although we have not directly assessed the psychological impact of knowing someone with breast cancer, one way to understand the results in the study herein might be in accordance with this first point of view, since a higher completion of BSE and CBE among women who reported knowing patients who had or have breast cancer was identified.

On the other hand, it is possible that such urgency may occur excessively, since, in this group, a higher proportion of submission to BUS and consultations with the breast specialist were also observed. Such actions, which are not considered effective initial methods of breast cancer screening for the general population, may generate negative consequences if performed, such as additional costs, besides the physical impact as an unnecessary biopsy and psychological shock in cases of false-positive results.[22,25]

A family member diagnosed with breast cancer seems to be an additional factor of concern, revealing itself in this study by the greater completion of BSE by women with a history of such disease in the family. This information, again, corroborates with the fact that the fear of diagnosis does not lead women to avoid it, insofar as the family history did not prove to be an impediment to the adherence to the appropriate screening measures.

Table 3 Correlation between family history of breast cancer and adherence to screening measures in the group of women who knew someone who had or has breast cancer

Screening	Family history of breast cancer?			
	Yes n (%)	No n (%)	*p*	OR (CI 95%)
BSE	130 (71.0)	205 (61.6)	0.03	1.53 (1.04–2.26)
CBE	170 (92.9)	302 (90.7)	0.39	1.34 (0.68–2.63)
MMG (> 50 years)*	65 (98.5)	136 (97.1)	0.56	1.91 (0.21–17.45)
Colpocytology (25 to 64 years)#	157 (96.3)	277 (94.9)	0.48	1.42 (0.54–3.73)

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination; CI, confidence interval; MMG, mammography; OR, odds ratio. *n= 820;* * *n = 206;* # *n = 455.*

In this scenario, health professionals are important to assist and educate women to minimize their apprehensions and deconstruct myths that exist around breast and cervical cancers. This is necessary, mainly, because the majority of women acquire information about screening measures through layman sources, such as television.[26] Misconceptions about cancer and risk factors can influence behavior toward other types of cancers; however, in this study, knowing someone with breast cancer did not affect cervical cancer screening, possibly due to the high adherence to the recommended practices.

Besides the psychological consequences, knowing someone with breast cancer can influence adherence to screening methods through other ways. For instance, beliefs about the effectiveness and importance of the diagnostic methods, perceived risk of cancer, attitudes toward the healthcare providers, and higher knowledge about the disease can play a role in women's decision to adhere or not to the screening recommendations.[10–14,20] Those aspects, however, were not assessed in this study and should be further investigated.

A positive finding of this study was that, among the recommended age groups by the Brazilian Ministry of Health, in the group researched at the university hospital, a rate of 97.1% reported having done a MMG, and more than 95.1% had undertaken cervical cytology examination. These values are higher than the World Health Organization goals, as well as the national coverage, which are 70.0 and 60.0%, respectively, for MMG, and 80.0 and 79.4% for colpocytology.[27]

The fact that the study sample comes from a university hospital limits the comparison of the results with the Brazilian general population, since all these women receive health-assistance. Furthermore, the prevalence was estimated based on the patients' reports, so it was not possible to verify the performance of the screening methods. Another limitation is the fact that some patients, who may have been considered to be at high risk of having breast cancer and, therefore, should have their screening individualized, may have been analyzed within the recommendations for the general population.

On the other hand, due to the fact that knowing someone with breast cancer may lead to a greater completion of the BSE, CBE and BUS, as well as conduct to consultations with the breast specialist, the present study highlights the health professionals' importance in the assistance and orientation of these patient groups. Additionally, it also serves as a theoretical support for researches that may provide a more comprehensive understanding of the emotional dynamics involved behind the greater search for the screening methods and early diagnosis by women with this context of life.

Conclusion

Knowing someone with breast cancer makes women more sensitive to this issue, which possibly justifies the increase in the implementation of BSE and CBE. The broad coverage of MMG and cervical cytology examinations proved to be important in ensuring that women have access to the main methods of screening, independently of their individual aspects. Finally, considering that most women know a breast cancer patient, health services should be adequate to accommodate and work more effectively on the apprehensions of this group of women.

Contributions

Brum I. V., Rodrigues T. C. G. F., Laporte E. G. J., Aarestrup F. M., Vitral G. S. F. and Laporte B. E. P. contributed with the project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

Conflicts to Interest

The authors of this article declared they have no conflicts of interest.

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A Critical Review on Obstetric Follow-up of Women Affected by Systemic Lupus Erythematosus

Uma Revisão Crítica Sobre o Acompanhamento Obstétrico de Mulheres com Lúpus Eritematoso Sistêmico

Danilo Eduardo Abib Pastore[1] Maria Laura Costa[1] Mary Angela Parpinelli[1] Fernanda Garanhani Surita[1]

[1] Department of Obstetrics and Gynecology, Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

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Address for correspondence Fernanda Garanhani Surita, MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Universidade Estadual de Campinas - Unicamp, Rua Alexander Fleming, 101, Campinas, SP, 13083-881, Brazil (e-mail: surita@unicamp.br).

Abstract

Objective To review the existing recommendations on the prenatal care of women with systemic lupus erythematosus (SLE), based on currently available scientific evidence.

Methods An integrative review was performed by two independent researchers, based on the literature available in the MEDLINE (via PubMed), EMBASE and The Cochrane Library databases, using the medical subject headings (MeSH) terms "systemic lupus erythematosus" AND "high-risk pregnancy" OR "prenatal care." Studies published in English between 2007 and 2017 were included; experimental studies and case reports were excluded. In cases of disagreement regarding the inclusion of studies, a third senior researcher was consulted. Forty titles were initially identified; four duplicates were excluded. After reading the abstracts, 7 were further excluded and 29 were selected for a full-text evaluation.

Results Systemic lupus erythematosus flares, preeclampsia, gestation loss, preterm birth, fetal growth restriction and neonatal lupus syndromes (mainly congenital heart-block) were the major complications described. The multidisciplinary team should adopt a specific monitoring, with particular therapeutic protocols. There are safe and effective drug options that should be prescribed for a good control of SLE activity.

Conclusion Pregnant women with SLE present an increased risk for maternal complications, pregnancy loss and other adverse outcomes. The disease activity may worsen and, thereby, increase the risk of other maternal-fetal complications. Thus, maintaining an adequate control of disease activity and treating flares quickly should be a central goal during prenatal care.

Keywords

- systemic lupus erythematosus
- pregnancy
- prenatal care
- maternal outcomes
- fetal outcomes

Resumo

Objetivo Revisar as recomendações existentes sobre o cuidado pré-natal às mulheres com lúpus eritematoso sistêmico (LES), com base em evidências científicas atualmente disponíveis.

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Métodos Revisão integrativa realizada por dois pesquisadores independentes, com base na literatura disponível nos bancos de dados MEDLINE (via PubMed), EMBASE e The Cochrane Library, usando os cabeçalhos de assuntos médicos, ou termos MeSH, "systemic lupus erythematosus" E "high-risk pregnancy" OU "prenatal care." Estudos publicados em inglês entre 2007 e 2017 foram incluídos; estudos experimentais e relatos de caso foram excluídos. Em caso de desacordo, um terceiro pesquisador sênior foi consultado. Quarenta títulos foram inicialmente identificados; quatro duplicatas foram excluídas. Após leitura dos resumos, mais 7 artigos foram excluídos e 29 foram selecionados para uma avaliação de texto completo.

Resultados Surtos de LES, pré-eclâmpsia, perda de gestação, parto prematuro, restrição de crescimento fetal e síndromes de lúpus neonatal foram as principais complicações descritas. A equipe multidisciplinar deve adotar um monitoramento específico, com protocolos terapêuticos apropriados. Há drogas seguras e eficazes que devem ser prescritas para um bom controle do LES.

Conclusão Gestantes com LES apresentam risco aumentado de complicações maternas, perda de gravidez e outros desfechos adversos. A atividade da doença pode piorar e, assim, aumentar o risco de outras complicações. Assim, manter um controle adequado da atividade da doença e tratar rapidamente os surtos deve ser um objetivo central durante o pré-natal.

Palavras-chave
- lúpus eritematoso sistêmico
- gravidez
- cuidado pré-natal
- resultados maternos
- resultados fetais

Introduction

General Aspects

Systemic lupus erythematosus (SLE) is an autoimmune and multisystemic disorder of the connective tissue that mainly affects women of childbearing age (about nine women for each man). Immune anomalies, particularly the production of a series of antinuclear antibodies, are another prominent feature of the disease.[1]

The SLE prevalence varies from 40 to 200 cases per 100,000 inhabitants, more common among Africans and Asians descendants. In Brazil, its prevalence is around 8.7 per 100,000 inhabitants.[1,2]

The broad spectrum of clinical presentations includes mucous-cutaneous, muscle-skeletal, hematological, cardiopulmonary, renal and central nervous system manifestations. The most severe forms of organ involvement are lupus nephritis and neuropsychiatric lupus, and these conditions may result in a significant reduction in life expectancy.[1] Lupus nephritis is one of the leading causes of death along with infections.[3]

The most common general symptoms are weight loss, anemia, arthralgia and/or arthritis, being the involvement of the osteoarticular system the most frequent clinical manifestation.[1] Antiphospholipid syndrome can occur in association with SLE, and it is characterized by arterial and venous thromboses, as well as recurrent morbidity in pregnancy.[4]

The American College of Rheumatology (ACR) proposed the criteria for the diagnosis of SLE (►**Table 1**).[5] To be classified as SLE, at least four criteria should occur in series or simultaneously.[1,4,6]

A consensus group of experts on SLE, the Systemic Lupus International Collaborating Clinics (SLICC), has proposed revised criteria for the diagnosis of SLE (►**Table 2**). It requires either that a patient satisfies at least 4 out of 17 criteria, including at least one of the 11 clinical criteria and one of the 6 immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE and positivity to antinuclear antibodies (ANA) or anti-double-stranded DNA (dsDNA) antibodies.[7]

Systemic Lupus Erythematosus and Pregnancy

Considering the predilection of SLE in affecting women of childbearing age, pregnancy is of particular importance, with

Table 1 American College of Rheumatology (ACR) criteria for the classification of systemic lupus erythematosus

1.	Erythema malar.
2.	Discoid lupus.
3.	Photosensitivity.
4.	Oral ulcers.
5.	Arthritis.
6.	Serositis (pleuritis or pericarditis).
7.	Nephropathy (persistent proteinuria greater than 0.5 g/day and/or glomerular hematuria).
8.	Neurological disorders (convulsion or psychosis).
9.	Hematologic disorders (hemolytic anemia, leucopenia, thrombocytopenia).
10.	Immune disorder (presence of LE cells, anti-DNA or anti-Sm antibodies, false positive VDRL test, anticardiolipin IgG or IgM antibodies, lupus anticoagulant).
11.	Antinuclear antibody (ANA).

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; LE, lupus erythematosus; Sm, smith; VDRL, venereal disease research laboratory.

Table 2 Systemic lupus international collaborating clinics (SLICC) criteria for the classification of systemic lupus erythematosus *(4 of 17 criteria, including at least one clinical criterion and one immunologic criterion; OR biopsy-proven lupus nephritis*[7]

Criterion	Clinical criteria
Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); **OR** subacute cutaneous lupus (nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; **OR** discoid lupus/lichen planus overlap
Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral or nasal ulcers	Palate, buccal, tongue, **OR** nasal ulcers (in the absence of other causes, such as vasculitis, Behçet disease, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Joint disease	Synovitis involving two or more joints, characterized by swelling or effusion **OR** tenderness in two or more joints and at least 30 minutes of morning stiffness
Serositis	Typical pleurisy for more than one day, pleural effusions, or pleural rub, **OR** typical pericardial pain (pain with recumbency improved by sitting forward) for more than one day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler's syndrome
Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, **OR** red blood cell casts
Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); **OR** acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hemolytic anemia	Hemolytic anemia
Leukopenia or lymphopenia	Leukopenia ($< 4{,}000/mm^3$ at least once) (in the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension), **OR** lymphopenia ($< 1{,}000/mm^3$ at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
Thrombocytopenia	Thrombocytopenia ($< 100{,}000/mm^3$) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
Immunologic criteria	
ANA	ANA level above laboratory reference range
Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or $>$ 2-fold the reference range if tested by ELISA)
Anti-Sm	Presence of antibody to Sm nuclear antigen
Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-β 2-glycoprotein I (IgA, IgG, or IgM)
Low complement	Low C3; low C4; **OR** low CH50
Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

Abbreviations: ANA, antinuclear antibodies; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus.

relevant impact in maternal and perinatal health.[8] The incidence of SLE among pregnant women ranges from 1:660 to 1:2.952; therefore, an understanding on how to manage these patients is essential.[9]

Although advances in the treatment of obstetric complications and improvements in neonatal care have enabled lupus women to have pregnancies with better outcomes, SLE persists associated with significant fetal and maternal morbidity.[8] Conditions with elevated levels of estrogen, such as pregnancy, have the potential to exacerbate SLE. The incidence of disease outbreaks during pregnancy varies between 15 and 63%.[10]

The impact of pregnancy in the course of lupus remains controversial, especially in relation to the incidence of flares. In contrast, the impact of lupus on gestation is more clearly understood. Women with lupus are no less fertile; outcomes are characterized by higher rates of fetal loss, preterm birth,

and fetal growth restriction (FGR), higher incidence of hypertensive disorders and maternal intensive care admission. Multiple factors have been identified in association with adverse outcomes, such as lupus activity during pregnancy, previous nephropathy, maternal hypertension, and positivity for anti-phospholipid antibodies.[8]

Thus, adopting a specific protocol of care for pregnant women with lupus should contribute to reduce the frequency of maternal and fetal adverse outcomes, directly or indirectly related to SLE, improving care standards and ensuring successful pregnancies. This review aims to disclose the existing recommendations on prenatal care among health professionals attending pregnant women affected by SLE, based on currently available scientific evidence.

Methods

Integrative reviews were conducted to develop an evidence-based context in relation to different perspectives of clinical science studies. The following medical subject headings (MeSH) terms were used for research: "systemic lupus erythematosus" AND "high-risk pregnancy" OR "prenatal care." Different scientific databases were analyzed: MEDLINE (via PubMed), EMBASE and The Cochrane Library.

The inclusion criteria comprised studies published in English language, between 2007 and 2017 Experimental articles and case reports were excluded. Two independent researchers performed the search strategy in the scientific databases and, if there were disagreements regarding the final inclusion, a third senior researcher was consulted.

We found a total of 40 articles; 29 were accessed in full-text and selected for a qualitative synthesis (►**Fig. 1**). ►**Table 3** summarizes their methodologies, results and conclusions.

Results

Preconception Orientation

Adequate counselling, planning and care before, during and after the pregnancy must be the goal of health professionals who look after women with SLE. Luckily, multidisciplinary units are increasingly integrating different medical specialists (including obstetricians, immunologists, rheumatologists, hematologists and nephrologists), which may allow for a more coordinated management of pregnancy along with disease activity.[35]

The care of pregnant women with SLE must focus on three mainstays: a coordinated medical-obstetrical care, a well-defined management protocol and a well-structured

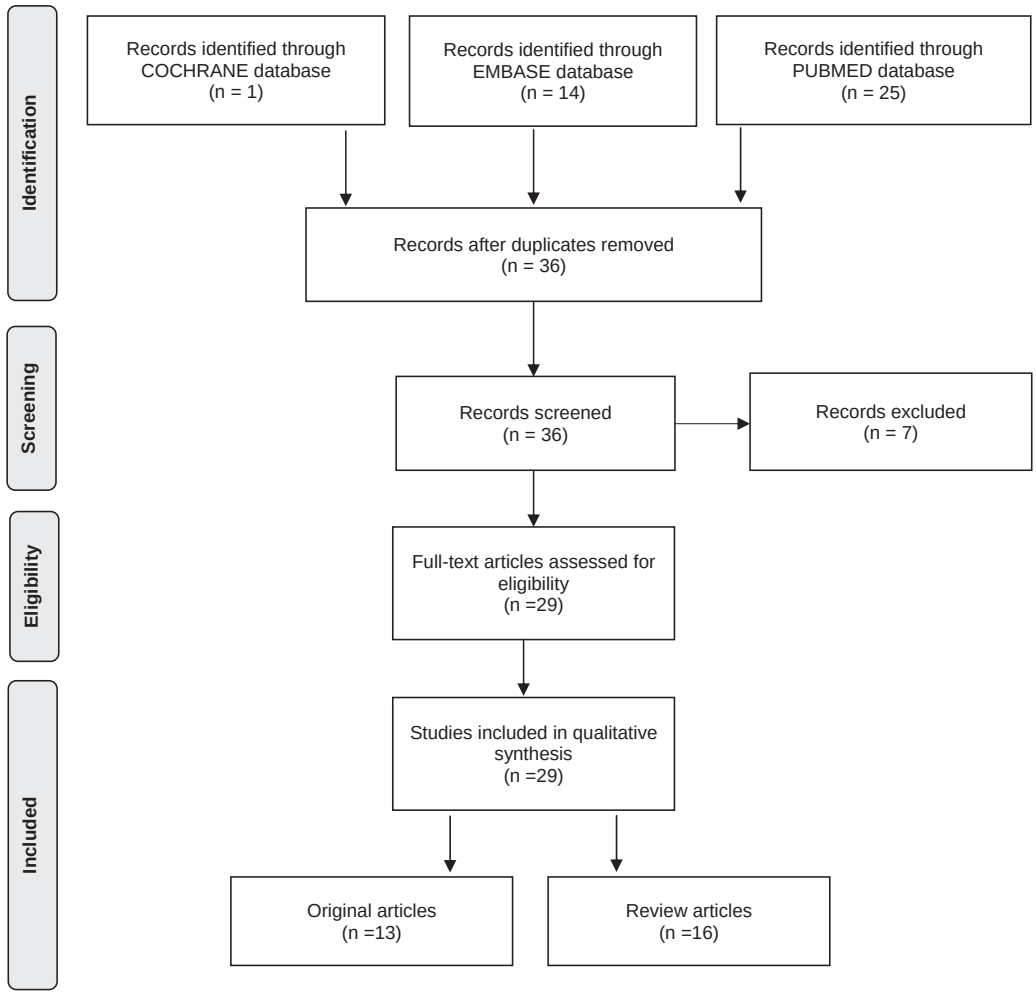

Fig. 1 PRISMA 2009 flow diagram for article's inclusion on obstetric follow-up of women affected by systemic lupus erythematosus.

Table 3 Original articles and review articles included on this integrative review

Original Articles			
Author, Year (Country)	**Study Design**	**Population Description**	**Main Results**
Zhan et al. (2017)[11](China)	Retrospective observational study	251 SLE patients with 263 pregnancies assisted at the First Affiliated Hospital of Sun Yat-Sen University, from 2001 to 2015.	APOs occurred in 70.0% of pregnancies, in which pregnancy loss in 28.5%; PTB in 21.3%; IUGR in 12.2%; and fetal distress in 8.0%. The use of antimalarial medications was associated with lower risk for APOs (OR 0.3, 95% CI 0.1–0.7, $p = 0.01$). Fetal umbilical artery Doppler in the third trimester showed higher resistance among SLE patients with APOs than the ones without APOs (2.9 ± 0.9 versus 2.4 ± 0.5, $p = 0.001$).
Simard et al. (2017)[12] (Sweden)	Retrospective observational study	742 births to women with SLE and 10,484 births to non-SLE women from the Swedish Lupus Linkage (SLINK) cohort, with at least one pregnancy/birth in the Medical Birth Register, from 2001 to 2012.	Among births to women with SLE, there were 32 (4.3%) diagnoses of early-onset PE, and among births to non-SLE women, there were 55 (0.5%). SLE was associated with an increased risk of early onset PE (RR 7.8, 95% CI 4.8–12.9, all pregnancies). The association remained similar upon restriction to women without pregestational hypertension.
Chiu et al. (2016)[13] (Taiwan)	Retrospective cohort study	Records of pregnant (1,526) and non-pregnant (2,932) women with SLE, and pregnant (3,052) and non-pregnant (3,052) women without SLE obtained from the Taiwan National Health Insurance Research Dataset, from 1997 to 2010.	Pregnant patients with SLE exhibited significantly increased risk of ESRD after adjusting for other confounders, like immunosuppressant and parity (HR = 3.19, 95% CI: 1.35 ± 7.52 for pregnant non-SLE; and HR = 2.77, 95% CI: 1.24 ± 6.15 for nonpregnant non-SLE patients). No significant differences in the ESRD incidence were observed in pregnant and nonpregnant SLE patients. Pregnant SLE patients exhibited better clinical condition at the baseline and a significantly lower risk of overall mortality than nonpregnant SLE patients.
Hussein Aly et al. (2016)[14](Egypt)	Prospective observational study	91 pregnancies (84 women) with SLE attending the antenatal clinic at the high-risk pregnancy unit at Cairo University Hospitals, from 2010 to 2015.	The most common manifestations of SLE were cutaneous (93%), articular (92%), lupus nephritis (53%), hypertension (39%) and secondary APS (38%). Incidence rates: abortion 15%, FGR 32%, PTB 13%, PE 12%, fetal death 8%, neonatal admission ICU 15%, LBW 22%, SLE antenatal flares 44%. There was association between hypertension and abortion ($p = 0.04$), PE ($p = 0.0001$) and SLE flares ($p = 0.0001$). Lupus nephritis and hypertension were predictors of PE ($p = 0.01$ and $p = 0.002$ respectively) and SLE flares ($p = 0.048$ and $p = 0.003$ respectively).
Tedeschi et al. (2016)[15](USA)	Retrospective observational study	114 SLE pregnant women referred to Brigham and Women's Hospital Lupus Center (Harvard Medical School), from 1990 to 2013.	Most pregnancies resulted in a live term delivery (76.5%). Factors significantly associated with adverse pregnancy outcomes were Nephritis (OR 3.6, 95% CI 1.0–12.8), cytopenias (OR 3.9, 95% CI 1.3–11.4), and serositis (OR 5.9, 95% CI 1.0–34.0).
Buyon et al. (2015)[16] (USA, Canada)	Prospective cohort study	385 patients (49% non-Hispanic white; 31% with prior nephritis) with SLE in the PROMISSE study, from 2003 to 2012	APOs occurred in 19.0% (95% CI, 15.2% to 23.2%) of pregnancies; fetal death in 4%, neonatal death in 1%, PTB in 9%, and SGA neonate in 10%. Severe flares in the second and third trimesters occurred in 2.5% and 3.0%, respectively. Baseline predictors of

(*Continued*)

Table 3 (*Continued*)

Original Articles			
Author, Year (Country)	**Study Design**	**Population Description**	**Main Results**
			APOs included presence of LAC (OR 8.32; CI 3.59 to 19.26), antihypertensive use (OR 7.05; CI 3.05 to 16.31]), and platelet count (OR 1.33; CI, 1.09 to 1.63 per decrease of 50 × 109 cells/L). Non-Hispanic white race was protective (OR 0.45; CI, 0.24 to 0.84). Maternal flares, higher disease activity, and smaller increases in C3 level later in pregnancy also predicted APOs. Among women without baseline risk factors, the APO rate was 7.8%. For those who were either LAC-positive or were LAC-negative but nonwhite or Hispanic and using antihypertensives, the APO rate was 58.0% and the fetal or neonatal mortality was 22.0%.
Chen et al. (2015)[17](China)	Retrospective observational study	83 pregnancies in 80 women with SLE attended at the Zhangzhou Affiliated Hospital of Fujian Medical University, from 2008 to 2013.	The sample was divided into three groups: group A (patients in remission for $>$ 6 months before pregnancy, proteinuria $<$ 0.5 g per day, without renal failure and discontinuation of cytotoxic drugs for $>$ one year); group B (patients with SLE disease activity in the six months before pregnancy); group C (patients with new onset SLE during pregnancy). In group A, 76.47% pregnancies achieved full-term deliveries and 80.39% achieved live born infants. In group B and C, the outcome was poor. Among 62 patients (64 pregnancies) diagnosed as SLE before pregnancy, SLE flares occurred in 27 (42.19%) pregnancies. SLE disease activity in the six months before pregnancy was significantly associated with lupus flare (OR 5.00, 95% CI 1.14–21.87, $p = 0.03$) and fetal loss. New onset lupus during pregnancy was independently associated with obstetric complications (OR 7.22, 95% CI 2.14–24.38, $p = 0.001$).
Jakobsen et al. (2015)[18] (Denmark)	Retrospective observational study	84 pregnancies in 39 women diagnosed with SLE referred to a Danish University Hospital during 1990–2010 (registered at the Danish National Registry)	SLE flares developed in 46.4%, PE in 8.3%, and HELLP syndrome in 4.8% of cases. Significantly higher rates of premature delivery ($p = 0.0032$), C-section ($p = 0.015$), hypertension ($p = 0.025$), and IUGR ($p = 0.003$) were found. Disease activity ($p = 0.021$) increased the risk of prematurity 3-fold. Two NLS and one congenital heart block were described. Birth weight and length were significantly lower in the SLE cohort.
Tedeschi et al. (2015)[19](USA)	Retrospective observational study	147 pregnancies among 113 women followed at the Brigham and Women's Lupus Center (Harvard Medical School), between 1990 and 2013.	Among women with organ-specific lupus activity during the 6 months before conception, the crude odds for the same type of activity during pregnancy was 7.7- to 32.5-fold higher compared with women without that type of activity immediately before conception.

Table 3 (*Continued*)

Original Articles			
Author, Year (Country)	**Study Design**	**Population Description**	**Main Results**
Madazli et al. (2014)[20] (Turkey)	Retrospective observational study	65 consecutive cases of SLE and pregnancy referred to a University Hospital, from 2002 to 2011.	Disease flare-up occurred in 7.7% of patients. Mean GA at delivery was 36.6 ± 4.2 and mean birth weight was 2,706 ± 927 g. Stillbirth, FGR, PE and PTB rates were 4.6, 18.5, 9.2 and 27.6%, respectively. Cases with uterine artery Doppler abnormalities had significantly poorer obstetric outcomes.
Fatemi et al. (2013)[21](Iran)	Retrospective observational study	72 pregnancies in 65 patients attending at Lupus Clinic in Isfahan University of Medical Sciences between 1998 and 2012.	No woman with LN experienced preterm Labor or stillbirth. 16 pregnancies either ended in abortion or experienced PE of which seven had LN. Lupus nephritis and positive ANA were related to PE, whereas age of SLE development was associated with preterm labor. LN was associated with PE and SLE flare.
Gaballa et al. (2012)[22](Egypt)	Case-control study	40 SLE pregnant women from inpatient and outpatient clinics of the rheumatology & rehabilitation and Ob&Gyn Departments of Zagazig University Hospitals; another 35 non-pregnant SLE patients attending rheumatology outpatient clinics were taken as a control group. The study was conducted from 2008 to 2010	Pregnant women comprised group A and non-pregnant women comprised group B. SLEDAI was increased in both groups, more in group A. Lupus flares were increased during pregnancy as it occurred in 62.5% of group A compared with 37.14% in group B. Severe flares were more frequent in group A. Gestational hypertension and SLEDAI showing disease activity were risk factors for poor maternal outcome. Fetal outcome included full term 37.5%, PTB 25%, FGR 22.5%, stillbirth 12.5%, abortion 7.5% and congenital heart block 2.5%. Factors associated with poor fetal outcome were severe flares and active renal disease. Full term pregnancy was more common in patients with no flares.
Surita et al. (2007)[23] (Brazil)	Observational cohort study	67 women with lupus (76 pregnancies) who received care at a tertiary clinic for high-risk pregnancies, at Universidade do Estado de Campinas, Brazil, between 1995 and 2002.	Flare-ups occurred in 85.3% of cases, especially when there was renal involvement (being the most significant). This was related to greater numbers of women with PE and poor perinatal outcome. In cases when there was active disease, IUGR was more common. The placental weight was significantly lower in the women with renal involvement. Flare-ups and renal involvement in lupus patients during pregnancy are associated with increased maternal and perinatal complications.

Review Articles			
Author, Year	**Type of Review**	**Main Results**	**Conclusions and Recommendations**
Knight and Nelson-Piercy (2017)[24]	Narrative review	SLE provides challenges in prepregnancy, antenatal, intrapartum, and postpartum periods for the medical, obstetric, and midwifery teams. Women are at risk of lupus flares, worsening renal impairment, onset of or worsening hypertension, PE, miscarriage, FGR, PTB, and/or neonatal lupus syndrome.	In pregnancy, early referral for hospital-coordinated care, involvement of obstetricians and rheumatologists, an individual management plan, regular reviews, and early recognition of flares and complications are all important. A C-section may be required in certain obstetric contexts (e.g., preterm delivery for maternal and/or fetal well-being), but vaginal birth should be the aim for the majority of women. Postnatally, an ongoing individual management plan remains important.
Lateef and Petri (2017)[25]	Narrative review	Outcomes for pregnancy in the setting of SLE have considerably improved but the maternal and fetal risks remain high. Disease flares, PE, pregnancy loss, PTB, FGR and neonatal lupus syndromes (especially heart block) remain the main complications.	Specific monitoring and treatment protocols need to be used for situations such as presence of specific antibodies (antiphospholipid antibodies and anti-SSA/SSB). Safe and effective treatment options exist and should be used to control disease activity during pregnancy. Close monitoring and judicious use of medications are the key to achieve optimal outcomes.
Ostensen (2017)[26]	Narrative review	Ideal conditions for pregnancy are conception at a stage of remission or minimal disease activity while on stable, pregnancy-compatible medication.	Points discussed during preconception counseling should be shared with all doctors and health professionals involved in the care of a pregnant patient. Address family planning in all patients of fertile age. Physicians should actively offer information on reproduction issues to all patients. Address medication concerns and the benefits of optimal disease control in pregnancy with all patients.
Moroni and Ponticelli (2016)[27]	Narrative review	Pregnancy is not contraindicated in women with SLE. However, pregnant patients with lupus nephritis may run increased risk of PE and PTB. The maternal and fetal outcome are strongly correlated with lupus activity, kidney function and the presence of aPL antibodies.	Ideally, a woman should plan a pregnancy only until her lupus has been under control for at least 6 months.
Yamamoto and Aoki (2016)[28]	Narrative review	Maternal and fetal risks are higher in females with SLE than in the general population. However, with appropriate management of the disease, sufferers may have a relatively uncomplicated pregnancy course.	Factors such as appropriate preconception counseling and medication adjustment, strict disease control prior to pregnancy, intensive surveillance during and after pregnancy by both the obstetrician and rheumatologist, and appropriate interventions play a key role.
Jesus et al. (2015)[29]	Narrative review	The risk of flares depends on the level of maternal disease activity in the 6–12 months before conception and is higher in women with repeated flares before conception, in those who discontinue useful medications and in women with active glomerulonephritis at conception.	It is a challenge to differentiate lupus nephritis from PE and, in this context, the angiogenic and antiangiogenic cytokines are promising. Prenatal care of pregnant patients with SLE requires close collaboration between rheumatologist and obstetrician. Planning pregnancy is essential to increase the probability of success.

Table 3 (*Continued*)

Review Articles			
Author, Year	**Type of Review**	**Main Results**	**Conclusions and Recommendations**
Singh and Chowdhary (2015)[30]	Narrative review	Established risk factors for adverse pregnancy outcomes include active disease within 6 months prior to conception and during pregnancy, active nephritis, maternal hypertension, antiphospholipid antibodies and hypocomplementemia.	Certain aspects such as prevention of PTB, treatment of congenital heart block due to neonatal lupus and recurrent pregnancy loss despite best management, remains challenging. Pregnant patients with SLE should be followed in a high-risk obstetric clinic, and care should be closely coordinated between the obstetrician and rheumatologist.
Lateef and Petri (2013)[31]	Narrative review	Although live births are achieved in the majority of the pregnancies in women with SLE, active disease and major organ involvement can negatively affect the outcomes. Disease flares during SLE pregnancy pose the unique issue of recognition and differentiation between physiologic changes and disease state. Similarly, PE and lupus nephritis may lead to diagnostic confusion.	A multidisciplinary approach, with close monitoring, is essential for optimal outcomes. Safe treatment options exist and should be appropriately used for disease activity during pregnancy.
Lateef and Petri (2012)[32]	Narrative review	Maternal and fetal mortality and morbidity are considerably increased among pregnancies with SLE, compared with the general population. Active maternal disease, renal involvement, specific autoantibody subsets and advanced organ damage are predictors of poor outcome.	Multidisciplinary care, close monitoring, high-risk surveillance, and judicious use of medications are essential to achieve good outcomes.
Stanhope et al. (2012)[33]	Narrative review	Renal involvement in the form of either active LN at the time of conception, or a LN new onset or flare during pregnancy increases the risks of PTD, PE, maternal mortality, fetal/neonatal demise, and FGR.	The major goal of immunosuppressive therapy in pregnancy is control of disease activity with medications that are relatively safe for a growing fetus. Therefore, the use of mycophenolate mofetil, due to increasing evidence supporting its teratogenicity, is contraindicated during pregnancy.
Baer et al. (2011)[34]	Narrative review	The frequency of pregnancy loss in lupus has dropped to a level commensurate with that of the general population. The outcomes of lupus pregnancies are better if conception is delayed until the disease has been inactive for at least 6 months, and the medication regimen has been adjusted in advance.	Monitoring should include baseline and monthly laboratory tests, serial ultrasonography, fetal surveillance tests, and fetal m-mode echocardiography for mothers with SSA (Ro) or SSB (La) antibodies. If hydroxychloroquine was in use before conception, it should be maintained throughout pregnancy. If a woman with SLE has antiphospholipid antibodies, prophylactic treatment with aspirin and/or low-molecular weight heparin is indicated to prevent fetal loss. Lupus flares during pregnancy are generally treated with hydroxychloroquine, low-dose prednisone, pulse intravenous methylprednisolone, and azathioprine. High-dose prednisone and cyclophosphamide are reserved for severe lupus complications.

(*Continued*)

Table 3 (*Continued*)

Review Articles			
Author, Year	**Type of Review**	**Main Results**	**Conclusions and Recommendations**
Ruiz-Irastorza and Khamashta (2011)[35]	Narrative review	Women with severe active disease or a high degree of irreversible damage, such as those with symptomatic pulmonary hypertension, heart failure, severe restrictive pulmonary disease or severe chronic renal failure should best avoid pregnancy.	Adequate pregnancy care of women with SLE rests on three pillars: a coordinated medical-obstetrical care, an agreed and well-defined management protocol and a good neonatal unit. Pregnancy should be planned following a preconceptional visit for counselling.
Buyon (2009)[36]	Narrative review	Flare rates are generally low for patients who are clinically stable at conception. For patients who have never had renal disease, there is no firm evidence that they will develop active renal disease simply due to being pregnant. For women with anti-SSA antibodies, the risk of having a child with congenital heart block is 2%, which rises to a recurrence rate of 18%.	For patients with aPL antibodies detected in the first trimester of pregnancy, the lupus anticoagulant is the strongest predictor of serious pregnancy complications.
Doria et al. (2008)[37]	Narrative review	Most SLE patients experience uncomplicated pregnancies. One of the major risks for SLE mothers is the occurrence of a disease flare during pregnancy. Another major risk of SLE relapse during pregnancy is glomerulonephritis, especially if active at the time of conception.	To reduce the risk of maternal and fetal complications, pregnancies must be planned when SLE is inactive and must be closely and appropriately monitored. Specific blood tests predict some pregnancy complications.
Clowse (2007)[38]	Narrative review	Pregnancy in a woman with SLE can be complicated by lupus activity and pregnancy mishaps. Recent studies found an increase in lupus activity during pregnancy, possibly worsened by hormonal shifts required to maintain pregnancy. An elevated risk for poor pregnancy outcomes, such as stillbirth, preterm birth, low birth weight and preeclampsia, is related to an increased lupus activity.	A rheumatologist and a high-risk obstetrician are best equipped to care for women with lupus who become pregnant. Careful planning and treatment may be required to achieve success of gestation.
Witter (2007)[39]	Narrative review	Interactions between SLE and pregnancy include the overall activity of lupus and pregnancy outcome, the effect of lupus nephritis on pregnancy, the effect of pregnancy on the progression of lupus nephritis, and the differentiation of hypertension related to lupus nephritis from PE.	A live birth can be achieved by close coordination of care between the patient's rheumatologist, obstetrician, and, in the case of renal involvement, her nephrologist.

Abbreviations: ANA, antinuclear antibodies; aPL, antiphospholipid; APOs, adverse pregnancy outcomes; APS, antiphospholipid syndrome; CI, confidence interval; ESRD, end-stage renal disease; FGR, fetal growth restriction; GA, gestational age; HR, hazard ratio; ICU, intensive care unit; IUGR, intrauterine growth retardation; LAC, lupus anticoagulant; LBW, low birth weight; LN, lupus nephritis; NLS, neonatal lupus syndrome; OR, odds ratio; PE, preeclampsia; PTB, preterm birth;; PTD, preterm delivery; RR, relative risk; SGA, small for gestational age; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

neonatal unit. Preconception counselling is vital to assess the chance of both potential fetal and maternal complications; that way, consistent information regarding specific risk for complications and the expected management plan should be provided (►**Table 3**).[35]

Pregnancy planning is a key-point for women with SLE. Postponing conception until the disease is considered inactive for at least six months significantly improves the outcomes of these pregnancies.[26,31,34,35] Women who present some form of irreparable organ injury are more likely to undergo complications and even additional damage during and after pregnancy. Some conditions should advise to delay pregnancy, such as severe disease flare within the previous six months, recent stroke and active lupus nephritis.[32] In some situations, pregnancy may be contraindicated (►**Table 4**).[26,34,35]

At the preconception visit, obtaining a complete set of autoantibody profile is recommended, including antiphospholipid (aPL) antibodies (anticardiolipin and lupus anticoagulant), complement serum levels, anti-SSA and anti-SSB antibodies. Evaluating the pregnancy risk and assessing the SLE activity and the organ function is important to maintain disease control only in safe medications.[32]

A higher risk of complications is found among women with severe impairment of organ function, with or without preexisting severe organ damage.[24] Besides, the diagnosis of SLE during pregnancy is also related to the occurrence of complications, significantly affecting maternal and fetal outcomes.[30]

Prenatal Follow-up

General Findings

The prenatal care of a woman with SLE requires close collaboration between the obstetrician and the clinicians (rheumatologist, nephrologist or hematologist), and management in a high-risk referral center. An evaluation by the clinician should occur every 4–6 weeks, whereas the obstetric visit should be every 4 weeks until 20 weeks of gestation; then, every 2 weeks until 28 weeks, and then, weekly until the expected delivery date.[34]

At every prenatal visit, blood pressure, weight gain, uterine size, fetal heart rate and urinalysis (through a quick outpatient analysis with the dipstick testing) should be assessed, as well as inquiring about symptoms related to lupus flares.[34]

The differential diagnosis of complications that may arise during pregnancy is not easy. Signs and symptoms of lupus flares often mimic the ones of normal pregnancy. Those flares are less frequent in the third trimester, although they may occur at any time during pregnancy or in the immediate postpartum period.[34]

Laboratory Evaluation during Prenatal Care

In addition to routine pregnancy booking, blood tests (which include a full blood count), baseline tests of renal and hepatic function and baseline urinary protein quantified by a 24-hour collection should be obtained.[24] Complement studies should comprise further tests (C3, C4, CH5O), anticardiolipin antibodies, anti-dsDNA, lupus anticoagulant and anti-SSA and SSB.

Disease Activity during Prenatal Care (Flares)

Changes in hormonal levels through pregnancy prompt to a shift from Th1 to Th2 lymphocyte dominance; consequently, autoimmune disorders involving Th2-response, such as SLE, are expected to flare.[24]

It is generally agreed that pregnancy may lead to higher rates of disease flares, with rates from 25 to 65% being reported.[18,31,37] Different organ systems may have variable response to pregnancy; musculoskeletal flares are less common, whereas renal and hematological flares are more common.[31] The risk of flare seems to be related to the occurrence of disease activity 6–12 months before conception.[15,19,22,24,30]

Table 4 Preconception visit checklist and contraindications to pregnancy in women with SLE[35]

Preconception visit checklist	Contraindications to pregnancy
Age?	Severe lupus flare within the previous 6 months
Any previous pregnancy?	Severe restrictive lung disease (FVC $<$ 1 L)
Previous pregnancy complications?	Heart failure
Presence of severe irreversible damage?	Chronic renal failure (Cr $>$ 28 mg/dL)
Recent or current lupus activity?	Stroke within the previous 6 months
Presence of antiphospholipid antibodies/syndrome?	Previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin
Other chronic medical conditions? (Hypertension, diabetes, etc.)	Severe pulmonary hypertension (estimated systolic PAP $>$ 50 mm Hg or symptomatic)
Current treatment: any “forbidden” drugs? (including cyclophosphamide, methotrexate, mycophenolate, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and statins)	
Positivity of anti-SSA /anti-SSB?	
Smoking?	

Abbreviations: FVC, forced vital capacity; PAP, pulmonary arterial pressure.

A higher risk of flare during pregnancy is noticed when lupus nephritis occurs at conception, even in women in remission.[13,21,24,30] One study showed a 30% flare rate during pregnancy or postpartum among 113 pregnancies in women with preexisting lupus nephritis evaluated; other studies suggest a likelihood of up to 60%.[24] Besides, different reports in the literature indicate lupus nephritis as a predictive of poor prognosis for pregnancy.[23]

It may be difficult to distinguish pregnancy-related signs and symptoms from those of SLE. Therefore, an appropriate assessment by experienced physicians is important.[24,37,38] Ambiguous manifestations include fatigue, headaches, arthralgia, edema, hair loss, dyspnea, malar and palmar erythema, anemia and thrombocytopenia. Hence, baseline blood counts and urinalysis with measurement of proteinuria assessed early in gestation are helpful to monitor disease status and identify flares.[24]

During pregnancy, liver production of serum C3 and C4 increases, so their levels may persist within the range of normality in cases of active SLE. Relative variations are more important, rather than absolute levels, with a drop of $\geq$ 25% in serum complement levels suggesting lupus flare.[24]

Pregnancy-specific disease activity scales (such as systemic lupus erythematosus pregnancy disease activity index [SLEPDAI] and lupus activity index in pregnancy [LAI-P]) have been developed, but mostly remain as research tools. In practice, the clinical judgment of an experienced clinician is still considered the gold standard.[25,31,32] The SLEPDAI scale is a similar instrument to the systemic lupus erythematosus disease activity index (SLEDAI) for assessment of lupus activity, assigning different scores for the various clinical and laboratory manifestations of lupus activity, however taking into account the physiological changes of gestation and the main pathologies of the pregnancy-puerperal cycle that can mimic SLE in activity. Its score ranges from zero to 105 and stratifies the disease activity: absent (up to 4 points), mild to moderate (5–12 points) and severe (up to 12 points) (►**Table 5**).[36]

A recent meta-analysis reported rates ranging from 1.5 to 83% for a lupus nephrites flare during pregnancy,[33] corroborating with data from previous studies.[38] Thus, it is strongly recommended a close monitoring, with monthly assessments of disease activity (with special attention to renal function). Besides, the risk of hypertensive disorders of pregnancy increases in the setting of active lupus nephritis.[14,33]

The frequency of preeclampsia varies from 7.5 to 22.5% for all women with SLE.[12,15,18,20,39] Lupus renal involvement is often associated with hypertension, and the preeclampsia diagnosis is difficult, since it may be superimposed on chronic hypertension.[39]

Likewise, in cases of SLE women with glomerular lesions, increased proteinuria may be observed, due to the enlarged glomerular filtration rate during pregnancy, with this fact not being related to preeclampsia. Thus, the diagnosis of preeclampsia can get more difficult because of increasing blood pressure and proteinuria at term.[38,39]

The differential diagnosis of preeclampsia in lupus patients may be facilitated by changes in the measures of C3, C4 and CH50, since a reduction in those levels is expected during lupus activity.[39] Other laboratory test findings may be helpful to successfully perform a differential diagnosis: abnormal urinary sedimentation with the presence of erythrocyte dysmorphism or cell casts and increased anti-DNA antibody titers (all found in lupus nephritis).[23]

New onset SLE during pregnancy can be considered as SLE activity and might be associated with worse outcome. Differentiating the diagnosis of preeclampsia from new onset SLE during pregnancy is a challenge and frequently delays the diagnosis of SLE. However, a Chinese study indicated that new onset SLE during the third trimester of pregnancy might have a better outcome.[17]

Among patients with stable condition at the time of conception, it is expected that disease activity will not worsen, and even if so, the flare is usually mild and occasionally involves some kind of treatment modification.[28]

Evaluation of Fetal Growth and Vitality

Fetal complications are frequently observed in patients with SLE. Overall, miscarriages and stillbirth may occur in $\sim$ 20% of pregnancies in SLE patients.[11,15,26,30] Patients with a history of nephritis, in special, have an increased risk for such adverse outcomes.[14,16]

The rate of FGR is estimated to be near of 30%, observed even in mild disease, with an increased risk if there is renal involvement. Small-for-gestational-age is a more common outcome in those born prematurely, but can occur at all gestational ages.[20,22,37,39] Several studies concluded that the small-for-gestational-age rate outcome among SLE women tends to be higher, condition strongly associated to the presence of disease flare-ups during pregnancy.[23]

Serial obstetric sonography is the most important method to guide surveillance for fetal growth. Crown–rump length measurement in the first trimester presents as the most precise measurement. At 16 to 22 weeks of gestation, an anatomic survey considering diagnosis of fetal anomalies should be followed, also serving to allow the first monitoring of growth. At each 4-week periods, new scans should take place, with measurement of amniotic fluid volume. If preeclampsia or FGR are diagnosed, the interval can be reduced to 3 weeks.[39]

Fetal vitality surveillance is an important part of the prenatal care of SLE patients. This should include the nonstress test (NST), the biophysical profile (BPP), and fetal umbilical artery Doppler velocimetry, starting at 26 to 28 weeks and continuing weekly until birth.[39]

In patients with SLE, alterations of umbilical artery Doppler velocimetry should be managed similarly to those without the condition. Normal evaluation of these tests has a high negative predictive value for fetal death.[29] Association between abnormal uterine artery Doppler and later fetal loss, preeclampsia, FGR and preterm labor were also described.[29]

Because of the risk of fetal congenital heart block, for women with anti-SSA/SSB antibodies, a fetal echocardiography should be performed at 18–20 weeks and 26–28 weeks to exclude fetal congenital heart block. An urgent referral to a tertiary care center should be prompted in case of any fetal heart rate abnormality, mostly a slow heart rate.[24]

Table 5 Systemic lupus erythematosus pregnancy disease activity index (SLEPDAI) instrument to stratify SLE activity during pregnancy[36]

Score	Descriptor	Modified for pregnancy	Considerations
8	Seizure	Yes	(r/o eclampsia)
8	Psychosis	No	
8	Organic brain syndrome	No	
8	Visual disturbance	No	(hypertension is already considered an exclusion in SELENA-SLEDAI and SLEDAI)
8	Cranial nerve disorder	Yes	(r/o Bell palsy)
8	Lupus headache	Yes	(r/o Bell palsy)
8	CVA	Yes	(r/o eclampsia)
8	Vasculitis	Yes	(consider palmar erythema)
4	Arthritis	Yes	(consider bland knee effusions)
4	Myositis	No	
4	Urinary casts	No	
4	Hematuria	Yes	(r/o cystitis and vaginal RBC reflective of placental problems)
4	Proteinuria	Yes	(r/o eclampsia)
4	Pyuria	Yes	(r/o infection)
2	Rash	Yes	(consider chloasma)
2	Alopecia	Yes	(consider normal postpartum alopecia)
2	Mucosal Ulcers	No	
2	Pleurisy	Yes	(hyperventilation may be secondary to progesterone, dyspnea secondary to enlarging uterus)
2	Pericarditis	No	
2	Low complement	Yes	(complements normally rise during pregnancy)
2	Increased DNA binding	No	
1	Thrombocytopenia	Yes	(r/o preeclampsia, HELLP syndrome, incidental thrombocytopenia of pregnancy)
1	Leukopenia	Yes	(consider normal rise of leukocyte count during pregnancy)
1	Fever	No	

Abbreviation: CVA, cerebrovascular accident; RBC, red blood cell; r/o: rule out, SELENA-SLEDAI, safety of estrogens in lupus erythematosus national assessment- systemic lupus erythematosus pregnancy activity index; SLEDAI, systemic lupus erythematosus pregnancy activity index.

Recommended SLE Treatment during Pregnancy

Considering the harmful effects of active disease on both mother and fetus, an appropriate reflection between the risks and benefits of this treatment must take place.[26,30]

In practice, it is frequent that SLE women to discontinue their medication before conception, due to fear of fetotoxicity, without proper doctor counseling. However, discontinuation of the medication may lead to active SLE and unfavorable pregnancy outcomes.[28]

Usually, the immunosuppressive treatment in pregnant women with quiescent lupus should not be changed. The most frequently used agents in lupus patients are glucocorticoids and hydroxychloroquine, which should be maintained.[27]

Prednisone at a dosage of 5–10 mg per day is usually considered safe.[27] Lupus flares that fit into mild activity can be treated with low-dose prednisone (less than 20 mg/d). Higher doses of corticosteroids, including pulse dose steroids, are options to treat moderate to severe lupus activity.[37,38]

Hydroxychloroquine is not a teratogenic drug. Its use is recommended to prevent disease activity and reduce the risk of cardiac-neonatal lupus in patients who are carriers of anti-SSA/-antibody.[11,27,28] In addition, it improves the prognosis of SLE nephritis and prevents death.[38]

Azathioprine is considered safe, especially if compared with other immunosuppressive drugs. Many studies sustain a transition to this option if the patient wishes to conceive. However, some other reports recently pointed out concerns about late developmental delays in children who were exposed to azathioprine during pregnancy,[28,38] as well as neonatal leucopenia and/or thrombocytopenia.[27]

Regarding cyclosporine and tacrolimus, the FDA classifies as category C; however, some meta-analysis studies did not find significant differences related to birth defects when pregnant women were exposed to them.[27,37]

Cyclophosphamide should not be prescribed during the first trimester, because of its association to chromosomal

impairment. During the second or third trimester, it should be reserved only to severe flares unamenable with methylprednisolone pulses or other drugs. The use of cyclophosphamide during the second and third trimesters does not seem to increase the risk for congenital abnormalities. Nevertheless, miscarriages and preterm birth may be more frequent.[27,37]

Leflunomide is associated to teratogenic and fetotoxic effects in animals, and its metabolite is detectable in plasma up to 2 years after discontinuation. Thus, in pregnant women, it is formally contraindicated; and pregnancy must be excluded before starting it.[27]

Methotrexate is another teratogenic drug, classified by the FDA as X (contraindicated in pregnancy). If used in the first trimester, it is associated to FGR and some major malformations, such as absence or hypoplasia of the frontal bones, craniosynostosis, large fontanelle and ocular hypertelorism.[27]

During the first trimester, rituximab has very low transplacental transfer, with some studies reporting safe pregnancies and deliveries in those cases of exposure. However, during the second or third trimester, it can cross the placenta and induce severe neonatal lymphopenia.[27,37] Hence, in these cases, live vaccines should be avoided in those children during the first 6 months of life.[27]

Handling some complications that often affect pregnant women with SLE justifies a short statement. Since arterial hypertension is a common condition among patients with lupus nephritis, an appropriate management of blood pressure in pregnancy may reduce the progression of the disease and avoid several adverse pregnancy outcomes. Labetalol, nifedipine or methyldopa are safe drugs for treating hypertension. Angiotensin-converting-enzyme inhibitors should be avoided due to their association to multiple congenital abnormalities.[27]

Low-dose aspirin is recommended, since it reduces the risk of preeclampsia and perinatal death; besides, it is associated with an increase in the birth weight of those with risk factors, including renal disease. Full anticoagulation with low-molecular weight heparin (LMWH) is recommended if there has been a previous thromboembolic event.[27]

Calcium supplementation is required, mainly for those women in use of corticosteroids and heparin. Supplemental vitamin D does not reduce the risks of unfavorable outcomes.[25]

Delivery Assistance

Women with SLE have an increased risk of preterm delivery. This may occur spontaneously or because of maternal and/or fetal complications (such as severe lupus flare, preeclampsia and FGR).[24]

In gestational age between 24 weeks and 34 weeks and 6 days, accelerating of fetal lung maturation is essential, with two intramuscular steroid injections (preferably, betamethasone), independently of any maternal steroids administrated before.[24]

Magnesium sulfate should be considered when gestational age is < 32 weeks, due to its neuroprotective benefits to the fetus. As it is well known, it ought to be administrated in cases of severe preeclampsia.[24]

The aim in a pregnant SLE patient should be to accomplish a spontaneous labor at term with vaginal delivery. However, available data have revealed that women with SLE are more expected to undergo a cesarean section ($> 33\%$; odds ratio [OR] 1.7; confidence interval [CI] 95% 1.6–1.9). In spite of that, it is recommended that C-sections should be reserved only for obstetric indications, due to its extra risk factor for venous thromboembolism (VTE), blood loss and infection, as well as repercussions for future gestations.[24]

Adjusting maternal medication for labor may be required. Intravenous hydrocortisone may be necessary to overcome the physiological stress of labor if long-term oral steroids have been taken. If a woman receives standard prophylactic LMWH, it should be discontinued at the onset of spontaneous labor, as well as on the night before induced labor or elective cesarean section. Regional anesthesia (epidural or spinal) can be performed 12 hours after the last LMWH dose.[24]

Postpartum Care

Rigorous monitoring for severe maternal exacerbations is strongly recommended for those who had anticipated delivery because of a SLE flare or coexisting preeclampsia. The treatment for postpartum active SLE is similar to that for nonpregnant women. Nonetheless, it should be noticed that several medications for aggressive therapy are not recommended during breastfeeding. Thus, the risks and benefits of continuing breastfeeding must be clarified to the lactating mother.[28]

All women who received antenatal LMWH should continue its use for 6 weeks postpartum, in a prophylactic dosage, since puerperium is also a period of increased VTE risk. Afterward, the postpartum VTE risk should be assessed.[24]

In patients with SLE, postpartum counseling to offer safe contraception is particularly important. Good choices are long-acting reversible contraception (LARC) methods. They are considered reliable and less dependent on patient commitment.[24] Progestogen-only methods are safe and may become a suitable option.[24]

Estrogen-containing contraceptives must not be used by women with aPL antibodies or antiphospholipid syndrome (APS), moderate to severe active SLE (including lupus nephritis) and some other conditions, such as hypertension, smoking, obesity or previous VTE, since they increase a woman's VTE risk. In cases of well-defined SLE with stable and/or low-active disease, the use of combined oral contraceptive may be suitable if wished.[24] Barrier methods present a high failure rate (15–32%); thus, they should not be used as single methods.[24]

Discussion

It is well established that pregnant women with SLE present a higher risk for maternal complications and pregnancy wastage, in spite of significant progress concerning success rates lately. During pregnancy, the disease activity may worsen and consequently rise the risk of other maternal and fetal complications. Therefore, holding an adequate control of disease activity and treating flares quickly must be a core-objective during prenatal care.

Multidisciplinary care, coordinated by obstetricians and clinicians, with close monitoring, should allow for early diagnosis of complications.

Considering the data obtained on this review, the disease activity should be systematically evaluated by SLEDAI,[25,31,32,36] since it presents as the factor that guides adjustment or change in medication. All pregnant women with clinical suspicion of active or poorly controlled disease should be hospitalized due to the severity of the maternal condition and fast deterioration of fetal vitality conditions that may be associated with this event.[24,25]

Regarding the appropriate treatment, prednisone is an immunosuppressant that can be safely used during pregnancy. The association with gestational diabetes in lupus is low and is not a limiting factor for the use of medication. However, pregnant women using high doses should be screened for gestational diabetes.[24] Hydroxychloroquine may be used during gestation, since it is associated with reduced disease activity.[27,40,41]

Azathioprine, tacrolimus and cyclosporine could be used as a therapeutic option in cases resistant to prednisone. Nonsteroidal anti-inflammatory drugs, leflunomide, cyclophosphamide, methotrexate and mycophenolate mofetil should not be prescribed.[27,28,37,40,41]

Furthermore, prophylaxis of preeclampsia should be performed with AAS 100mg/d between 12 and34 weeks of gestation and calcium carbonate 1.5 g/d throughout the entire gestational period.[24,40]

We strongly recommend follow-up of fetal growth and vitality with serial sonography (at least one per trimester), Doppler velocimetry assessment from 26 weeks (repeated every 2 weeks if normal and weekly if altered), NST from 28 weeks and fetal echocardiography between 24 and 30 weeks for patients with anti-SSA.[29,39,42]

Labor delivery must be determined according to obstetric indication and should occur no later than full-term. In the cases of patients taking corticosteroids at immunosuppressive dose (1 mg/kg), we recommend prophylactic antibiotics due to the risk of infections and sepsis.[27,31]

Contraceptive counseling may include LARC or progestogen-only methods and surgical sterilization (with social or medical indication). Combined oral contraceptives present relative contraindication, considering the risk of VTE.[24,40]

After all, it is important to notice that the present study had some limitations: randomized trials did not integrate this review, which would certainly increase its degree of evidence. However, it should be emphasized that SLE in pregnancy is a condition whose incidence is not so high, which could justify the lack of these trials. In addition, one cannot deny the existence of a publication bias, with often the best results disclosed to the scientific community.

On the other hand, there are strengths of this study that should be underlined: a wide variety of studies performed in different countries, with the opinions of several experts, each with varied backgrounds, were part of this integrative review. Besides, the lack of available meta-analysis reinforces the importance of including other reviews made by these specialists.

Conclusion

In conclusion, SLE pregnant women present an increased risk for maternal complications, pregnancy loss and other adverse perinatal outcomes. The diagnosis of the disease during pregnancy may be highly difficult, as well as the identification of worsening disease activity. These conditions, therefore, increase the risk of other maternal-fetal complications. Thus, close prenatal care, multidisciplinary team, adequate control of disease activity and treating flares quickly should be a central goal for better results

Conflicts of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Treatment of Non-neurogenic Overactive Bladder with OnabotulinumtoxinA: Systematic Review and Meta-analysis of Prospective, Randomized, Placebo-controlled Clinical Trials*

*Tratamento da bexiga hiperativa não neurogênica com toxina botulínica A: revisão sistemática e metanálise de ensaios clínicos prospectivos, randomizados e placebo-controlados**

Raquel Martins Arruda[1] Claudia Cristina Takano[1] Manoel João Batista Castelo Girão[1]
Jorge Milhem Haddad[2] Gabriel Francisco Aleixo[3] Rodrigo Aquino Castro[1]

[1] Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil
[2] Universidade de São Paulo (USP), São Paulo, SP, Brazil
[3] Universidade do Oeste Paulista, Presidente Prudente, SP, Brazil

Address for correspondence Rodrigo de Aquino Castro, Universidade Federal de São Paulo, Rua Botucatu, 720, 04023-062, São Paulo, SP, Brazil (e-mail: rodrigo.castro@uol.com.br).

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Abstract

We performed a systematic review and meta-analysis of randomized placebo-controlled trials that studied non-neurogenic overactive bladder patients who were treated with 100 units of onabotulinumtoxinA or placebo. The primary purpose of our study was to evaluate the clinical effectiveness with regard to urinary urgency, urinary frequency, nocturia, and incontinence episodes. Our secondary purpose consisted of evaluating the adverse effects. Our initial search yielded 532 entries. Of these, seven studies met all the inclusion criteria (prospective, randomized, placebo-controlled studies, $\geq$ 3 points on the Jadad scale) and were selected for analysis. For all primary endpoints, the toxin was more effective than placebo ($p < 0.0001$; 95% confidence interval [95CI]), namely: urgency (mean difference = -2.07; 95CI = [-2.55–1.58]), voiding frequency (mean difference = -1.64; 95CI = [-2.10–1.18]), nocturia (mean difference = -0.25; 95CI = [-0.39–0.11]) and incontinence episodes (mean difference = -2.06; 95CI= [-2.60–1.52]). The need for intermittent catheterization and the occurrence of urinary tract infection (UTI) were more frequent in patients treated with onabotulinumtoxinA than in patients treated with placebo ($p < 0.0001$). Compared with placebo, onabotulinumtoxinA had significantly and clinically relevant reductions in overactive bladder symptoms and is associated with higher incidence of intermittent catheterization and UTI.

Keywords

- overactive bladder
- systematic review
- botulinum toxin
- randomized controlled trials

Resumo

Realizou-se revisão sistemática e metanálise de estudos clínicos prospectivos, randomizados e placebo-controlados que comparavam a toxina botulínica ao placebo no tratamento da

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bexiga hiperativa. O objetivo primário desta metanálise foi avaliar a eficácia da toxina botulínica em relação à urgência urinária, frequência miccional, noctúria e episódios de incontinência. O objetivo secundário foi avaliar os efeitos adversos. Selecionamos estudos que incluíram somente pacientes com bexiga hiperativa não-neurogênica tratada com 100 unidades de onabotulinum toxina A ou placebo (grupo controle). Foram encontrados 532 estudos após as buscas iniciais, dos quais sete apresentaram todos os critérios de inclusão (estudos prospectivos, randomizados, placebo-controlados, ≥ 3 pontos na escala de Jadad) e fizeram parte desta análise. Para todos os objetivos primários a toxina foi mais eficaz do que o placebo, com $p < 0,0001$ e intervalo de confiança (IC) de 95%: urgência (diferença média = -2,07, IC = [-2,55; -1,58]), freqüência miccional (diferença média = -1,64, IC = [-2,10; -1,18]), noctúria (diferença média = -0,25, IC = [-0,39; -0,11]) e episódios de incontinência (diferença média = -2,06, IC= [-2,60; -1,52]). A necessidade de cateterização intermitente e a ocorrência de infecção urinária (ITU) foram mais frequentes no grupo toxina na comparação com o grupo placebo ($p < 0,0001$). A toxina botulínica promoveu melhora significativa dos sintomas de bexiga hiperativa na comparação com o placebo. Entretanto, está associada a uma maior incidência de cateterismo intermitente e infecção do trato urinário.

Palavras-chave
- bexiga hiperativa
- revisão sistemática
- incontinência urinária
- toxina botulínica
- estudos randomizados controlados

Introduction

The International Continence Society defines overactive bladder as a syndrome characterized by urinary urgency, with or without urgency urinary incontinence, usually accompanied by nocturia and an increase in urinary frequency, in the absence of infection, metabolic or local factors.[1]

Different population studies concluded that overactive bladder is highly prevalent both in males and females, with relevant negative impact on the patients' quality of life (social, physical, psychological, sexual, personal relationships, work, and domestic domains); moreover, it has a considerable financial impact on patients themselves and thus on the health care system.[2–5]

Patients who do not satisfactorily respond to behavioral and/or pharmacological treatment are diagnosed with refractory overactive bladder. This group includes patients with contraindications and intolerable side effects to medication.[6]

While both the European Association of Urology (EAU) and the American Urological Association (AUA) recommend intravesical injection of botulinum toxin A in refractory overactive bladder cases, a vast majority of articles discusses only neurogenic cases of this dysfunction.[7,8]

Our systematic review followed by meta-analysis included only non-neurogenic overactive bladder patients who were treated with 100 units of onabotulinumtoxinA.

Methods

Our study was registered in the PROSPERO database in 2016, under the reference number CRD42016035815.

Prospective randomized placebo-controlled studies featuring Jadad scale methodological quality ≥ 3 were selected.[9] The study populations should necessarily include patients aged 18 years or older with a diagnosis of non-neurogenic overactive bladder syndrome treated with 100 units of onabotulinumtoxinA, at least in one of the arms of the study.

Patients with mixed urinary incontinence and a clear prevalence of overactive bladder complaints were also included. Performance of urodynamic study was not considered a prerequisite for inclusion in our analysis, since overactive bladder diagnosis is clinically suspected and detrusor overactivity may or may not be present. The exclusion criteria comprised use of a dose other than 100 units of onabotulinum toxin A, use of botulinum toxin other than onabotulinumtoxinA, neurogenic cases and literature or systematic reviews.

Primary Outcomes

The primary outcome of our study was to evaluate the clinical effectiveness with regard to the following variables: urgency (complaint of a sudden compelling desire to pass urine that is difficult to defer),[1] urinary frequency (complaint by the patient who considers that he/she voids too often by day),[1] nocturia (complaint that the individual has to wake up at night one or more times to void),[1] and incontinence episodes (complaint of any involuntary leakage of urine).[1]

Secondary Outcomes

The secondary outcome was to evaluate all adverse effects reported in the studies included in the meta-analysis.

Study Search and Selection

We performed a search for randomized clinical trials (RCTs) in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE.

The MEDLINE search included the following terms: "overactive bladder," "detrusor overactivity," "bladder overactivity," "botulinum toxin," "onabotulinumtoxinA" and "botox."

Only studies in English were selected, and the search was done from the inception of the database, given that the use of botulinum toxin in the treatment of non-neurogenic overactive bladder is relatively recent. Two authors (R. M. A. and C. C. T.) independently reviewed all the abstracts and titles to select the papers that were relevant for review, later analyzing the full

text of the selected studies to determine eligibility. The last online search was performed on June 20th, 2015. A spreadsheet for data collection was created to extract the data of interest in each article, which were then retyped in a single database to avoid loss of data or mistyping of any kind. Any disagreements were resolved by consulting a third author (R. A. C.). Outcomes verified in two articles or more were grouped for meta-analysis.

Statistical Analysis

We summarized binary outcomes based on the number of events using Peto odds ratio in situations with zero number of events in one of the groups, or the Mantel-Haenszel method in situations of a very low event rate. Furthermore, we summarized continuous outcomes (incontinence, urgency, frequency and nocturia) using the mean difference (MD), calculated by the inverse variance method. Precision of estimates appear as 95% confidence intervals (95CIs).

Heterogeneity across studies was evaluated using Cochran Q statistic and Higgins I2.[10] We quantified statistical heterogeneity using I2, informing its value together with the estimates. We considered I2 elevated whenever it was higher than 60%. However, a fixed-effect model was considered when a very small number of studies were included.[10]

In addition to the heterogeneity analyses described above, sensitivity analyses excluding one study at a time were performed to evaluate the influence of individual studies on the overall result. We used the RevMan 5.3 statistical package (Nordic Cochrane Center, Copenhagen, Denmark) to perform the analysis.

Quality Assessment

The quality of studies included in the analysis was independently assessed by two authors (R. M. A. and C. C. T.) using the Jadad scale for RCTs classification.[9] Studies scoring ≥ 3 were considered eligible for inclusion. Any disagreements were resolved by consulting a third author (R. A. C.).

The Jadad scale assesses the quality of published clinical trials based on methods relevant to random assignment, double blinding, and patient flow. There are seven items, but points may be deducted in the last two, which means that the range of possible scores is 0 (bad) to 5 (good).[9] The bias risk was assessed by the use of a Cochrane collaboration tool.[1]

Results

Description of Studies

►**Fig. 1** describes the flow chart for this review. Five hundred and thirty-two articles were retrieved after research on the Cochrane and Medline databases, using the keywords "overactive bladder" OR, "detrusor overactivity" OR "bladder overactivity" AND "botulinum toxin" OR "onabotulinumtoxinA" OR "botox."

Out of those, 333 articles were selected after reading the title and abstract, whereas 271 were excluded since they did not meet selection criteria. Therefore, 62 articles were considered eligible and read in full by two authors. After this initial reading, 53 articles were excluded for using onabotulinumtoxinB and/or for including patients with neurogenic overactive bladder. Eventually, 9 studies met all the inclusion criteria and were selected for this meta-analysis (►**Fig. 1** and ►**Table 1**)

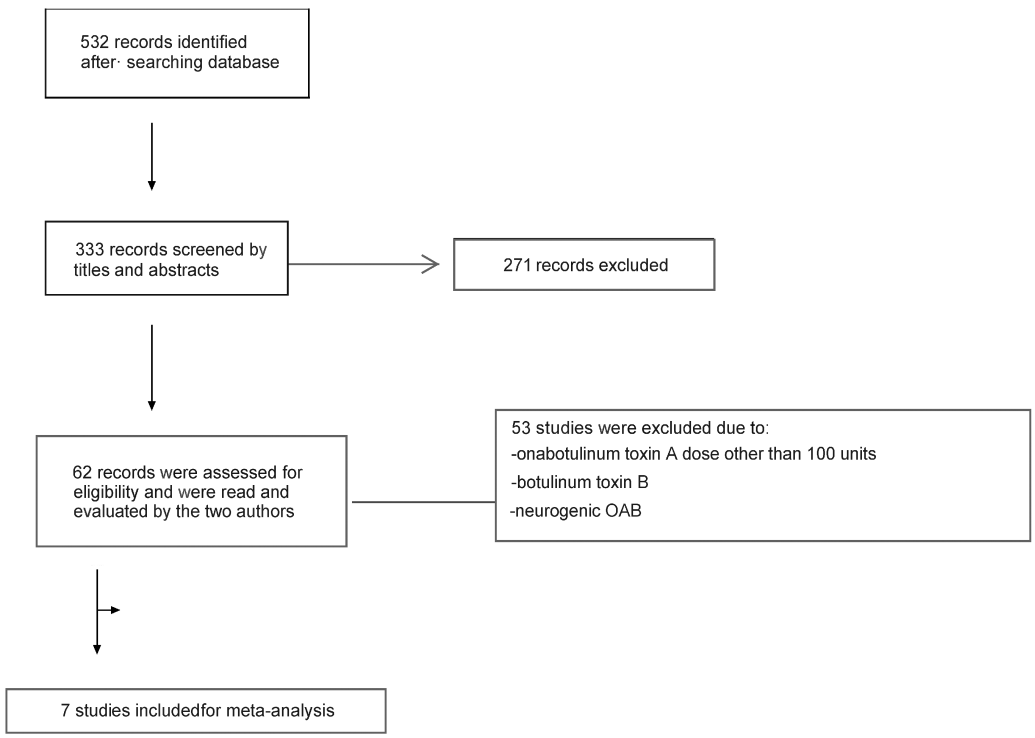

Fig. 1 Flow diagram of article selection.

Table 1 Articles included in the meta-analysis

References	Study design	Jadad scale	N placebo/toxin	Weeks follow-up
Chapple et al.[11]	Multicenter, randomized, double-blind	5	271/277	12
Denys et al.[12]	Multicenter, randomized, double-blind	5	29/70	24
Dmochowski et al.[13]	Multicenter, randomized, double-blind	5	43/268	36
Dowson et al.[14]	Single-center, randomized, double-blind	5	11/10	24
Flynn et al.[15]	Single-center, randomized, double-blind	5	7/15	6
Nitti et al.[16]	Multicenter, randomized, double-blind	5	44/54	36
Rovner et al.[17]	Multicenter, randomized, double-blind	5	44/269	36

Two studies could be included for analysis of urinary urgency, urinary frequency, nocturia, and incontinence episodes. There was no evidence of heterogeneity among the articles, except for urinary incontinence. However, because the number of articles is very small, the fixed-effect model was considered.

It can be observed in ►**Fig. 2** that there was significant reduction in urinary urgency episodes in the toxin group (experimental group) in comparison with the placebo group (control group) (MD = -2.07, 95CI = [-2.55; -1.58]; $p < 0.0001$).

►**Fig. 3** shows that there was significant reduction in urinary frequency in the toxin group (experimental group) when compared with the placebo group (control group) (MD = -1.64, 95CI = [-2.10; -1.18]; $p < 0.0001$).

A similar result was observed in analyzing nocturia episodes (►**Fig. 4**). There was significant reduction in nocturia in the toxin group (experimental group) in relation to the placebo group (control group) (MD = -0.25, 95CI = [-0.39; -0.11]; $p < 0.0001$).

In ►**Fig. 5** we further confirmed that there was significant reduction in the number of urinary incontinence episodes in the toxin group (experimental group) in relation to the placebo group (control group) (MD = -2.06, 95CI = [-2.60; -1.52]; $p < 0.0001$).

Secondary Purposes

Adverse Effects of Catheterization

For analysis of vesical catheterization occurrence, it was possible to include five studies. According to the data (►**Fig. 6**), it is possible to verify that the need for catheterization was significantly higher in the toxin group (experimental

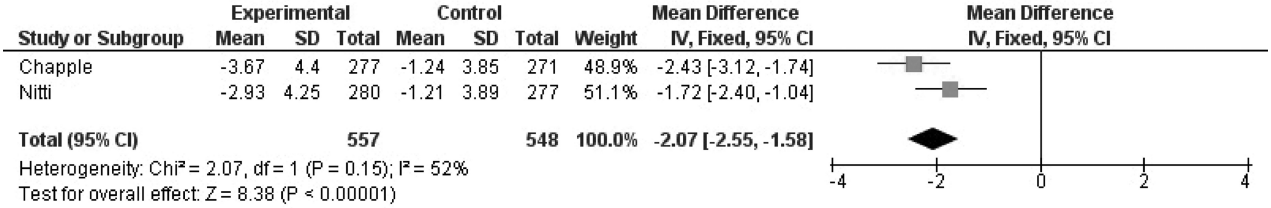

Fig. 2 Forest plot of change in urgency after onabotulinumtoxinA (experimental) and placebo (control) injections.

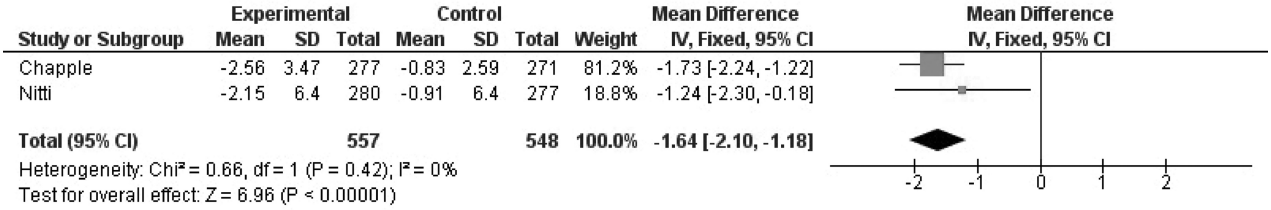

Fig. 3 Forest plot of change in frequency after onabotulinumtoxinA (experimental) and placebo (control) injections.

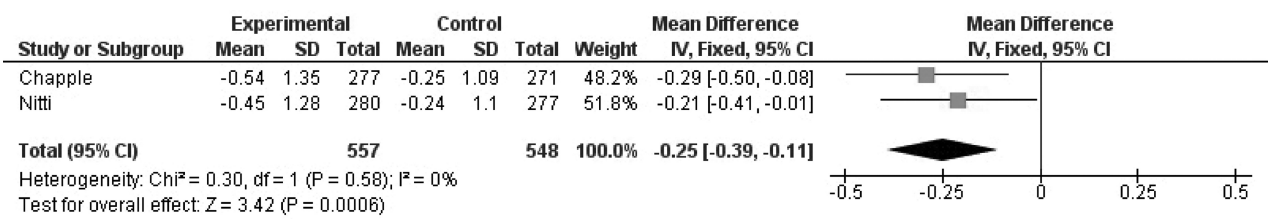

Fig. 4 Forest plot of change in nocturia episodes after onabotulinumtoxinA (experimental) and placebo (control) injections.

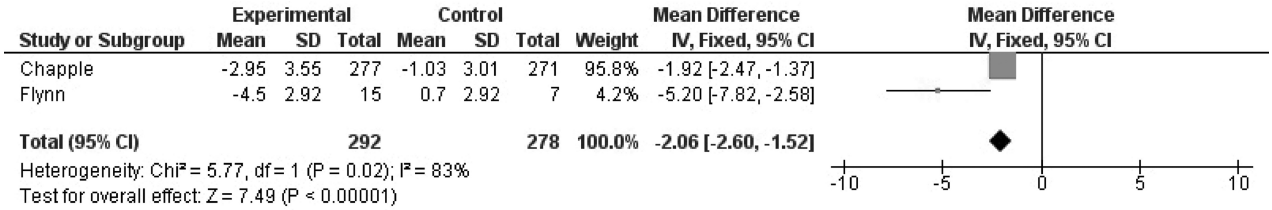

Fig. 5 Forest plot of change in urinary incontinence episodes after onabotulinumtoxinA (experimental) and placebo (control) injections.

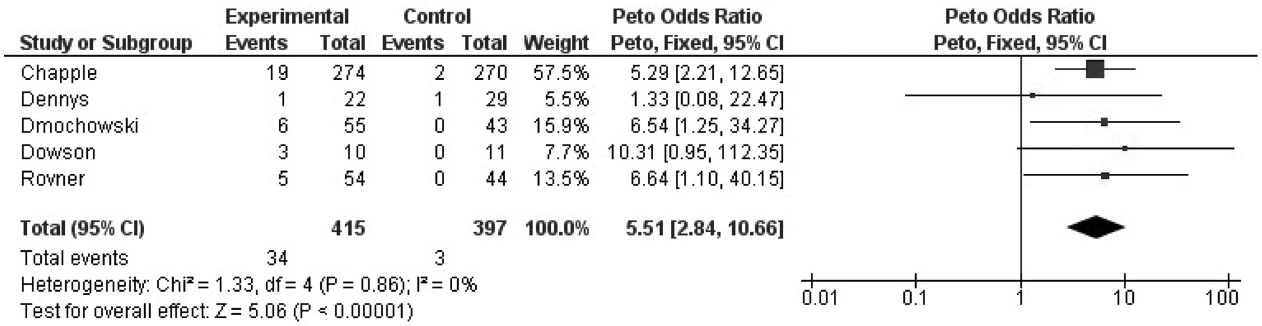

Fig. 6 Forest plot of change of pulmonary vascular resistance-related catheterization after 100 units of onabotulinumtoxinA (experimental) and placebo (control) injections.

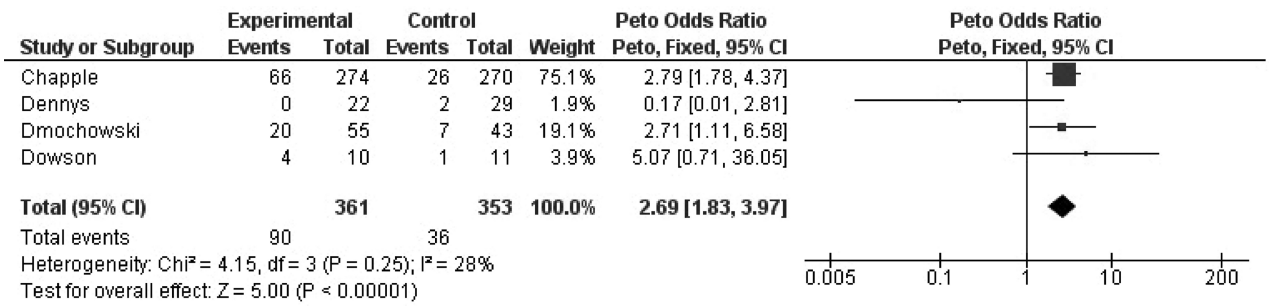

Fig. 7 Forest plot of change of urinary tract infection after 100 units of onabotulinumtoxinA (experimental) and placebo (control) injections.

group) when compared with the placebo group (control group), with no heterogeneity in this analysis.

In ►**Fig. 7** we present the forest plot graph for the data referring to urinary tract infection occurrence. We note in the plot forest graph that the Peto odds ratio meta-analytical value (OR = 2.69, IC (95%) = [1.83; 3.97]; *p* value < 0.0001) is located fully to the right of the vertical line. Such result demonstrates higher probability of urinary infection in the toxin group (experimental) when compared with the placebo group (control). Homogeneity among studies was confirmed by Q (Chi) in the Cochran test (p value = 0.25).

Regarding the quality of life evaluation, it was not possible to perform the meta-analysis, since the authors used different questionnaires, which made it impossible to evaluate this item.

Discussion

Our results demonstrated that the onabotulinumtoxinA had greater efficiency when compared with the placebo in relation to the all the symptoms analyzed (urinary frequency, nocturia, and urinary incontinence episodes). Such results are also in agreement with other systematic reviews and meta-analyses in respect to the subject.[18,19]

There was significant reduction in the number of urinary urgency episodes in the group treated with toxin in comparison with the placebo group. However, none of the studies evaluated urgency intensity, probably because it is a subjective symptom, and it is very difficult to be characterized.

The last Cochrane review (2011)[19] on this topic included 19 studies, mostly with neurogenic patients. In our study, we were interested in demonstrating the efficacy of onabotulinumtoxinA in the treatment of non-neurogenic overactive bladder, which is usually followed by the gynecologist.

We chose to include only articles in which the toxin used was onabotulinumtoxinA because it is the toxin most frequently indicated in Brazil, and it is available to treat overactive bladder in both private and public health services.

Although most studies included analyzed the patients' quality of life, unfortunately it was not possible to perform a systematic review of this variable given that the authors used different tools for this evaluation. Nevertheless, different studies have concluded that botulinum toxin significantly improves patient symptoms and quality of life.[11,20]

In the articles included in our study, the only side effects significantly higher in the toxin group in comparison with the placebo were urinary tract infection and urinary retention. Such

side effects were both more frequent in the 100 units dose. Furthermore, other possible side effects are dry mouth, hematuria, respiratory depression, and general muscular weakness.[21]

Urinary retention was the main complication reported in the studies. According to the literature data, its incidence ranges from 0–72%, depending on the toxin dose used and the definition of urinary retention with or without need for catheterization (which is extremely variable among the authors).[19,20] Most articles included in this meta-analysis considered as urinary retention the presence of post-urination residue $\geq$ 200 mL.[11–13,17]

The need for intermittent catheterization at the 100 units dose, which is the most frequently used dosage in non-neurogenic cases, ranged from 6.9[11]–30%.[14]

It should be noted, however, that the indication of catheterization was varied among the studies. The lowest rate was in Chapple et al,[11] which only indicated it in asymptomatic cases if post-urination residue was $\geq$ 350 mL. In turn, Brubaker et al (2008)[21] indicated intermittent catheterization in cases with post-urination residue $>$ 200 mL after 4 weeks from the injection, regardless of the symptoms. Such differences between the definitions for urinary retention and the need for catheterization render comparison among studies difficult. In addition, possible clinical consequences of asymptomatic urinary retention are not clear. Regardless, such retention is transitory and dose-dependent.[11,20,22]

The primary strength of this systematic review was to only include prospective, randomized, placebo-controlled articles featuring Jadad scale methodological quality $\geq$ than 3.[9] The fact that we have only included patients treated with 100 units of onabotulinumtoxinA and non-neurogenic cases also contributed to facilitate the interpretation of results.

The limitations refer mainly to the differences between injection application techniques, the follow-up time, and the evaluation of quality of life, which undoubtedly renders greater generalization of results.

Conclusion

In comparison with the placebo, onabotulinumtoxinA promotes significant improvement of urinary urgency, urinary frequency, nocturia, and incontinence symptoms. There is higher incidence of urinary retention and urinary tract infection among patients in the toxin group in relation with the placebo group. It was not possible to evaluate the effects on quality of life. This systematic review is endorsed by the Urogynecology Committee of the Federação das Associações Brasileiras de Ginecologia e Obstetrícia (Brazilian Federation of the Societies of Gynecology and Obstetrics, [FEBRASGO, in the Portuguese acronym]) and suggests that the dose of 100 units of onabotulinumtoxinA is effective in the treatment of non-neurogenic refractory overactive bladder.

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Mammary Hibernoma: A Case Report of a Rare Disease

Hibernoma mamário: relato de caso de uma doença rara

Eduardo Henrique Cunha Neves Filho[1] Geórgia de Aguiar Feitosa Lima[2] Ângelo Roncalli Melo Alves[1] Valdenrique Macêdo de Sousa[2] Maria do Perpétuo Socorro Saldanha da Cunha[1]

[1] Section of Pathology, Instituto do Câncer do Ceará, Fortaleza, CE, Brazil
[2] Section of Mastology, Instituto do Câncer do Ceará, Fortaleza, CE, Brazil

Address for correspondence Eduardo Henrique Cunha Neves Filho, MD, Instituto do Câncer do Ceará, Rua Papi Junior, 1222, Fortaleza, CE, 60430-230, Brazil (e-mail: edu0689@yahoo.com.br).

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Abstract

Mammary hibernomas are extremely rare benign tumors composed of brown fat cells, with only five cases previously reported in the literature. We report the case of a 42-year-old female patient with a painless growing mass in her right breast. A partial mastectomy was performed, and the diagnosis of hibernoma was confirmed by the histological features and the immunohistochemical profile. Although hibernoma is a benign tumor, its main differential diagnoses include aggressive lesions, making the accurate diagnosis essential to provide adequate care to the patient.

Keywords
- hibernoma
- breast benign neoplasia

Resumo

Hibernomas mamários são tumores benignos extremamente raros compostos por gordura marrom, com apenas cinco casos previamente relatados na literatura. Relatamos o caso de uma paciente do sexo feminino, de 42 anos de idade, apresentando-se com uma massa indolor em sua mama direita. Realizou-se uma mastectomia parcial e o diagnóstico de hibernoma mamário foi confirmado pelo padrão morfológico e pelo perfil imuno-histoquímico. Embora hibernomas constituam neoplasias benignas, seus principais diagnósticos diferenciais incluem lesões agressivas, sendo o diagnóstico acurado extremamente importante para o correto manejo clínico do paciente.

Palavras-chave
- hibernoma
- neoplasia mamária benigna

Introduction

Hibernomas are rare benign neoplasms composed of brown fat cells.[1] These tumors arise from remnants of fetal brown fat, which commonly tends to involve by the first weeks after birth and be replaced by white adipocytes.[2] Histologically, this kind of adipose tissue is very similar to the one found in hibernating animals, thus the term hibernoma.[1]

Although uncommon, it has been described that hibernomas occur more often in areas where residual brown fat is found, such as the interscapular region, axilla and the groin.[3] Mammary hibernomas are extremely rare, with only a few cases described in the literature.[2–6]

Case Report

A 42 years-old female patient presented with a 6 months history of a lump in the upper outer quadrant of her right breast. The lesion was painless, with no association to either edema or papillary discharge. She had her menarche when she was 12, her obstetric history was G1P1A0 and she had been using oral contraception for 6 years. There was no familiar history of breast cancer.

The initial clinical assessment showed a 10.0 × 10.0 cm lobulated, well-defined soft mobile mass, with no evidence of axillary or supra/infraclavicular fossae lymphadenopathy. A previous mammography revealed a regular, partially defined

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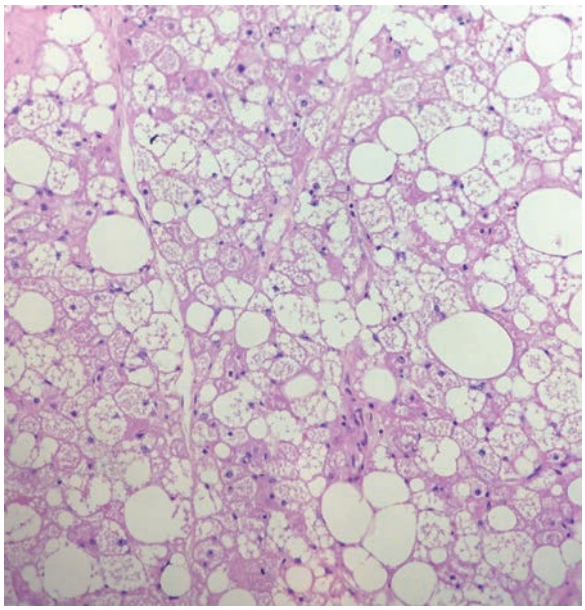

Fig. 1 High power microscopic view (H&E stain) demonstrating large polygonal cells with abundant multivacuolated, eosinophilic, cytoplasm.

nodule in the upper outer quadrant of her right breast. Additionally, an ultrasound scan of the lesion confirmed a hypoechoic solid nodule of ~ 10.2 × 5.0 cm, which occupied most of the upper outer and the upper inner quadrants of the right breast.

The histopathological evaluation of this mass by core biopsy showed fibrous-adipose tissue associated with areas of steatonecrosis, without any evidence of neoplasia in those samples. Therefore, the patient was submitted to partial mastectomy.

The surgical specimen was constituted by a yellowish round mass of 12.0 × 8.0 × 4.0 cm, with well-defined boundaries and elastic consistency, showing compact surface after being sectioned. The resection was marginal. Microscopically, the tumor was composed predominantly by lobules of large round to polygonal cells with abundant multivacuolated cytoplasm, well-defined membrane and central nuclei with fine chromatin and prominent nucleoli, which is consistent with a brown fat tumor, admixed with regular white adipocytes and small blood vessels (►**Fig. 1**). In addition, the surgical margins were microscopically negative. The diagnosis of mammary hibernoma was confirmed by immunohistochemistry, which revealed positivity for S100 protein; the tumor cells were negative for CD31, CD34, CD68 and topoisomerase (►**Fig. 2**).

Discussion

Hibernomas are uncommon benign tumors histologically composed of a specialized form of adipose tissue known as brown fat.[2] Although the brown adipocytes are gradually replaced by white fat after birth, foci of remnant brown fat may persist in adults; thus, hibernomas might theoretically arise in any area where these foci are found, although a de novo brown fat differentiation is reported as possible.[2,5] These tumors are mainly being reported in the thigh, shoulder, back, neck, chest, arm, abdominal cavity and retroperitoneum, accounting for only 1.6% of benign lipomatous neoplasms, with a slight predominance in adult men and a higher incidence between the third and fourth decades of life.[5,7]

Among the mammary benign tumors, hibernomas are one of the rarest with only five cases previously described in the literature.[2–6] Most cases present with an asymptomatic growing mass, although this tumor might cause symptoms due to adjacent structures compression, or it can be even diagnosed as an incidental finding at a radiological routine examination.

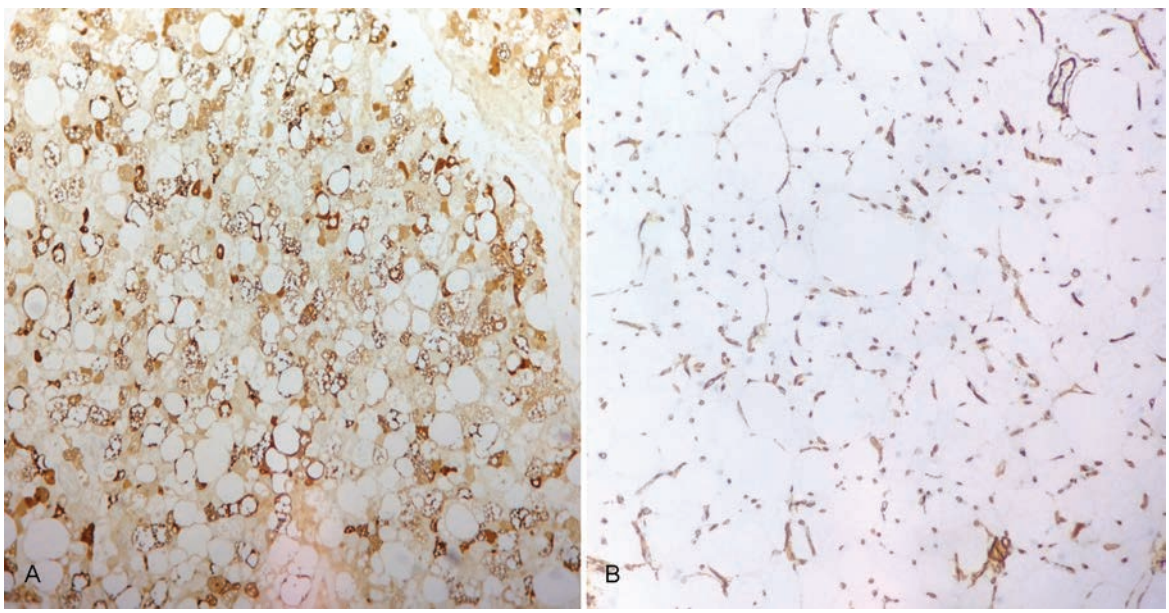

Fig. 2 Microscopic view demonstrating immunohistochemical positivity for S100 (A) and negativity for CD34 (B).

Grossly, hibernomas are well-circumscribed, lobulated and sometimes partly encapsulated. As sectioned, the cut surface has a yellowish brown hue with a rubbery texture.[6] On histological examination these tumor exhibit a lobular pattern with pale and eosinophilic multivacuolated fat cells with small, central, or eccentric nuclei admixed with capillaries with a varying degree of differentiation.[5,6] Nuclear atypia and mitotic figures are exceptionally rare.[7] The histopathological diagnosis is based upon morphological features. However, although not necessary, immunohistochemistry may be used to confirm adipocyte differentiation.[5]

Corroborating with our findings, immunohistochemical studies of hibernomas show global positivity for S100 protein in both eosinophilic and pale cells with variably intensity and negativity of CD34.[5,6] Although CD31 was previously reported to might be positive in normal and neoplastic brown fat cells, in our case it was negative.[5]

Differential diagnosis include other lipomatous neoplasms, such as lipoblastoma and well-differentiated liposarcoma, adult rhabdomyoma and fat necrosis.[6] The likelihood of diagnostic confusion with other tumors with a complete surgical excision is, however, minimal.

The present case was resected with marginal excision. The largest series published to date about hibernomas (170 cases derived from the files of the Armed Forces Institute of Pathology – AFIP) revealed no recurrence or aggressive behavior, even though many of these tumor were incompletely excised with a mean follow-up period of 7.7 years.[7]

In conclusion, hibernomas are benign tumors closely related to brown adipose tissue, which is rarely present in the human breast. Nevertheless, differential diagnosis must be done to rule out malignant neoplasias.

Conflicts to Interest
None to declare.

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Intestinal Perforation due to Deep Infiltrating Endometriosis during Pregnancy: Case Report

Rotura intestinal durante a gravidez devido a endometriose profunda infiltrativa: relato de caso

Márcia Mendonça Carneiro[1] Luciana Maria Pyramo Costa[1] Maria Das Graças Torres[1] Patrícia Salomé Gouvea[1] Ivete de Ávila[1]

[1] Department of Obstetrics and Gynecology, Universidade, Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

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Address for correspondence Márcia Mendonça Carneiro, MD, PhD, Universidade Federal de Minas Gerais, Rua Antonio Torres 186, Belo Horizonte, MG 31030-130, Brazil (e-mail: marciamc.ufmg@gmail.com).

Abstract

We report the case of a 33 year-old woman who complained of severe dysmenorrhea since menarche. From 2003 to 2009, she underwent 4 laparoscopies for the treatment of pain associated with endometriosis. After all four interventions, the pain recurred despite the use of gonadotropin-releasing hormone (GnRH) analogues and the insertion of a levonorgestrel intrauterine system (LNG-IUS). Finally, a colonoscopy performed in 2010 revealed rectosigmoid stenosis probably due to extrinsic compression. The patient was advised to get pregnant before treating the intestinal lesion. Spontaneous pregnancy occurred soon after LNG-IUS removal in 2011. In the 33rd week of pregnancy, the patient started to feel severe abdominal pain. No fever or sings of pelviperitonitis were present, but as the pain worsened, a cesarean section was performed, with the delivery of a premature healthy male, and an intestinal rupture was identified. Severe peritoneal infection and sepsis ensued. A colostomy was performed, and the patient recovered after eight days in intensive care. Three months later, the colostomy was closed, and a new LNG-IUS was inserted. The patient then came to be treated by our multidisciplinary endometriosis team. The diagnostic evaluation revealed the presence of intestinal lesions with extrinsic compression of the rectum. She then underwent a laparoscopic excision of the endometriotic lesions, including an ovarian endometrioma, adhesiolysis and segmental colectomy in 2014. She is now fully recovered and planning a new pregnancy. A transvaginal ultrasound (TVUS) performed six months after surgery showed signs of pelvic adhesions, but no endometriotic lesions.

Keywords

- deep infiltrating endometriosis
- intestinal endometriosis
- intestinal rupture
- pregnancy complications

Resumo

Relatamos o caso de uma mulher de 33 anos que apresentava de dismenorreia grave desde a menarca. Entre 2003 e 2009, a paciente foi submetida a quatro laparoscopias para o tratamento de dor associada à endometriose. A dor persistiu apos as 4 cirurgias apesar do uso de análogos do hormônio de liberação de gonadotropina (GnRH) e da inserção de um sistema intrauterino de levonorgestrel (SIU-LNG). Finalmente, uma

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colonoscopia realizada em 2010 revelou estenose rectosigmoide, provavelmente devido à compressão extrínseca. A paciente foi aconselhada a engravidar antes de tratar a lesão intestinal. A gravidez espontânea ocorreu logo após a remoção de LNG-IUS em 2011. Na 33ª semana de gestação, a paciente começou a sentir dor abdominal intensa, sem febre ou sinais de peritonite. Como a dor piorou consideravelmente, a paciente foi submetida à cesariana com nascimento prematuro de um menino saudável. Durante a cesárea foi identificado rotura intestinal com peritonite grave e sepse. Uma colostomia foi realizada, e a paciente admitida no centro de terapia intensiva por 8 dais. A colostomia foi fechada e um novo SIU-LNG inserido. A paciente passou a ser tratada pela nossa equipe multidisciplinar de endometriose. A avaliação diagnóstica revelou a presença de lesões intestinais com compressão extrínseca do reto. Foi então submetida a uma excisão laparoscópica das lesões endometrióticas, incluindo um endometrioma ovariano, adesiólise e colectomia segmentar em 2014. Ela está agora totalmente recuperada e planeja nova gravidez. Uma ultrassonografia transvaginal (TVUS) realizada seis meses após a cirurgia revelou sinais de aderências pélvicas sem lesões de endometriose.

Palavras-Chave
- endometriose infiltrativa profunda
- endometriose intestinal
- rotura intestinal
- complicações na gravidez

Introduction

Endometriosis is a progressive and benign estrogen-dependent disease defined by the presence of endometrial tissue (glands and stroma) outside the uterine cavity. Deep infiltrating endometriosis (DIE) is considered a specific entity, which has been arbitrarily defined in histological terms as endometriotic lesions extending more than 5 mm underneath the peritoneum, and it is responsible for painful symptoms, with some women experiencing severe symptoms, while others remain asymptomatic.[1] Due to the variable clinical presentation, the lack of pathognomonic symptoms, and the fact that no useful noninvasive clinical tests to diagnose the symptomatic disease are available, a delay in the diagnosis that averages from 5 to 11 years is observed.[1,2]

Deep infiltrating endometriosis is found in 20% of women with endometriosis. Bowel involvement is diagnosed in 5% to 12% of patients with endometriosis, with most lesions (90%) located in the colorectum. The role of colorectal endometriosis in women with infertility remains to be established.[1,3] Unfortunately, in most published studies, fertility and pregnancy data are underreported or not fully considered.[4] Intestinal DIE is a severe disease that may affect young women desiring pregnancy. Digestive symptoms may be found in association with deep dyspareunia, infertility, and impaired quality of life. In order to determine the best approach to bowel endometriosis, several factors such as clinical symptoms, extent of the disease and imaging evaluation results should be taken into consideration.[2,4,5]

Case Summary

We report the case of a 33 year-old woman who complained of severe dysmenorrhea since menarche. From 2003 to 2009, she underwent 4 laparoscopies for the treatment of pain associated with endometriosis (dysmenorrhea, dyschezia). The first surgery, which was performed in 2003, revealed endometriosis grade IV. A gonadotropin-releasing hormone (GnRH) analogue (goserelin) was administered to her for 6 months after surgery, but the pain recurred soon after her menses returned. As the pelvic pain persisted, a new laparoscopy was performed in 2006, and the levonorgestrel intrauterine system (LNG-IUS, Mirena, Bayer, Leverkusen, Germany) was inserted, with partial pain relief. In 2008, she started complaining of dyschezia, and underwent a third laparoscopy, for which no records are available. In spite of using Mirena, the pain, as well as the dyschezia, persisted. Thus, she underwent a fourth surgery in 2009. Finally, a colonoscopy performed in 2010 revealed rectosigmoid stenosis probably due to extrinsic compression. She was advised to get pregnant before attempting to treat the intestinal lesion, in view of the risks involved in such a surgery.

Spontaneous pregnancy occurred soon after the LNG-IUS was removed in 2011. When the patient was in the 33rd week of pregnancy, she started feeling severe abdominal pain. No fever or sings of pelviperitonitis were present, but as the pain worsened, a cesarean section was performed, with the delivery of a premature healthy male. Unfortunately, an intestinal rupture was also identified. Severe peritoneal infection and sepsis ensued. A colostomy was performed, and the patient recovered after 8 days in intensive care. Three months later, the colostomy was closed, and a new Mirena was inserted. Only then did the patient come for treatment of the intestinal endometriosis with our multidisciplinary endometriosis team. The diagnostic evaluation, including a transvaginal ultrasound (TVUS) with intestinal preparation and a magnetic resonance imaging (MRI) scan (►**Fig. 1**), revealed the presence of intestinal lesions, while the colonoscopy confirmed stenosis due to extrinsic compression of the rectum (►**Fig. 2**).

The patient then underwent a laparoscopic excision of the endometriotic lesions, including an ovarian endometrioma, adhesiolysis and segmental colectomy on November 2014. She is now fully recovered and planning a new pregnancy. A TVUS performed six months after surgery showed signs of pelvic adhesions, but no endometriotic lesions.

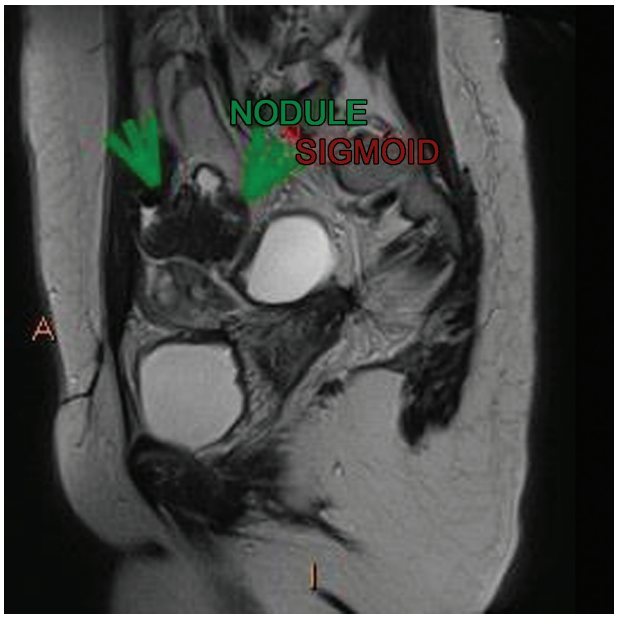

Fig. 1 Magnetic resonance imaging scan showing an endometriotic nodule in the rectosigmoid.

Discussion

Intestinal evaluation is extremely important for the surgical planning, since the number of lesions and the depth of invasion influence the composition of the surgical team, the equipment used and the technique chosen. Bowel involvement is frequently multifocal, and the most commonly affected areas are the rectosigmoid colon, the appendix, the cecum and the distal ileum.[1,5] Although the rectal endoscopic sonographic approach is the most precise approach for the evaluation of the involvement of intestinal layers, such identification is also possible by TVUS.[4,5] It has been shown that lesions that affect more than 40% of the bowel circumference reach beyond the inner muscular layer.[3–5]

Women presenting with intestinal symptoms and those with previous endometriosis surgery are at increased risk of bowel resection.[4,5] Our patient presented with recurrent symptoms, including dyschezia, despite four laparoscopies and the continuous use of medical treatments. The decision to perform surgery for DIE is mainly clinical.[4,5] The TVUS and other imaging techniques such as the MRI can be useful tools to make a preoperative estimate of the size and lateral extension of the lesions, and they play a vital role in the surgical planning and approach. It remains unclear, however, to what extent the preoperative ultrasonography or the MRI should influence the decision to perform the surgery, or the decision regarding the type of intervention to undertake for DIE.[5,6] According to the European Society of Human Reproduction and Embryology (ESHRE) Guideline,[2] the ureter, the bladder and the bowels should be assessed if DIE is suspected, in order to establish the extent of the disease. Even though the colonoscopy performed in 2010 revealed rectosigmoid stenosis probably due to extrinsic compression, the patient was advised to get pregnant before attempting to treat the intestinal lesion, in view of the risks involved in such a surgery. As the patient only came to our multidisciplinary team after intestinal rupture in 2013, we do not know why she was not operated earlier, even though the decision to perform surgery may vary according to the literature.

Although the accuracy of the colonoscopy for the identification of intestinal involvement in DIE is debatable[7] in view of the rarity of mucosal involvement, it was indicated in our patient due to the persistent intestinal symptoms. Indeed, the colonoscopy showed stenosis due to extrinsic compression. Therefore, surgery should have been contemplated before pregnancy, even though there is no consensus in the medical literature as to what is the best approach in such clinical settings.[3,6] Once again, she was not previously under our care, and no record of clinical decisions was available to us.

Surgery is considered the treatment of choice for symptomatic DIE, as the complete removal of lesions results in significant pain relief and improvement in quality of life scores.[2,4,5] The best therapeutic approach for women with DIE involving the sigmoid and/or rectum remains to be established.[4,5] A variety of factors such as clinical symptoms, lesion location and results from imaging studies (TVUS and MRI), as well as the recurrence rates and impact on fertility and quality of life should be taken into consideration.[5,6] Some advocate that a bowel resection is rarely justified,

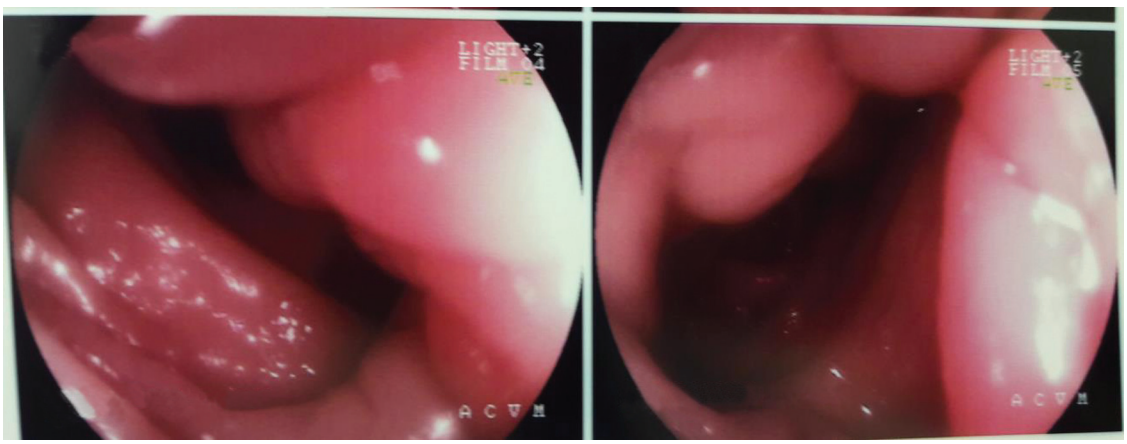

Fig. 2 Colonoscopy performed before surgery in 2014 showing extrinsic compression in the rectum by an endometriotic nodule.

and that in many cases involving the rectovaginal septum or the bowel, DIE can be appropriately managed without the surgical excision of such lesions.[8] A conservative approach seems justified in younger patients wishing to conceive, although segmental bowel resection and anastomosis result in better outcomes, without interfering in pregnancy rates.[5] This may have been the case when our patient was first operated, as she was not infertile. Her clinical history, however, showed intestinal symptoms (dyschezia), and the medical treatment she underwent apparently was not enough to stop the progression of her intestinal endometriosis. In addition, the colonoscopy had already showed stenosis probably related to extrinsic compression. Unfortunately, none of the previous surgeries were performed by a multidisciplinary endometriosis team. It is advisable to refer women with DIE to a center of expertise in endometriosis that can offer multidisciplinary management, as the surgery is associated with significant complication rates.[2]

Disastrously, intestinal rupture during pregnancy occurred. Although rare, intestinal obstruction due to endometriosis during pregnancy may happen, with rather severe complications. Unfortunately, DIE might be overlooked, as symptoms can be elusive and unspecific, and intestinal lesions may be missed even during laparoscopy. Furthermore, smaller deep lesions, especially at the level of the sigmoid, may be missed during the diagnostic workup and laparoscopy. Last, but not least, one expects endometriosis to regress during pregnancy.[2,9] Regrettably, there may be more cases, as many may not have been published. We have received personal communication of two other cases of intestinal rupture after controlled ovarian stimulation for in vitro fertilization (IVF). As a matter of fact, acute complications of endometriosis occurring during pregnancy remain rare. Setúbal et al[9] published a review on intestinal complications caused by DIE either during pregnancy or IVF. Their literature search revealed 12 articles describing 12 complications related to the progression of DIE during pregnancy, and 1 article reporting 6 cases of bowel occlusion during IVF. Surgery is not mandatory in all cases, and when infertility is involved, IVF appears to be the best option.[2]

Women presenting with intestinal symptoms and those with previous endometriosis surgery are at increased risk of bowel resection. The decision to perform surgery in this setting, however, remains mainly clinical. Available published data on the long-term outcomes reveals a cumulative probability of pain recurrence between 20% and 40%, and need of another surgical procedure between 15% and 20%. Therefore, the decision to perform radical or conservative surgery or no surgical intervention at all should be evaluated individually.[10] Accurate information on the benefits and risks involved in the procedure versus treatment without bowel resection should be available to all patients. The management of women with bowel endometriosis remains a challenge due to the lack of published studies evaluating the real risk of symptom recurrence, the effects on fertility, and the need for further surgical interventions. Decisions, however, should be individualized to the needs of each woman after providing information on the potential benefits, harms, and costs of each treatment alternative, as well as after evaluating the presence of pelvic pain, the woman's age, lesion location, and previous treatments.[10] In such a setting, the evaluation by a multidisciplinary endometriosis team is a fundamental step in order to achieve successful results.

Conflicts to Interest

The authors have no conflicts of interest to disclose.

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Instructions to Authors

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The material submitted for analysis cannot be simultaneously submitted for publication in other journals or previously published. In the selection of manuscripts for publication, are evaluated the originality, relevance of the theme, quality of the methodology used, and adequacy to the editorial standards adopted by the journal. The published material becomes intellectual property of the Brazilian Journal of Gynecology and Obstetrics and Febrasgo.

Manuscripts evaluation

The manuscripts submitted to the journal are received by the Editorial Office that checks the mandatory documentation and examines if the editorial norms contained in the Instructions to Authors have been fulfilled. If the process is in compliance, the manuscript is sent to the Editor-in-Chief, who will make a merit evaluation of the material. If the Editor-in-Chief concludes the work is in favorable scientific and technical conditions, the manuscript is forwarded to the Associate Editors, who will designate reviewers (double mind process) to evaluate it. Then, the reviewers' opinions and editor's instructions are sent to authors to inform them about changes to be made. Then, the authors resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections should be highlighted in yellow. In cases of disagreement with the suggestions, observations should be included in the comments balloons. Be assertive and punctual with the inquiry, and support the hypothesis with references.

IMPORTANT! Authors must comply with the deadlines, since non-attendance will result in delay of manuscript publication or even archiving of the process. At any point in the process of analysis and editing of the text, the authors may request the process suspension and withdrawal of the manuscript, except when it is accepted for publication. The concepts and statements contained in the articles are of the authors' responsibility.

Preparing a manuscript for submission

Mandatory submission documents

When submitting a manuscript to RBGO, attach the documents listed below on the ScholarOne submission platform. Note that not attaching the documents will result in cancellation of the submitted process. Mandatory documentation for online submission:

- Authorization of copyright transfer signed by all authors (scanned and attached as supplementary document) **Model;**
- In accordance with chapter XII.2 of Res. CNS 466/2012, in Brazil, research involving human subjects needs to inform the registration number referring to the Certificate of Ethical Assessment (CAAE) or the approval number of the research (CEP/CONEP) in the Ethics Committee. International manuscripts must present local ethical documentation to proceed with the submission process;
- Cover Letter: written to justify the publication. The authors should be identified, together with the title of the team that intends to publish, origin institution of the authors and intention of publication;
- Title page;
- Manuscript.

Title Page

- Title of the manuscript in English with a maximum of 18 words;
- Authors' full name without abbreviations (maximum six);
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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 American Medical Association (AMA) Citation Style to format your references.

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

Submission of papers

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

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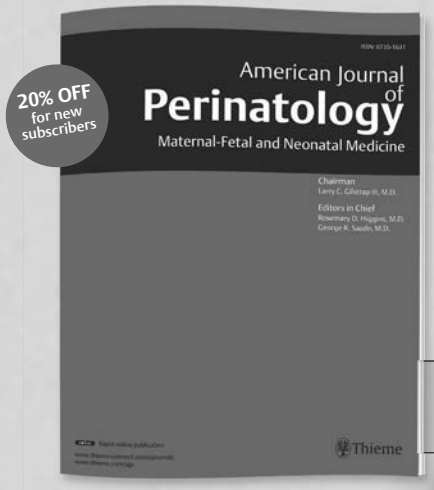

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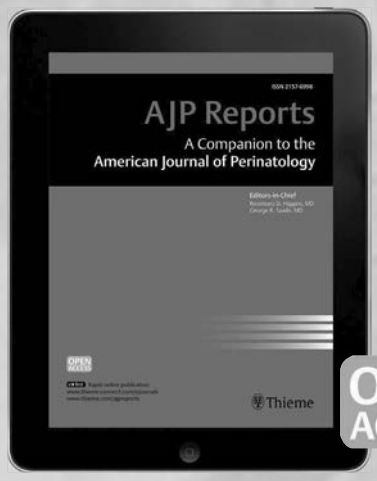

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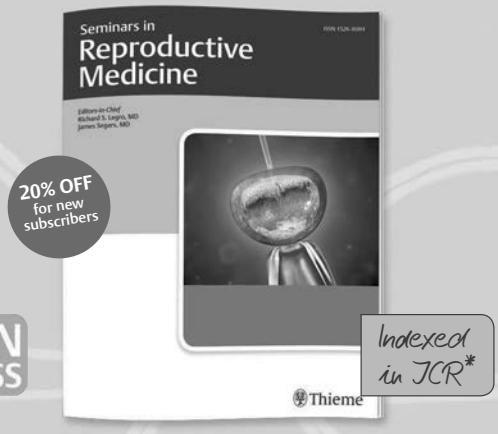

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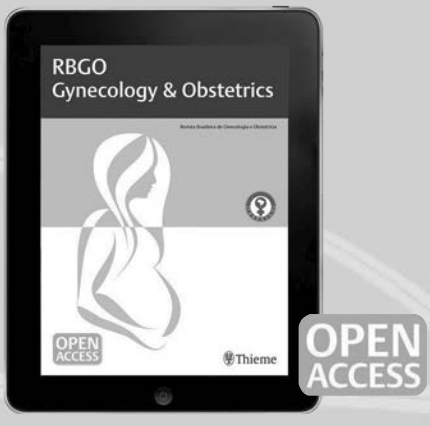

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