

RBGO

ISSN 0100-7203
eISSN 1806-9339

Gynecology & Obstetrics

Revista Brasileira de Ginecologia e Obstetrícia
Number 6 • Volume 44 • Pages 557–636 • June 2022



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RBGO Gynecology and Obstetrics

Revista Brasileira de Ginecologia e Obstetrícia

Editorial

- 557 The Placenta and its Underestimated Role in Clinical Practice and Research

Maria Laura Costa

Original Articles

Obstetrics

- 560 Support Systems and Limitations in Therapeutic Abortion Care by the Gynecologist-Obstetrician of Public Hospitals in Peru

Juan Matzumura, Hugo Gutierrez-Crespo, Enrique Guevara, Luis Meza, and Mauricio La Rosa

- 567 Maternal Deaths from COVID-19 in Brazil: Increase during the Second Wave of the Pandemic

Carlos André Scheler, Michelle Garcia Discacciati, Diama Bhadra Vale, Giuliane Jesus Lajos, Fernanda Garanhani Surita, and Julio Cesar Teixeira

Gynecological Endocrinology

- 573 Practical Prediction Model for Ovarian Insufficiency after Radiation

Gabriel Oliveira Bernardes Gil, Cassiano Asano, Warne Pedro de Andrade, Maria Luísa Braga Vieira Gil, Eduardo Batista Cândido, Marcos Regalin, Izabella Nobre Queiroz, Farley Soares Cantídio, Darly Gomes Soares Delfino, and Agnaldo Lopes Silva-Filho

Assisted Reproduction

- 578 One Plus One is Better than Two: An Approach Towards a Single Blastocyst Transfer Policy for All IVF Patients

Pedro Felipe Magalhães Peregrino, Tatiana Carvalho de Souza Bonetti, Alessandra Prado Gomes, Hamilton de Martin, José Maria Soares Júnior, Edmund Chada Baracat, and Pedro Augusto Araújo Monteleone

Menopause

- 586 Does Obesity Aggravate Climacteric Symptoms in Postmenopausal Women?

Juliane Gonçalves Costa Dechichi, Raquel Moreira Rodrigues, Guilherme Morais Puga, and Nádia Carla Cheik

Review Articles

- 593 Main Complications during Pregnancy and Recommendations for Adequate Antenatal Care in Sickle Cell Disease: A Literature Review

Camilla Olivares Figueira, Fernanda Garanhani Surita, Kleber Fertrin, Guilherme de Moraes Nobrega, and Maria Laura Costa

- 602 Coronavirus Disease 2019 Vaccination for Cancer Patients: Risk or Benefit?

Bruno Eduardo Pereira Laporte, Estela Gelain Junges Laporte, Paula Fonseca Aarestrup, Matheus Fonseca Aarestrup, and Fernando Monteiro Aarestrup



- 609 Pregnancy in Patients with Non-cirrhotic Portal Hypertension: A Literature Review
Suprabhat Giri and Shradhanjali Sahoo
- 614 The Correlation between *Chlamydia Trachomatis* and Female Infertility: A Systematic Review
Laura Gazal Passos, Paula Terraciano, Nicole Wolf, Fernanda dos Santos de Oliveira, Isabel de Almeida, and Eduardo Pandolfi Passos
- 621 Breaking Bad News in Obstetrics and Gynecology: We Must Talk About It
Luísa Silva de Carvalho Ribeiro, Bárbara Flecha D'Abreu, Aline Evangelista Santiago, Eduardo Batista Cândido, Gustavo Salata Romão, Marcos Felipe Silva de Sá, and Agnaldo Lopes da Silva Filho

Letter to the Editor

- 629 Has the COVID-19 Pandemic Affected the Epidemiology of Syphilis in Brazil?
Yago Tavares Pinheiro and Richardson Augusto Rosendo da Silva

Febrasgo Statement Position

- 631 Human papillomavirus vaccination for adult women
Cecília Maria Roteli-Martins, Valentino Magno, André Luis Ferreira Santos, Júlio César Teixeira, Nilma Antas Neves, and Susana Cristina Aidé Viviani Fialho



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ISSN 0100-7203

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Editorial

The Placenta and its Underestimated Role in Clinical Practice and Research

A placenta e seu papel subestimado na prática clínica e na pesquisa

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Rev Bras Ginecol Obstet 2022;44(6):557–559.

A few years ago, when I was on my post-doctoral training abroad, on placental biology and immunology, I started to understand the amazing potential within studying the placenta. At the time, my 5-year-old daughter was asked to share with her classmate's information regarding her family and when talking about my background, she said I was a medical doctor. The kids asked: "what kind of doctor?" and without a doubt she answered: "My mom is a placenta doctor." They further asked what that was, and she finished the subject saying: "something very important." I believe she was correct. This editorial aims to explain the relevance of the placenta for clinical practice and its research potential. All obstetricians should value the placenta.

It is only fair to start by acknowledging that one of the most significant researchers on the maternal-fetal interface was a Brazilian-British biologist, called Peter Medawar, with special interest in understanding graft rejection and immune tolerance that brilliantly used the placenta as a model for such theories. For his scientific work he was rewarded the 1960 Nobel Prize in Physiology "for discovery of acquired immunological tolerance."¹ Medawar was born and lived in Brazil during his childhood but decided to move to United Kingdom (UK) and renounced his Brazilian citizenship at the age of 18, when he was obligated to serve in the Brazilian army. Therefore, his academic accomplishments happened in UK, with theories that lasted for long and were essentially: (a) anatomical separation between mother and fetus by the placenta, (b) immaturity of fetal antigens, impairing their ability to produce a maternal immune response, and (c) immunological inertness of the maternal immune system during pregnancy. Nevertheless, we have much evolved and these theories, that guided research in reproductive immunology for decades, have not withstood. For a successful pregnancy, immune function is a complex series of tightly

controlled immune modulations, with intense cellular communication in the maternal-fetal interface.

The placenta is the organ that transfers nutrients, gases, electrolytes, antibodies, and other components from the maternal to the fetal environment and simultaneously receives excreta from the fetus.² It is also an endocrine organ, with significant hormone production (progesterone, estrogen hormones, human chorionic gonadotropin and somatotropin). The placenta is a discoid-shaped organ measuring 15 to 20 cm diameter, 2 to 3 cm thickness, and around a sixth of the full-term fetal weight, i.e., ~500 g. It is composed of different cell types, involved in diverse functions that also include adhesion, invasion, vascular remodeling and cell fusion. These characteristics account for similarities between cancer and placental development, since trophoblasts, mimic various malignant cell features. Interesting to note that the placenta invades the adjoining uterus and modulates the maternal immune system, like cancer cells invade neighboring organs, suppressing local immune response.³

In clinical practice, the placenta is mostly considered a biohazard and discharged after childbirth.² However, it is very important to systematically revise its overall aspect and to request a morphological analysis (–**Figure 1**), especially in the presence of adverse maternal and perinatal outcomes. Findings can support or even explain such outcomes. Among the perinatal conditions that should trigger placental examination are stillbirth or perinatal death, fetal growth restriction, hydrops, severe neonatal depression (encephalopathy, seizures), Apgar score less than 3 in the fifth minute, suspected infection, congenital anomalies and thick meconium. Among the conditions associated to childbirth conditions, the indications for placental examination are prematurity (especially <32 weeks), post-maturity or post-date (>42 weeks), oligohydramnios, polyhydramnios, fever or maternal infection, placental abruption.⁴

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DOI [https://doi.org/
10.1055/s-0042-1750156](https://doi.org/10.1055/s-0042-1750156).
ISSN 0100-7203.

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To retrieve valuable information, placental evaluation needs to be performed by a trained pathologist, and preferably using standardized methods and reports. Since 2016, after an expert meeting, an agreement was established, called Amsterdam Consensus for the sampling and definitions of macro- and microscopic lesions, broadly classified as: maternal vascular lesions, obstruction of fetal circulation and inflammatory lesions.⁵ It is no longer acceptable to have poor reports, that limit findings to a non-helpful sentence such as: “placenta compatible with third trimester” and do not add information to guide clinicians or help in counseling patients.

Congenital infections for example, that represent an important cause of morbidity and mortality worldwide, can benefit from placental analysis. CMV (cytomegalovirus), many times difficult to diagnose during antenatal care, can present with the classical CMV owl’s eye inclusions and chronic villitis. Toxoplasmosis shows chronic granulomatous villitis, with immune multinucleated giant cells; parvovirus infection can cause villous edema, erythroblastosis, hobnau cell hyperplasia and red blood cells with giant viral nuclear inclusions in the pathology evaluation.⁶ These findings can answer clinical questions such as: why was this fetus hydropic or why did this case progress to a stillbirth?

Adverse outcomes also rise other concerns, including litigation. The steep increase in litigation in medical practice is a broad and complex subject and urges a support of combined effort between obstetrics, neonatology and pathology, including the examination of the placenta.⁷

Some conditions, such Preeclampsia are very studied, with known morphological abnormal findings in the placenta. Preeclampsia, especially when early onset (<34 weeks) is associated to increased maternal vascular malperfusion (MVM), including findings of hypoxia, villous infarctions, and hypoplasia. These findings also support increased risk of recurrence and long term consequences for women, such as increased risk of cardiovascular disease later in life.⁸

In research, the placenta has a great potential and is rising as a novel resource for explaining underlying causes of adverse outcomes. Advances in molecular biology, cellular isolation and immune assays have enabled such advances. A clear example of the research relevance of studying the placenta is very recent. During the Zika (ZIKV) pandemic, the severe fetal involvement had everyone question the role of the maternal-fetal barrier. The placenta was shown to be a viral reservoir and a possibility for accurate diagnosis, especially when timely investigation was not performed in the onset of symptoms (that were mostly mild).⁹

In Brazil, the Ministry of Health soon recognized the potential of examining the placenta and therefore requested that a piece (one 3.0cm fragment) should be sent for analysis in a certified laboratory, as part of the implemented national protocol for ZIKV care. However, there are very relevant procedures to use placental samples, such as timing between delivery and sampling, method of sampling to allow for representative tissue and mostly the storage, with freezing the material as sampled. This explains why none of the sent biopsies to the official laboratories had positive results on viral investigation, while the same placentas, studied in a

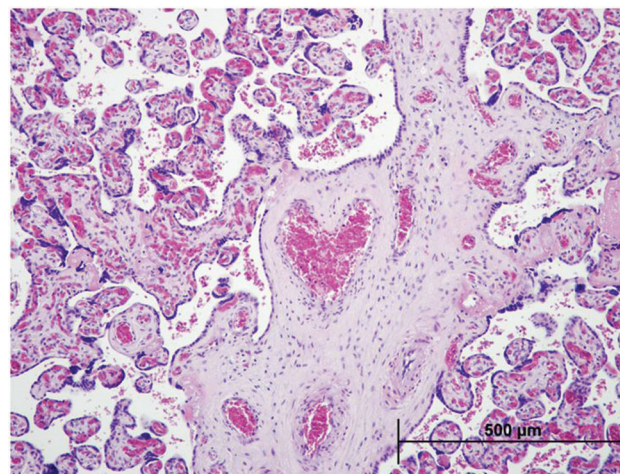


Fig. 1 Placental histopathology assessed by H&E staining. A heart shaped vessel within a stem villi in the placenta.

research protocol (systematically sampled with 4 fragments), showed high frequency of positivity for ZIKV. Nevertheless, the detection of ZIKV RNA in the placenta does not distinguish between fetal and maternal infection. Thus, questions arise as to possible individual characteristics of immune response or placental function, that still need answers.⁹ Mouse models that supported ZIKV replication and trans-placental transmission in pregnant dams were also described in the attempt of facilitating the study of viral pathogenesis, in utero transmission, and testing of therapies and vaccines to prevent congenital malformations.¹⁰

The new challenge is the SARS-CoV-2 infection and its possible impact in placental function.¹¹ This pandemic presented with very low rates of vertical transmission and mild disease in newborns, however, the involved mechanisms are still not clear and the possible impact of arising Variants of Concern (VOCs) on placental function are under investigation.

Awareness about placental relevance is key to understand major factors underlying maternal and perinatal outcomes. Future advances in imaging and also in testing biomarkers produced by placental cells might change clinical management of disease in the near future.

Conflicts to Interest

None to declare.

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Support Systems and Limitations in Therapeutic Abortion Care by the Gynecologist-Obstetrician of Public Hospitals in Peru

Sistemas de apoio e limitações na atenção ao aborto terapêutico pelo ginecologista-obstetra de hospitais públicos do Peru

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Rev Bras Ginecol Obstet 2022;44(6):560–566.

Abstract

Objective To identify the barriers to provide to women and adequately train physicians on therapeutic abortions in public hospitals in Peru.

Methods Descriptive cross-sectional survey-based study. We invited 400 obstetrics and gynecology specialists from 7 academic public hospitals in Lima and 8 from other regions of Peru. Expert judges validated the survey.

Results We collected survey results from 160 participants that met the inclusion criteria. Of those, 63.7% stated that the hospital where they work does not offer abortion training. Most of the participants consider that the position of the Peruvian government regarding therapeutic abortion is indifferent or deficient. The major limitations to provide therapeutic abortions included Peruvian law (53.8%), hospital policies (18.8%), and lack of experts (10.6%).

Conclusion Most surveyed physicians supported therapeutic abortions and showed interest in improving their skills. However, not all hospitals offer training and education. The limited knowledge of the physicians regarding the law and institutional policies, as well as fear of ethical, legal, and religious repercussions, were the main barriers for providing abortions.

Keywords

- ▶ abortions
- ▶ therapeutic
- ▶ hospitals
- ▶ training
- ▶ participants

Resumo

Objetivo Identificar as barreiras para oferecer às mulheres e capacitar adequadamente os médicos sobre abortos terapêuticos nos hospitais públicos do Peru.

received
February 11, 2021
accepted
February 25, 2022

DOI <https://doi.org/10.1055/s-0042-1746198>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave

- ▶ abortos
- ▶ terapêutico
- ▶ hospitais
- ▶ treinamento
- ▶ participantes

Métodos Estudo descritivo transversal baseado em inquérito. Convidamos 400 especialistas em obstetrícia e ginecologia de 7 hospitais públicos acadêmicos de Lima e 8 de outras regiões do Peru. Juízes especialistas validaram a pesquisa.

Resultados Coletamos os resultados da pesquisa de 160 participantes que atenderam aos critérios de inclusão. Destes, 63,7% afirmaram que o hospital onde trabalham não oferece treinamento sobre aborto. A maioria dos participantes considera que a posição do governo peruano em relação ao aborto terapêutico é indiferente ou deficiente. As principais limitações para fornecer abortos terapêuticos incluem a lei peruana (53,8%), políticas hospitalares (18,8%) e falta de especialistas (10,6%).

Conclusão A maioria dos médicos pesquisados apoiava o aborto terapêutico e demonstrava interesse em aprimorar suas habilidades. No entanto, nem todos os hospitais oferecem treinamento e educação. O conhecimento limitado dos médicos sobre a lei e as políticas institucionais, além do medo de repercussões éticas, legais e religiosas, foram as principais barreiras para a realização do aborto.

Introduction

There are 73 million abortions reported worldwide every year. Approximately 45% of these are considered unsafe. In developing countries, this percentage increases to 56%.¹ In Latin America, 10 to 16% of maternal deaths are caused by unsafe abortions.²

In developing countries, suboptimal access to abortion services is a serious problem. Women from low socioeconomic groups and other vulnerable women are disproportionately affected by the lack of information and lack of access to family planning services.³ Therapeutic abortion must be aligned within a context of respect for sexual and reproductive rights, a fundamental part of human rights.

In Peru, “an abortion can be performed by a doctor with the pregnant woman’s consent when it is the only way to save the patient’s life or to avoid a serious long-term illness in her health.”⁴ Despite the progress made by approving the national guideline for therapeutic abortion, women still experience inadequate access to this service. This inadequate access results in high rates of maternal mortality.^{4,5} Annually, ~ 376,000 unsafe abortions are performed in this country.^{6,7}

There have been several initiatives to promote the use of guidelines for therapeutic abortion and to provide specialized training to doctors.⁸ Nevertheless, there are still significant gaps. Training in the management of therapeutic abortions is not routine in several residency programs in the United States. The inappropriate methodology used, the absence of simulators, and limited legal support for the institutions, also limit training.^{9,10} Turk et al.⁹ performed a survey of residency program directors around the United States to describe their perspective of support for and resistance to abortion training. Almost 75% of them reported at least some institutional or government restriction, with an average of 3 types of restrictions. They reported that hospital policy restrictions were common, followed by state law restrictions.⁹

In 2016, Távora Orozco et al.⁸ reported the status of safe therapeutic abortion in Peru based on interviews and data collection from 10 hospitals. They found that the rate of

therapeutic abortions was still low, with lethal fetal abnormalities being the most common indication.⁸

There is no data on the main barriers to adequate training of specialists in the management of therapeutic abortion care in Peru. Our objective is to identify the barriers to provide adequate physician training and to perform therapeutic abortions for women in public hospitals in Peru.

Methods

We performed a descriptive cross-sectional survey-based study. We invited 400 participants, obstetrics and gynecology specialists from 7 academic public hospitals in Lima and 8 from other regions of Peru. We included obstetrics and gynecology specialists that worked in these 15 hospitals, and we excluded participants who were not routinely assigned to clinical duties or did not complete the survey. We developed our survey based on previously published surveys.^{8,9} Our survey evaluated the support systems and limitations for the training and performance of therapeutic abortions. It consisted of a total of 43 questions.

The validation of the instrument was performed in two phases: content validity followed by instrument reliability phase. Six Peruvian experts performed the content validity. They had to meet the following criteria: work experience in the subject, original research on this subject, and have an academic master’s or doctor’s degree. The concordance index, according to the Kappa index, was 0.61. For the instrument reliability phase, we performed a pilot test with the participation of 30 gynecologists. The total reliability was 0.77.

The questionnaires were sent to the participants by email and reminder phone calls from May to November 2020. The data processing and analysis were performed using estimates to calculate absolute and relative frequencies using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA).

The Faculty of Medicine of the Universidad Nacional Mayor de San Marcos Research Ethics Committee approved the research project.

Table 1 Characteristics of the Participants

Variables	n	%
Age (years old) (mean ± SD)	46.8 (±12)	
Male	109	68.1
Female	51	31.9
Married	107	66.9
Single	41	25.6
Divorced	9	5.6
Widow	3	1.9
Hospital region		
Lima	120	75
Other region	40	25
Religion		
Catholic	141	88.1
None	11	6.9
Other	8	5
Position		
Faculty	141	88.1
Department director	15	9.4
Department chairman	4	2.5
Does your hospital provide therapeutic abortion?		
No	76	47.5
Yes	84	52.5
Do you think that therapeutic abortions should be provided?		
No	28	17.5
Yes	132	82.5

Results

We enrolled 160 participants who completed the survey and met the inclusion criteria. The characteristics of the participants are shown in ►Table 1. Almost half of the participants reported that their hospital did not provide therapeutic abortions, but > 80% support the idea of this procedure and thought it should be provided.

►Table 2 described the barriers identified by the participants to train and provide therapeutic abortion at their institution.

Most of the participants consider that the position of the Peruvian government' regarding therapeutic abortion is indifferent or deficient (►Fig. 1).

Regarding training at their institution, 63.7% of the respondents stated that the hospital does not offer abortion

Table 2 Barriers to train physicians and to provide therapeutic abortion

	n	%
Training in therapeutic abortion is limited as a result of:		
Peruvian law	73	45.6
Institutional policies	53	33.1
No relationship with an institution that provides abortion	23	14.4
Lack of medications/equipment	11	6.9
Providing therapeutic abortion is limited as a result of:		
Peruvian state law	80	50.0
Institutional policies	43	26.8
No relationship with an institution that provides another type of abortion	24	15.0
Lack of expert physicians	13	8.1

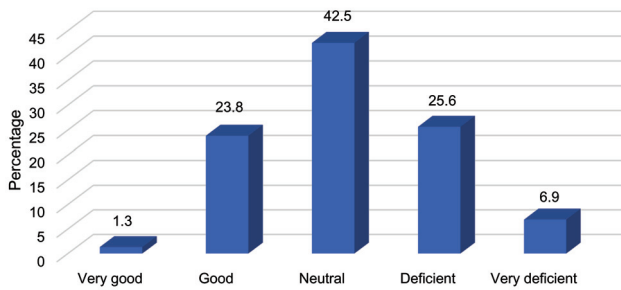


Fig. 1 Position of the Peruvian government regarding therapeutic abortion.

training. Also, 46.9% reported that the training is performed in other institutions, such as scientific societies, universities, or private institutions. ►Table 3 describes the levels of support at their institution for training in therapeutic abortion.

More than half of the participants (56.3%) thought that abortion training should be integrated into the residency program, while 20% thought it should be part of family planning rotation. Two-thirds had availability for abortion training 1 to 3 days per week, and 22.5% between 4 and 6 days per week. The personal reasons not to participate in therapeutic abortion training were religious reasons in 17.5% and to avoid legal problems in 8.1%.

Almost half of the participants (45%) did not receive training on abortions, 10% received training only in early failed pregnancies, and 45% received training for the management of therapeutic abortions. Almost half of the physicians (44.4%) stated that they did not perform any therapeutic abortions during residency, and only 16.9% did > 10 procedures. On the other hand, 85% stated that they had competencies for the management of abortion complications. The major barriers to providing therapeutic abortions included Peruvian law (53.8%), hospital policies (18.8%), and lack of experts (10.6%). ►Figures 2 and 3 describe the internal and external barriers to adequately incorporate therapeutic abortion services in their institution.

Regarding conferences that provide wellbeing resources for physicians who perform abortion, 30.6% reported that

they participate once every year, while 36.3% more than once per year. The remaining did not participate in such sessions during the last years. A total of 40.6% of the participants were unaware of tools to handle emotions during and after performing therapeutic abortions.

Discussion

To improve women's health, women's rights, and health promotion, interventions should be supported.⁵

Our study showed that almost half of the specialists do not provide therapeutic abortions at their institution, although most of them support the idea of therapeutic abortion care. Access to safe abortion is crucial in the care of women's health.¹¹ In Latin America, each country has different laws; some limit access to safe abortion, while others make this procedure widely available for their population.^{12,13} To provide safe abortion to a population, the availability of a significant number of institutions and doctors with training in this service is required.¹⁴ The majority of physicians report limited exposure to therapeutic abortion during residency training. The lack of doctors trained in performing abortions is a problem described not only in Peru. Prior studies have reported limited access to abortions in obstetrics and gynecology training programs.^{15,16} The lack of doctors trained for this procedure leads to limited or no access to safe abortion. This lack of access can lead to clandestine abortions or pregnancies carried to term despite the risk they may pose to women.

For example, in the United States, most abortions performed occur in nonacademic institutions, limiting the exposure of residents to these types of procedures. Academic institutions in that country must make different efforts to ensure the exposure of their residents to training in safe abortion.¹⁷

As in other countries, legal regulations are one of the main barriers that limit the exposure to this procedure during specialty training. These legislative barriers are pronounced in training centers, which are public hospitals with government funding. Also, many academic centers require procedures that make the abortion process difficult; for example, consents that must be signed a few days before the procedure can be performed. These common barriers to providing safe

Table 3 Level of support for training

	Lot of support		Support		Neutral		Limitations		Lot of limitations		None	
	n	%	n	%	n	%	n	%	n	%	n	%
Department leadership	12	7.5	50	31.3	47	29.4	28	17.5	16	7	4.4	
Hospital director	9	5.6	33	20.6	70	43.8	22	13.8	16	10	6.3	
Nurses	14	8.8	53	33.1	61	38.1	19	5.6	12	7.5	11	6.9
Anesthesiologist	5	3.1	40	25	61	38.1	25	15.6	19	11.9	10	6.3
Medical staff and equipment	18	11.3	52	32.5	42	26.3	25	15.6	13	8.1	10	6.3
Interaction with other specialties	8	5	60	37.5	53	33.1	19	11.9	10	6.3	10	6.3
Residents	49	30.6	52	32.5	37	23.1	12	7.5	9	5.6	1	0.6

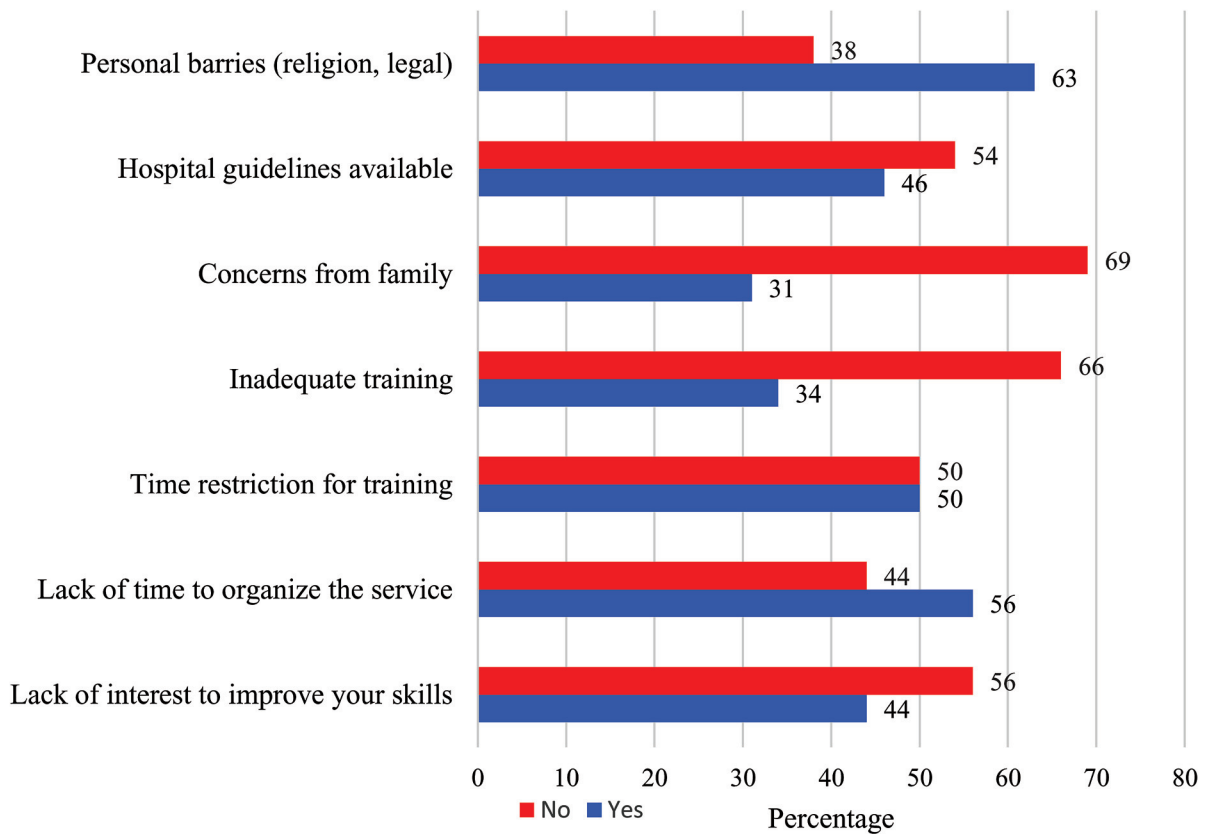


Fig. 2 Internal barriers to provide therapeutic abortions.

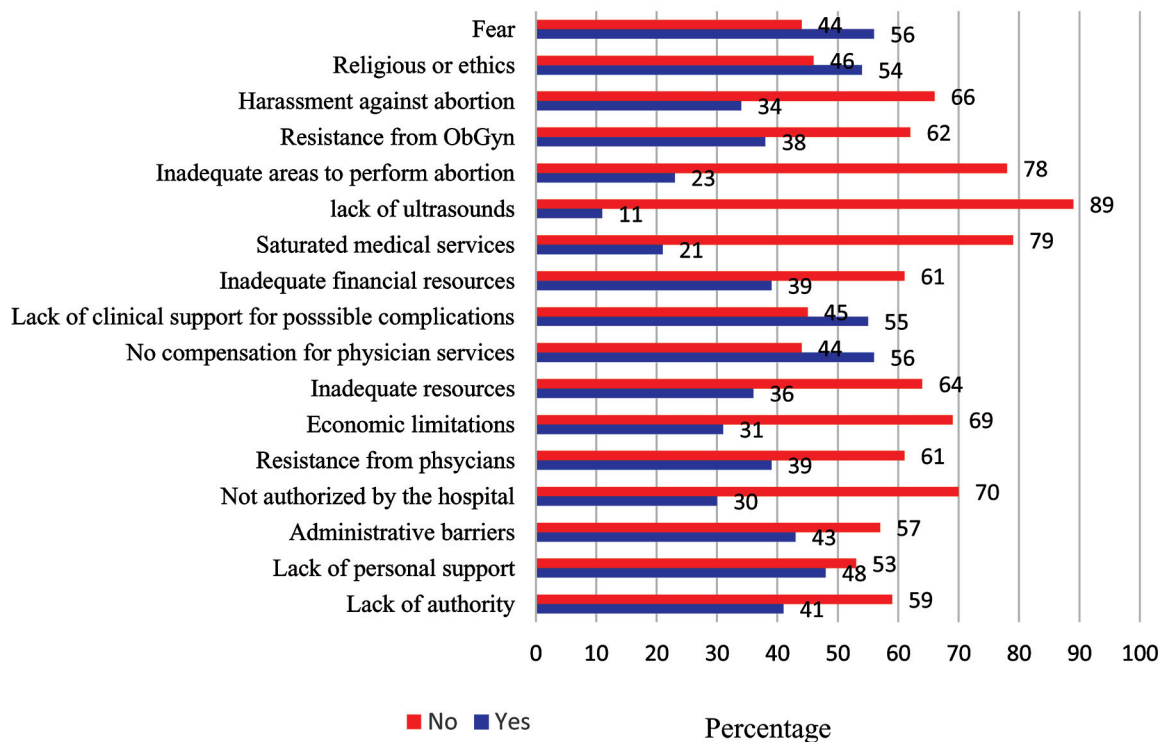


Fig. 3 External barriers to provide therapeutic abortions.

therapeutic abortion in academic centers are consistent with the responses of the participants in our study.

In a study published by Freedman et al.,¹⁸ most doctors who wanted to provide abortion services to their community did not perform it, mainly due to legal barriers or to the institution where they worked. A study in Latin America showed that most doctors who provided services in public hospitals were not aware of the grounds on which abortion is not punishable. In this study, > 60% favored decriminalizing abortion, while only 1 in 5 had performed a therapeutic abortion in their medical practice.¹⁹ One study in Brazil, where it is legal to perform abortions in the case of rape based on a woman's statement, showed that 82% of the physicians required police reports or judicial authorization. This requirement is a major barrier for these women to access safe abortions.²⁰

Access to therapeutic abortions in public institutions in Peru is limited, with just a few public hospitals providing this service. A study published in 2016 reported that in the 10 hospitals where this procedure is performed in Lima, only 257 procedures were performed in the previous 5 years.⁸ A survey conducted with doctors from public hospitals in Lima showed that 44% of them did not agree with some of these legal limitations since they violate the right to doctor-patient confidentiality.²¹

The impact of religion on access to training in therapeutic abortion has also been described. The fact that the institution is associated with a religious entity limits the ability to train residents in therapeutic abortion.^{2,22} In our study, > 80% of the participants considered themselves catholic. However, < 20% of the participants reported that religion was a reason for not participating in therapeutic abortion training.

A recent study by Turk et al.⁹ showed that the most common constraints to physician training identified by directors of residency programs in the United States included institutional or legal policies. The directors of programs that included this training as an integral part of the residency identified fewer restrictions than the directors of programs where they did not train in abortions.⁹

More than 60% of the participants reported that the hospital where they practice does not offer training in therapeutic abortion, and < 50% have trained under the responsibility of another institution. On the other hand, almost 50% of the participants did not carry out a therapeutic abortion during their training, while only 17% performed > 10 procedures. The model of inclusion of abortion training during medical residency has an important impact.

The American College of Obstetricians and Gynecologists (ACOG)¹⁴ reports three types of abortion training models in gynecology and obstetrics residencies in the United States. The first is known as "opt-out," in which the academic center has an abortion program integrated into its curriculum. It is standard for residents to regularly perform this procedure, except for residents who opt out due to religious or moral objections. The second is the "opt-in," in which the academic center provides training only if the resident requests to be trained in that procedure. And the third type of residency is that without abortion training. Turk et al.¹⁵ demonstrated

that residents who were trained in "opt-out" residency programs had a greater number of abortions, greater exposure to abortion procedures, and felt more comfortable in their abilities to perform this procedure. On the other hand, residents of residency programs of the "opt-out" type had the same results as residents of hospitals where this training was not performed.¹⁵ Other studies have shown that residents graduated from "opt-out" training feel more confident in their abilities, not only to provide abortions, but also to manage other procedures and counseling in gynecology and obstetrics.²²⁻²⁴

The training of residents in therapeutic abortion should be comprehensive and should include training in patient counseling, 1st-trimester ultrasound, pain management, cervical dilation, as well as medical and surgical management.¹⁴ Many studies have shown that graduates of training centers where family planning, including abortion, was an integral part of the program, have greater skill in handling not only the procedure, but also all the other aforementioned aspects.^{15,21,22,25}

It is crucial to be able to make changes to improve the training of physicians in family planning, including therapeutic abortion. The ACOG¹⁴ recommends continuing efforts to stop stigmatizing abortion and include it in medical training. They suggest that some measures are to include sexual education and therapeutic abortion in the curriculum of medical schools, as well as to improve exposure to residents for this procedure. Allen et al.²⁶ showed that the factor most strongly associated with whether the obstetrician-gynecologist provides abortion service was whether the provider was interested in training in it before starting residency. This is why it is vitally important to be able to expose medical students to these topics during their undergraduate studies.²⁶

Our study is the first to evaluate the perceptions of therapeutic abortion of a significant number of physicians from academic institutions in Peru. There are many barriers to training and access, and our study describes the most common and prevalent in Peru. For the development of our survey, we used tools previously used by other authors. In addition, we describe the different possible barrier areas such as leadership, resources, and support from other specialties, among others.

Our study also has limitations. The main limitation of our study is that the vast majority of the participants work in Lima, so it is possible that these results do not apply to different areas of Peru. Our study has a few limitations due to its design, such as the possibility of non-honest answers, different interpretations of the questions for each participant, and the possibility that some answers may be guided by the moral and/or religious position of the respondent regarding abortion treatment. Despite its limitations, the present study contributes significantly to knowledge about therapeutic abortion training in Latin America and plays a role in this important public health measure.

Conclusion

Most doctors support therapeutic abortions and show interest in improving their skills; however, not all hospitals offer adequate training and education. During training,

therapeutic abortion procedures are performed in a limited number. Also, lack of knowledge of the law and of institutional policies are common, making fear of ethical, legal, and religious repercussions the main barriers.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Maternal Deaths from COVID-19 in Brazil: Increase during the Second Wave of the Pandemic

Mortes maternas por COVID-19 no Brasil: Aumento durante a segunda onda da pandemia

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Rev Bras Ginecol Obstet 2022;44(6):567–572.

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Abstract

Objective To compare death rates by COVID-19 between pregnant or postpartum and nonpregnant women during the first and second waves of the Brazilian pandemic.

Methods In the present population-based evaluation data from the Sistema de Informação da Vigilância Epidemiológica da Gripe (SIVEP-Gripe, in the Portuguese acronym), we included women with c (ARDS) by COVID-19: 47,768 in 2020 (4,853 obstetric versus 42,915 nonobstetric) and 66,689 in 2021 (5,208 obstetric versus 61,481 nonobstetric) and estimated the frequency of in-hospital death.

Results We identified 377 maternal deaths in 2020 (first wave) and 804 in 2021 (second wave). The death rate increased 2.0-fold for the obstetric (7.7 to 15.4%) and 1.6-fold for the nonobstetric groups (13.9 to 22.9%) from 2020 to 2021 (odds ratio [OR]: 0.52; 95% confidence interval [CI]: 0.47–0.58 in 2020 and OR: 0.61; 95%CI: 0.56–0.66 in 2021; $p < 0.05$). In women with comorbidities, the death rate increased 1.7-fold (13.3 to 23.3%) and 1.4-fold (22.8 to 31.4%) in the obstetric and nonobstetric groups, respectively (OR: 0.52; 95%CI: 0.44–0.61 in 2020 to OR: 0.66; 95%CI: 0.59–0.73 in 2021; $p < 0.05$). In women without comorbidities, the mortality rate was higher for nonobstetric (2.4 times; 6.6 to 15.7%) than for obstetric women (1.8 times; 5.5 to 10.1%; OR: 0.81; 95%CI: 0.69–0.95 in 2020 and OR: 0.60; 95%CI: 0.58–0.68 in 2021; $p < 0.05$).

Conclusion There was an increase in maternal deaths from COVID-19 in 2021 compared with 2020, especially in patients with comorbidities. Death rates were even higher in nonpregnant women, with or without comorbidities.

Keywords

- ▶ COVID-19
- ▶ SARS-CoV-2
- ▶ coronavirus
- ▶ pregnancy
- ▶ acute respiratory distress syndrome
- ▶ maternal death
- ▶ maternal mortality
- ▶ mortality rate
- ▶ case-fatality

received
February 21, 2022
accepted
March 4, 2022
published online
June 1, 2022

DOI <https://doi.org/10.1055/s-0042-1748975>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Palavras-chave

- ▶ COVID-19
- ▶ SARS-CoV-2
- ▶ coronavírus
- ▶ gestação
- ▶ síndrome respiratória aguda grave
- ▶ morte materna
- ▶ mortalidade materna
- ▶ taxa de mortalidade

Objetivo Comparar as taxas de mortalidade por COVID-19 entre gestantes ou puérperas e não gestantes durante a primeira e segunda ondas da pandemia brasileira.

Métodos Na presente avaliação dos dados do Sistema de Informação da Vigilância Epidemiológica da Gripe (SIVEP-Gripe), incluímos mulheres com síndrome respiratória aguda grave por COVID-19: 47.768 em 2020 (4.853 obstétricas *versus* 42.915 não obstétricas) e 66.689 em 2021 (5.208 obstétricas *versus* 61.481 não obstétricas) e estimamos a frequência de óbito intra-hospitalar.

Resultados Identificamos 377 óbitos maternos em 2020 e 804 em 2021. A taxa de mortalidade por COVID-19 aumentou 2,0 vezes no grupo obstétrico (de 7,7 para 15,4%) e 1,6 vezes no grupo não obstétrico (de 13,9 para 22,9%) de 2020 a 2021 (odds ratio [OR]: 0,52; intervalo de confiança [IC] 95%: 0,47–0,58 em 2020 e OR: 0,61; IC95%: 0,56–0,66 em 2021; $p < 0,05$). Em mulheres com comorbidades, a taxa de óbitos aumentou 1,7 vezes (de 13,3 para 23,3%) e 1,4 vezes (de 22,8 para 31,4%) para os grupos obstétricos e não obstétricos, respectivamente (OR: 0,52; IC95%: 0,44–0,61 em 2020 para OR: 0,66; IC95%: 0,59–0,73 em 2021; $p < 0,05$). Em mulheres sem comorbidades, a taxa de mortalidade foi maior para as não obstétricas (2,4 vezes; de 6,6% para 15,7%) do que para mulheres obstétricas (1,8 vezes; de 5,5 para 10,1%; OR: 0,81; IC95%: 0,69–0,95 em 2020 e OR: 0,60; IC95%: 0,58–0,68 em 2021; $p < 0,05$).

Conclusão Houve aumento das mortes maternas por COVID-19 em 2021 em relação a 2020, principalmente naquelas com comorbidades. As taxas de mortalidade foram ainda maiores em mulheres não grávidas, com ou sem comorbidades.

Introduction

Since the first case of COVID-19 was notified in Brazil on February 26, 2020, the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has spread out at an accelerated pace. According to the Brazilian Ministry of Health, from the beginning of the pandemic up to December 09, 2021, a total of 21,184,824 people were infected by SARS-CoV-2, and 616,691 died in Brazil.¹

In the face of a viral pandemic of unpredictable and unknown evolution, the primary concern among obstetricians was whether pregnancy could be a risk factor for severe COVID-19 outcomes, as was seen for respiratory disease caused by the influenza virus in the past decades.^{2,3} The first Brazilian studies using 2020 data from the Acute Respiratory Distress Syndrome (ARDS) Surveillance System (SIVEP-GRIPE, in the Portuguese acronym) reported many maternal deaths. However, they did not define whether pregnant women have a higher risk of severe outcomes than the general female population. Furthermore, early data on maternal mortality from COVID-19 were scarce and limited.⁴⁻⁷

In 2020, the peak of the Brazilian pandemic occurred in the 30th epidemiological week, when 319,653 new cases of SARS-CoV-2 infections were reported in one week. After a short period of slowdown of the pandemic in late 2020, Brazil experienced a rapid acceleration in 2021, reaching 539,903 new cases in the 12th epidemiological week of 2021.¹ Although official obstetric data from the first and second waves have not been fully consolidated in Brazil, we have seen an increase in COVID-19 serious outcomes in

pregnant women at our healthcare center, a referral hospital for high-risk pregnancy care that covers a population of > 6 million people in the Southeast of Brazil (unpublished data).

In the present study, we aim to compare death rates due to ARDS by COVID-19 in pregnant or postpartum and nonpregnant women during the first and second waves of the Brazilian pandemic.

Methods

We conducted an exploratory analysis of death rates due to ARDS by COVID-19 in women aged between 15 and 49 years old with SARS-CoV-2 confirmed by real-time polymerase chain reaction (RT-PCR) or serological antibodies. We compared pregnant and postpartum (up to 45 days after delivery) women, namely the obstetric group, with nonpregnant and nonpostpartum women, who composed the nonobstetric group. We collected data from the SIVEP-GRIPE⁸ from the 8th to the 53rd epidemiological weeks of 2020 (February 26, 2020, to January 2, 2021)⁹ and from the 1st to the 26th epidemiological weeks of 2021 (January 3 to June 30, 2021).¹⁰

Outcomes were defined as crude rates of death or cure among persons included in the SIVEP-GRIPE Brazilian databank. Women were also categorized according to the presence or absence of the following comorbidities: chronic respiratory disease, cardiovascular disease, diabetes, pregestational obesity and/or other conditions (immune deficiency, hematologic disease, hepatopathy, genetic syndrome, kidney chronic pathology, neurology disorder).

We also determined a maternal mortality ratio (MMR) for each Brazilian state as a proportion between the number of deaths due to ARDS by COVID-19 in the obstetric group in the years of 2020 or 2021 and the number of liveborn infants in the year of 2019, obtained from the Brazilian Information System on Live Births (SINASC, in the Portuguese acronym).¹¹ Only births from women aged between 15 and 49 years old were considered.

The detailed database used in the present study is available at the Mendeley Data repository.^{9,10} We evaluated public and unidentified data from a national database that did not require prior ethical committee approval.

We calculated the mean age between the 2 groups and compared it with the Student t-test and the odds ratio (OR) with a 95% confidence interval (CI) to compare mortality. We used the software EPI-Info version 7.2.2.16 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Results

We identified 47,768 women with ARDS by COVID-19 in 2020, of which 4,853 were from the obstetric group and 42,915 were nonobstetric. In the first 6 months of 2021, we identified a total of 66,689 female patients, of which 5,208 were from the obstetric group and 61,481 were from the nonobstetric group (► **Table 1**).

In the 10 pandemic months of 2020, we identified 377 (7.7%) deaths of pregnant or postpartum women (OR: 0.52; 95%CI: 0.47–0.58), whereas, in the first 6 months of 2021, this number increased to 804 (15.4%; OR: 0.61; 95%CI: 0.56–0.66), as shown in ► **Table 1**. Overall, we observed an increase in women deaths from 2020 to 2021: from 7.7 to 15.4% (2.0-fold) in the obstetric group, and from 13.9 to 22.9% (1.6-fold) in the nonobstetric group (► **Table 1**).

Considering the concurrent medical conditions, we observed an OR increase from 0.52 (95%CI: 0.44–0.61) in 2020 to 0.66 (95%CI: 0.59–0.66) in 2021, which not happened with the group of women with no comorbidities. We observed

that the increase in deaths was more pronounced in the obstetric group (1.7-fold; from 13.3 in 2020 to 23.3% in 2021) than in the nonobstetric group (1.4-fold; from 22.8 to 31.4%). However, the inverse was observed for women without comorbidities, in whom the increase in the number of deaths was more expressive in the nonobstetric group (2.4-fold; from 6.6% in 2020 to 15.7% in 2021) compared with the obstetric group (1.8-fold; from 5.5% in 2020 to 10.1% in 2021).

As illustrated in ► **Figure 1**, there was an expressive increase in MMR by COVID-19 in 2021 in almost all Brazilian states. Nonetheless, this increase was most prominent in the North of Brazil, specifically in the states of Amazonas and Roraima, the epicenter of the P.1 emergence.

Moreover, nonpregnant women enrolled in the present study had a significantly higher mean age than pregnant and postpartum women ($p < 0.0001$, t-test; data not shown in tables). This difference was observed both in the 2020 (32 versus 29 years old) and 2021 study periods (38 versus 29 years old).

Discussion

Main Findings

The main findings of the present study were: 1) maternal death rates more than doubled in the second pandemic wave in 2021 ($n = 804$), even considering a shorter period that corresponded to nearly half of the one analyzed in the first wave in 2020 ($n = 377$); 2) there was a remarkable increase in maternal mortality ratio by COVID-19 in 2021 in almost all Brazilian states, after the emergence of the P.1 variant; 3) this increase in mortality was prominent in pregnant or postpartum women with comorbidities; 4) in both periods, deaths were higher in nonpregnant women than in pregnant or postpartum women.

Results in Context with the Scientific Literature So Far

When interpreting any evidence of the impact of COVID-19 on pregnancy, some considerations should be made. Studies

Table 1 Association between acute respiratory distress syndrome by COVID-19 and final outcomes in the obstetric and nonobstetric groups, with or without comorbidities

Group	ARDS/COVID-19 in 2020 (8 th to 53 rd weeks)				ARDS/COVID-19 in 2021 (1 st to 26 th weeks)				Death rate 2020–2021
	Deaths (%)	Cure (%)	OR (95%CI)	n	Deaths (%)	Cure (%)	OR (95% CI)	n	
All Women									
Obstetric	377 (7.7)	4476 (92.2)	0.52 (0.47–0.58)	4853	804 (15.4)	4404 (84.6)	0.61 (0.56–0.66)	5208	2.0
Nonobstetric	5946 (13.9)	36969 (86.1)		42915	14073 (22.9)	47408 (77.1)		61481	1.6
Women with comorbidity									
Obstetric	190 (13.3)	1239 (86.7)	0.52 (0.44–0.61)	1429	487 (23.3)	1598 (76.6)	0.66 (0.59–0.73)	2085	1.7
Nonobstetric	4376 (22.8)	14804 (77.2)		19180	8824 (31.4)	19280 (68.6)		28104	1.4
Women without comorbidity									
Obstetric	187 (5.5%)	3237 (94.5%)	0.81&& (0.69–0.95)	3424	317 (10.1%)	2806 (89.9%)	0.60&& (0.53–0.68)	3123	1.8
Nonobstetric	1570 (6.6)	22165 (93.4)		23735	5249 (15.7)	28128 (84.3)		33377	2.4

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; OR, odds ratio.

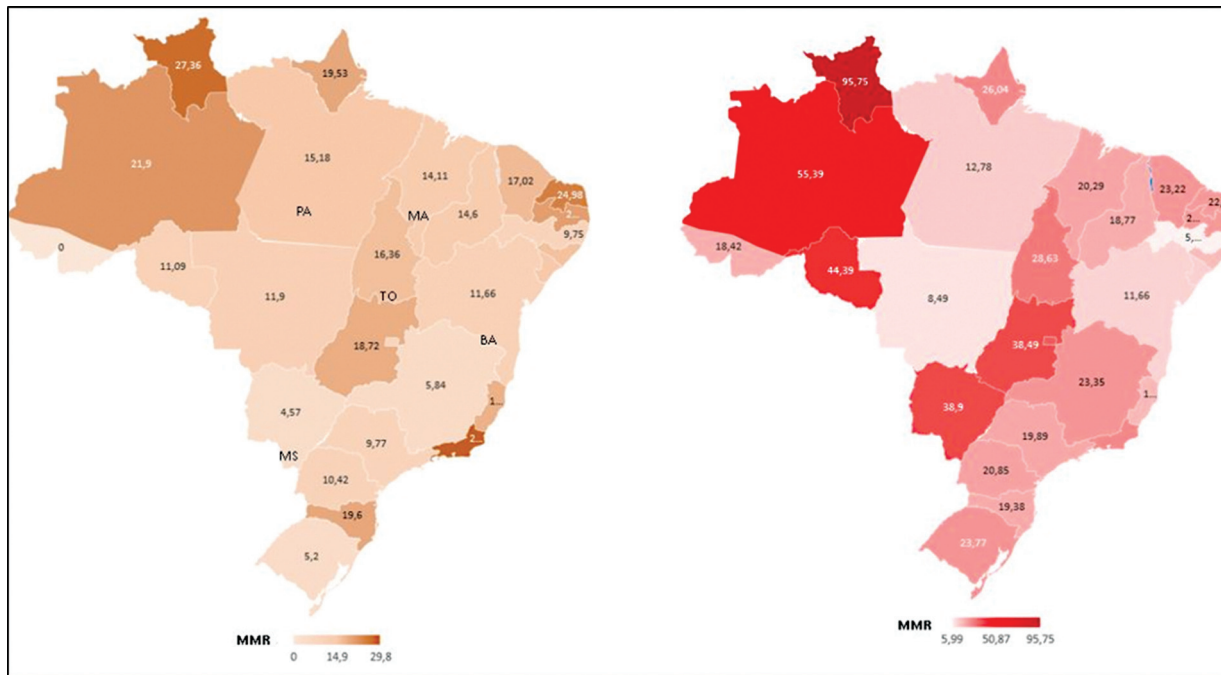


Fig. 1 Maternal mortality ratio (MMR) by acute respiratory distress syndrome (ARDS) by COVID-19 in each Brazilian state for the years of 2020 (February to December) and 2021 (January to June).

focusing on the effects of COVID-19 on pregnant women are often based on symptomatic patients, thus underestimating the rates of unfavorable outcomes in women without COVID-19. Equally scant is the evidence from studies comparing pregnant with nonpregnant women with severe forms of COVID-19.^{12–14}

Our results are in agreement with data from the literature showing that COVID-19 is a sufficient factor for serious clinical outcomes in pregnant/postpartum women and for worse neonatal outcomes.¹⁵ A prospective cross-sectional study conducted at the beginning of the pandemic with a smaller sample size showed an increase in adverse neonatal outcomes in pregnant women with COVID-19 compared with pregnant women without COVID-19, especially in pregnant women with comorbidities.¹⁶ Although the database we used does not provide information on pregnant women without COVID-19, we show a significant rate of maternal deaths by COVID-19, especially in patients with some comorbidity.

A meta-analysis conducted by Khalil et al.¹⁷ showed that maternal intensive care admission due COVID-19 was higher in cohorts with higher comorbidity rates. A small cohort of pregnant patients with initial asymptomatic COVID-19 showed that the development of severity appears similar to that found for nonpregnant women.¹⁴ In our study, the mortality rates of nonpregnant women were higher than those of the obstetric groups in all conditions analyzed. Even so, the increase in maternal mortality from 2020 to 2021 that we found is an important factor, since pregnant women constitute a vulnerable group with restricted access to medications and generally do not participate in clinical research to combat COVID-19, such as vaccine trials.

Comorbidity appeared to be a more significant risk factor for COVID-19 in the nonobstetric group than in its counterpart. Moreover, nonpregnant women enrolled in the present study had a significantly higher mean age than pregnant and postpartum women. We observed this difference in the 2020 (32 versus 29 years old) and 2021 study periods (38 versus 29 years old). It is well-known that aging is associated with worse COVID-19 clinical outcomes, as was demonstrated by Khalil et al.,¹⁷ who indicated that maternal intensive care admission was higher in cohorts with maternal age > 35 years. In our study, the average age difference between the obstetric and nonobstetric groups may be a confounding factor on the influence of comorbidities in older women from the obstetric group. An extension of the present study, adjusting the effect of age and comorbidities in the analyzed groups, is currently being outlined by our research team.

Recently, the world has followed with concern the health-care system collapsing in the city of Manaus, the capital of the state of Amazonas, due to the upsurge of the COVID-19 pandemic. The raised hypothesis of the emergence of a more transmissible variant was confirmed by Faria et al.,¹⁸ who identified a novel SARS-CoV-2 variant of concern in samples collected in November and December 2020 in Manaus. The so-called P.1 lineage acquired 17 mutations, including a trio in the spike protein (K417T, E484K, and N501Y). These researchers also estimated that the P.1 lineage may be more transmissible and more likely to evade protective immunity elicited by previous infection with non-P.1 lineages.

Although the SIVEP-GRIPE database does not provide information on the virus variant, the acceleration of the

Brazilian pandemic observed in late 2020 and early 2021 coincides with the identification of the P.1 lineage. The spread of the newly mutated virus throughout the Brazilian population, consequently infecting more younger women, probably reflected in the observed increase in maternal deaths. As illustrated in **Figure 1**, there was an expressive increase in MMR by COVID-19 in 2021 in almost all Brazilian states. Nonetheless, this increase was most prominent in the North of Brazil, specifically in the states of Amazonas and Roraima, the epicenter of the P.1 emergence. As a comment, in our hospital, there were no deaths in pregnant women in 2020 and, in 2021, 5 deaths in until April. These five cases were positive for SARS-CoV-2; RNA sequencing identified four of them as the P.1 variant and one was identified as a British variant (unpublished data).

Implications for Clinicians and Public Health Managers

The national pandemic scenario presented herein highlights the need for coordinated strategies to contain the pandemic and avoid further spreading of other potentially dangerous variants. Brazil is a continental country, with ethnic, social, cultural and economic disparities that impact access to the health system in different regions. The irregular distribution of the number of deaths throughout the Brazilian states is probably related to different patterns of population exposure and to the deficient infrastructure available to assist severe cases.

Pregnant women represent a unique and vulnerable group. In this context, our study provides crucial epidemiological information for the scientific community and public health managers about the impact of the COVID-19 pandemic on pregnant women. We analyzed data from an extended period, allowing the evaluation of the Brazilian pandemic evolution from its onset in 2020 to its worsening in 2021, the latter coinciding with the emergence of the P.1 variant in Manaus.

Knowledge about the benefits of vaccination in mitigating the pandemic is a consensus all over the world. In Brazil, 63,276,223 people received all the doses prescribed by the vaccination protocol until September 7, 2021.¹⁹ Although there is no consolidated information on the efficacy and safety of COVID-19 vaccines in pregnant women, current guidelines recommend their administration even during pregnancy, as the risks of COVID-19 outweigh the hypothetical risks of the vaccines.²⁰ Vaccination against SARS-Cov-2 in Brazil started on January 17, 2021, in the priority groups defined by the National Immunization Program of the Ministry of Health.²¹ In May 2021, pregnant and postpartum women with comorbidities were included in this priority group, which is consistent with the concerns raised by our results on maternal mortality.

The present study is based on a comprehensive public database that provides information on large numbers of women. Epidemiological information about the deaths of pregnant women is particularly important for the scientific community and public policy managers to fight this pandemic in Brazil.

The present study shows findings that raise the need for actions to protect the health of all women during the

pandemic, since COVID-19 is an important cause of women deaths in Brazil, especially in second wave after the emergence of the P.1 variant of SARS-Cov-2. The increase in maternal deaths in 2021 fosters the debate on the expansion of coverage and acceleration of the vaccination in pregnant women before more dangerous SARS-CoV-2 variants emerge.

Strengths and Weaknesses of the Study

The present study is based on a comprehensive public database on COVID-19, which allowed us to include a large sample size comprising pregnant and postpartum women and compared them with nonpregnant women, all hospitalized with the severe form of COVID-19 confirmed by laboratory and clinical tests.

Although notification of COVID-19 is mandatory in Brazil, we cannot guarantee that the databank covers all women hospitalized due to COVID-19. Data entry is done manually by health professionals throughout the national territory; therefore, there is probably a significant amount of data gaps.

The present study is a comparative analysis of the number of deaths due to COVID-19 between obstetric and nonobstetric women in the years of 2020 and 2021, in the presence or absence of comorbidities. The inclusion of a postpartum group could bias the data analysis, as there is the possibility that some pregnant women with viable fetuses could have been hospitalized with ARDS and underwent childbirth due to the worsening of the clinical condition. Eventual deaths are registered as having occurred in the postpartum period when they resulted from the evolution of the disease since pregnancy. The public database on which the present study is based did not have the necessary data for this evaluation.

Conclusion

There was an increase in maternal deaths from COVID-19 in 2021 compared with 2020, especially in patients with comorbidities. Death rates were even higher in nonpregnant women, with or without comorbidities.

Contributions

Scheler C. A. and Discacciati M. G.: conception and design, analysis and interpretation of data, writing of the manuscript, critical review of the intellectual content, final approval of the version to be published. Scheler C. and Discacciati M. contributed equally to the present paper. Vale D. and Surita F. G.: analysis and interpretation of data, writing of the manuscript, critical review of the intellectual content, final approval of the version to be published. Lajo G.: analysis and interpretation of data. Teixeira J.: conception and design, analysis and interpretation of data, writing of the manuscript, critical review of the intellectual content, final approval of the version to be published.

Conflict of Interests











The authors have no conflict of interests to declare.

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Practical Prediction Model for Ovarian Insufficiency after Radiation

Modelo prático de previsão para insuficiência ovariana após radiação

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Rev Bras Ginecol Obstet 2022;44(6):573–577.

Abstract

Objective The present study aimed to develop a useful mathematical model that predicts the age at which premature ovarian insufficiency might occur after teletherapy radiation. A diagnosis of premature or early menopause has physical and psychological consequences, so women may need support and long-term medical follow-up.

Methods To correlate ovarian radiation dose with ovarian function, we used the formula described by Wallace et al.: $\sqrt{g(z)} = 10^{(2-0.15z)}$, where “g(z)” and “z” represent oocyte survival rate and the radiation dose (in Gray), respectively. By simulating different ages and doses, we observed a pattern that could be used to simplify the relationship between radiation dose and remaining time of ovarian function.

Results We obtained a linear function between ovarian radiation dose and loss of ovarian function (LOF) that is the percentage of decrease in the time to the ovarian failure compared with the time expected for a woman at the same age without irradiation exposition. For patients < 40 years old and with ovarian radiation doses < 5 Gy, the equation $LOF = 2.70 + (11.08 \times \text{Dose})$ can be applied to estimate the decrease in time to premature ovarian insufficiency.

Keywords

- ▶ radiotherapy
- ▶ ovarian insufficiency
- ▶ ovarian function
- ▶ ovarian radiation

received
April 25, 2021
accepted
February 14, 2022
published online
May 26, 2022

DOI <https://doi.org/10.1055/s-0042-1746199>.
ISSN 0100-7203.

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Resumo

Palavras-chave

- ▶ radioterapia
- ▶ insuficiência ovariana
- ▶ função ovariana
- ▶ radiação ovariana

Conclusion The present study reports a practicable theoretical method to estimate the loss of ovarian function. These findings can potentially improve the management and counseling of young women patients submitted to radiotherapy during their reproductive years.

Objetivo O presente estudo teve como objetivo desenvolver um modelo matemático útil que prediz a idade na qual a insuficiência ovariana prematura pode ocorrer após a radioterapia externa (teleterapia). O diagnóstico de menopausa prematura ou precoce tem consequências físicas e psicológicas; portanto, as mulheres podem precisar de apoio e acompanhamento médico de longo prazo.

Métodos Para correlacionar a dose de radiação ovariana com a função ovariana, foi usada a fórmula descrita por Wallace et al.: $\sqrt{g(z)} = 10^{(2-0,15z)}$, na qual “g(z)” e “z” representam a taxa de sobrevivência do oócito e a dose de radiação (em Gray), respectivamente. Ao simular diferentes idades e doses, observamos um padrão que poderia ser usado para simplificar a relação entre a dose de radiação e o tempo restante da função ovariana.

Resultados Obtivemos uma função linear entre a dose de radiação ovariana e a perda da função ovariana (LOF, na sigla em inglês) que é a porcentagem de diminuição no tempo até a falência ovariana em relação ao tempo esperado para uma mulher da mesma idade sem exposição à radiação. Para pacientes < 40 anos de idade e com doses de radiação ovariana < 5 Gy, a equação $LOF = 2,70 + (11,08 \times Dose)$ pode ser aplicada para estimar a redução no tempo até a insuficiência ovariana.

Conclusão O presente estudo relata um método teórico viável para estimar a perda da função ovariana. Estes achados podem melhorar potencialmente o manejo e o aconselhamento de pacientes jovens submetidas à radioterapia durante seus anos reprodutivos.

Introduction

Radiation is an integral component of therapy for a variety of tumors that may affect young people. Most of these tumors are associated with high cure rates; therefore, treatment results in potential risk for survivorship issues.¹⁻³ For young women, premature ovarian insufficiency and decreased reproductive potential are important risks related to this treatment, with consequences regarding bone and cardiovascular health.⁴⁻⁶ Total body craniospinal axis, whole abdominal, or pelvic irradiation potentially expose the ovaries to irradiation.⁷⁻⁹ Radiotherapy is now a well-known cause of ovarian damage. The amount of injury is related to several variables, including the total radiation dose, the fractionation schedule, and age at the time of treatment.¹⁰

The human ovary contains a limited number of primordial oocytes that reaches a peak at 5 months after conception and declines with increasing age in a biexponential fashion. This decline culminates in the menopause, when the number of oocytes is < 1,000, at an average age of 51 years old.¹¹ The ovaries are highly radiosensitive organs. Some authors have suggested that doses > 6 Gy in total body irradiation in young women induce premature ovarian insufficiency, whereas prepubertal women can tolerate even higher radiation doses.² In a large cohort of childhood cancer survivors, 215

cases (6.3%) developed premature ovarian insufficiency. Radiotherapy to the ovaries was the most significant risk factor for premature ovarian insufficiency, especially at doses $\geq 1,000$ Gy, and exposure to the alkylating agents procarbazine and cyclophosphamide, at older ages.¹² Presumably, this reflects the number of oocytes at the time of exposure: a younger patient has more oocytes and, therefore, a wider fertility window.

Wallace et al.¹³ created a mechanism to predict ovarian insufficiency according to the age of the patient and to the fractionated radiation dose received by the ovaries. In that model, they reported sterilizing dose of radiation for a known age at treatment and the age of ovarian insufficiency for total body radiation maximum dose of 3, 6, 9, and 12 Gy. This is the first model to predict with reliability the age at which ovarian insufficiency will supervene for any patient after treatment with a known dose of radiotherapy received by the ovaries. However, the described model does not allow an accessible evaluation of the decrease of the time for ovarian insufficiency for other doses and has limited use in clinical practice. Therefore, the present study aimed to review the model created by Wallace et al. and to develop a mathematical model to facilitate the prediction of ovarian insufficiency in the era of modern computed tomography (CT) radiotherapy planning.

Methods

The present study was approved by the Ethics Committee of the involved institutions (CAAE number: 77681317.3.0000.5128). To correlate ovarian radiation dose with ovarian function, we used the formula described by Wallace et al.:¹³ $\sqrt{g(z)} = 10^{2.10,14}$ where “g(z)” and “z” represent oocyte survival rate and the radiation dose (in Gray), respectively. To solve the differential equation, we applied the fourth order of Runge-Kutta method using a Matlab algorithm and obtained the number of oocytes at a given age and calculated the residual number after irradiation at any dose.¹⁴ The Runge-Kutta is an iterative method used in temporal discretization for the approximate solutions of ordinary differential equations. It has enabled a more accurate estimate of the radiosensitivity of the human oocyte. We considered 701,200 the initial number of oocytes at birth and 1,000 the number necessary at menopause.¹⁵

For the statistical analysis, R software, version 3.4.2 (R Foundation, Vienna, Austria) was used. The loss of ovarian function (LOF) was defined as the percentage of decrease in the time to ovarian insufficiency compared with the time expected for a woman at the same age without irradiation exposition. Assuming that oocyte decay after irradiation was the same as that for nonirradiated oocytes, we simulated the remaining time for women aged between 10 and 50 years old for exposure to 0.5 Gy to doses that cause immediate ovarian insufficiency. From these remaining times, we could obtain a simple equation relating dose and time until menopause.

To define the relationship between loss of ovarian function and dose, a linear regression was fitted.¹⁶ To verify the performance of the model, a cross-validation was performed with the leave-one-out method. At the end of the cross-validation process, the root-mean-square error (RMSE) was calculated.

Results

The numerical solution of the differential equation obtained from the Matlab algorithm is shown in **Figure 1**. The blue curve represents the number of oocytes in a healthy woman

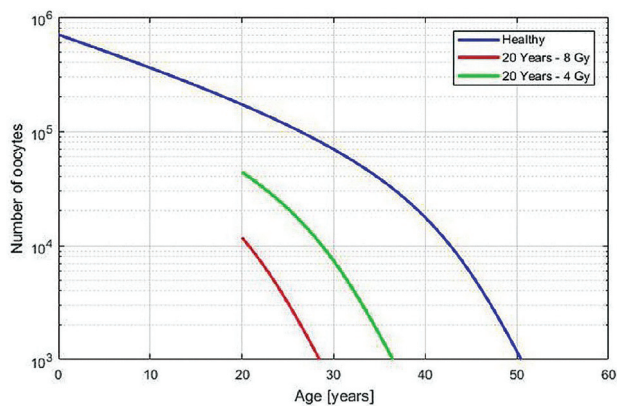


Fig. 1 The influence of aging and fractionated radiation on oocyte number. Blue curve: healthy women; Green curve: woman who received 4 Gy in ovaries at 20 years old; Red curve: woman who received 8 Gy in ovaries at 20 years old.

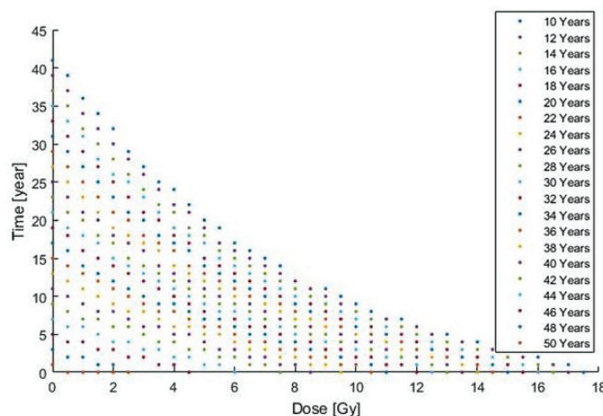


Fig. 2 Expected time of ovarian function remaining after a certain radiation dose for different ages.

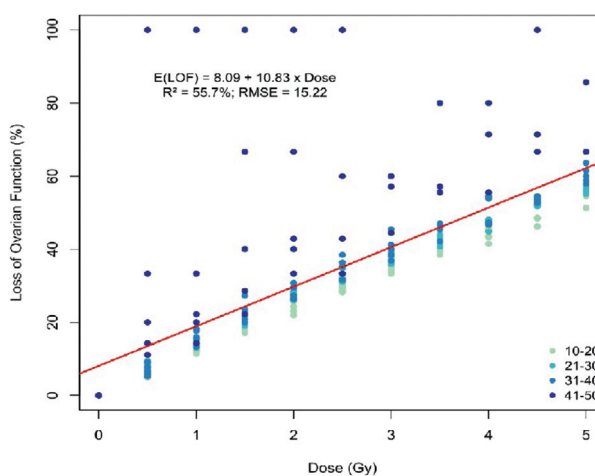


Fig. 3 Relationship between loss of ovarian function and ovarian radiation dose for the complete database.

at a given age. The green curve shows oocyte decay in a 20-year-old patient who received a 4-Gy dose to the ovaries. The red curve shows the same simulation with an 8-Gy dose. From these simulations, it is clear that the radiation dose greatly affects the remaining time until ovarian insufficiency.

Figure 2 shows the remaining time of ovarian function for ages between 10 and 50 years old for doses ranging from zero to those that cause ovarian insufficiency. The first proposed model (**Figure 3**) included the entire database but did not represent a satisfactory adjustment (RMSE = 15.22; $R^2 = 55.7\%$), as the ovarian function loss for women > 40 years old revealed a distinct pattern. Therefore, we readjusted the model excluding women > 40 years old. This new model, represented in **Figure 4**, obtained the equation $LOF = 2.70 + (11.08 \times Dose)$ with an RMSE of 3.05, indicating that the value generated by the formula can range from - 6 to + 6 years (3.05×1.96) with a 95% confidence interval (CI).

Discussion

The equation proposed in the present study can be considered a readily accessible way to predict ovarian insufficiency

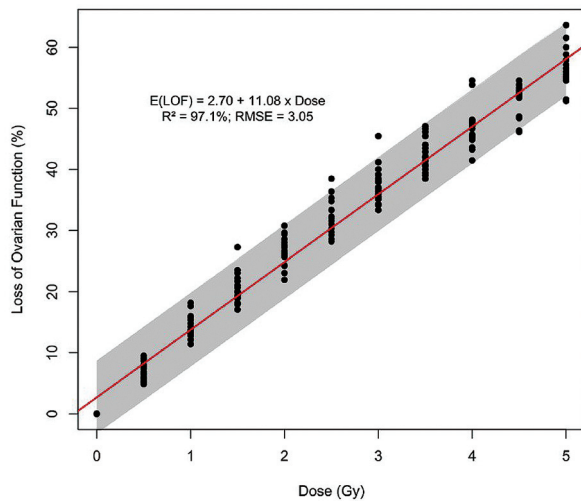


Fig. 4 Relationship between the loss of ovarian function according to the radiation dose in women aged 10 to 40 years.

after radiotherapy with a known dose received by the ovaries. For example, if the ovaries were exposed to 4 Gy at age 27, the patient would have a decrease in time to ovarian insufficiency of 47% [$2.7 + (11.08 \times 4)$] to what would be expected in women of the same age without radiation exposure. In other words, considering 51 years old as the median age of natural menopause, if a 27-year-old patient was exposed to 4 Gy, she would lose 11 years of ovarian function, and would enter menopause at 40 years old.

With no biochemical markers available to predict premature ovarian insufficiency, such a model that determines the extent of radiotherapy-induced damage and allows an assessment of the “fertile window” will have a significant impact on reproductive counseling for young women with cancer. For those young women who are at risk of a very early menopause, it is possible to consider counseling them on the options currently available to preserve their fertility before their treatment starts. Making decisions about preserving future fertility requires that patients receive information from their doctors.

Limitation of radiation dose to the ovary is practiced in adult women with cervical cancer in childbearing age submitted to adjuvant radiotherapy. In the era of radiotherapy, treatment planning based on CT and sophisticated external beam irradiation techniques, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT), sharp dose gradients against normal tissue with a considerable reduction of ovarian radiation dose are possible.¹⁷ In order to minimize the effects of induced menopause, ovarian transposition can be surgically performed and modern radiation techniques can spare the ovaries from high radiation doses (→ **Figure 5**).^{18–20} Calculation of the dose of radiation received by each ovary, combined with a more accurate estimate of the radiosensitivity of the human oocyte, could facilitate our ability to provide more scientific fertility counseling to young women at risk of premature menopause following the successful treatment of cancer. Wallace et al.¹³ reported

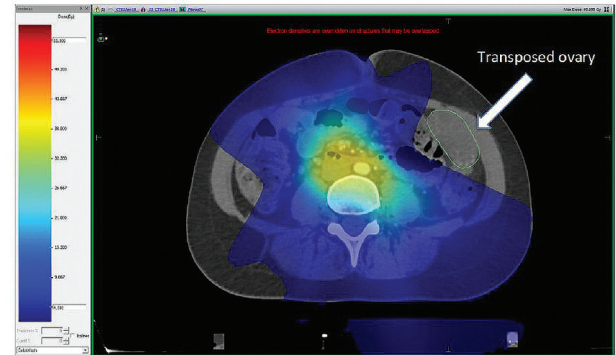


Fig. 5 Computed tomography planning with volumetric arc therapy (VMAT) (Monaco TPS – version 5.51) of a 27-year-old patient in adjuvant radiation for cervical cancer. Isodose (blue color wash) of 4 Gy does not touch the transposed ovary (white arrow).

the first model to predict the age of ovarian insufficiency after treatment with a known dose of radiotherapy. In their publication, they provided a table with the predicted age of onset of ovarian insufficiency for ages of treatment from 0 to 30 years old for fixed doses of 3, 6, 9, and 12 Gy.¹³ Our mathematical model has a sharp CI and yields similar results to those of the table developed by Wallace et al. We observed by our model that the pattern of oocyte/ovarian function loss occurs with different patterns for women younger or older than 40 years old. This can be explained by an increased rate of oocyte loss that occurs around the age of 37 years old, when ~ 25,000 follicles remain.^{21,22}

It is important to note that we did not consider the ovaries receiving different doses, and the results can only be applied to both ovaries receiving the same radiation dose. We acknowledge that this is a predictive model based on preclinical work and that it does not take into account the current use of combined modality treatments. The results do not contemplate the chemotherapy impact on oocytes damage. Radiotherapy is frequently used in combination with chemotherapy for the treatment of cancer. Potentially gonadotoxic chemotherapy may be a contributory factor to the development of premature menopause. It is also important to consider the effect of radiation towards the uterus in terms of fertility. Radiation towards the uterus reduces the size of the organ, makes it less elastic, and, therefore, enhances the risk of spontaneous abortion and premature birth.^{3,4,23}

Conclusion

In summary, the present study enables counseling women on their reproductive potential following the successful treatment of their cancer. We have constructed a mathematical model that could be used to quickly estimate ovarian insufficiency after radiotherapy. More studies with clinical outcomes and follow-up of the patients are needed to validate and optimize the proposed model.

Conflict of Interests








The authors have no conflict of interests to declare.

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One Plus One is Better than Two: An Approach Towards a Single Blastocyst Transfer Policy for All IVF Patients

Um mais um é melhor que dois: Uma abordagem pela prática da transferência de embrião único para todos os pacientes de FIV

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Rev Bras Ginecol Obstet 2022;44(6):578–585.

Abstract

Objective It is known that the single embryo transfer (SET) is the best choice to reduce multiples and associated risks. The practice of cryopreserving all embryos for posterior transfer has been increasingly performed for in vitro fertilization (IVF) patients at the risk of ovarian hyperstimulation syndrome or preimplantation genetic testing for aneuploidy. However, its widespread practice is still controversial. The aim of this study was to evaluate how effective is the transfer of two sequential SET procedures compared with a double embryo transfer (DET) in freeze-only cycles.

Methods This retrospective study reviewed 5,156 IVF cycles performed between 2011 and 2019, and 506 cycles using own oocytes and freeze-only policy with subsequent elective frozen-thawed embryo transfers (eFET) were selected for this study. Cycles having elective SET (eSET, n = 209) comprised our study group and as control group we included cycles performed with elective DET (eDET, n = 291). In the eSET group, 57 couples who had failed in the 1st eSET had a 2nd eFET, and the estimated cumulative ongoing pregnancy rate was calculated and compared with eDET.

Results After the 1st eFET, the ongoing pregnancy rates were similar between groups (eSET: 35.4% versus eDET: 38.5%; $p = 0.497$), but the estimated cumulative ongoing pregnancy rate after a 2nd eFET in the eSET group (eSET + SET) was significantly higher (48.8%) than in the eDET group ($p < 0.001$). Additionally, the eSET + SET group had a

Keywords

- ▶ single embryo transfer
- ▶ freeze-only
- ▶ multiple pregnancy
- ▶ in vitro fertilization
- ▶ pregnancy rate

received
June 23, 2021
accepted
October 21, 2021
published online
May 16, 2022

DOI <https://doi.org/10.1055/s-0042-1743096>.
ISSN 0100-7203.

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2.7% rate of multiple gestations, which is significantly lower than the eDET group, with a 30.4% rate ($p < 0.001$).

Conclusion Our study showed the association of freeze-only strategy with until up to two consecutive frozen-thawed eSETs resulted in higher success rates than a frozen-thawed DET, while drastically reducing the rate of multiple pregnancies.

Resumo

Objetivo Sabe-se que a transferência de embrião único (SET) é a melhor escolha para reduzir as gestações múltiplas e riscos associados. A prática da criopreservação de todos os embriões para transferência posterior tem sido cada vez mais utilizada para fertilização in vitro (FIV), em especial quando há risco de síndrome de hiperestimulação ovariana ou realização de teste genético pré-implantacional. Entretanto, sua utilização disseminada ainda é controversa. O objetivo deste estudo foi avaliar a eficácia de duas SET sequenciais em comparação com uma transferência de embrião dupla (DET) em ciclos de FIV onde todos os embriões foram criopreservados.

Métodos Neste estudo retrospectivo foram revisados 5.156 ciclos de FIV realizados entre 2011 e 2019, e 506 ciclos usando oócitos próprios e criopreservação de todos os embriões com transferências eletivas subsequentes de embriões descongelados, foram selecionados para este estudo. Ciclos com transferência eletiva de embrião único (eSET, $n = 209$) compuseram nosso grupo de estudo e como grupo de controle incluímos os ciclos com transferência eletiva de dois embriões (eDET, $n = 291$). No grupo eSET, 57 casais que falharam na 1ª tentativa de eSET tiveram uma 2ª eFET e a taxa de gravidez em curso cumulativa foi estimada para o grupo eSET e comparada com o grupo eDET.

Resultados Após a 1ª eFET, as taxas de gravidez em curso foram semelhantes entre os grupos (eSET: 35,4% versus eDET: 38,5%; $p = 0,497$), mas a taxa de gravidez em curso cumulativa estimada após a 2ª eFET no grupo eSET (eSET + SET) foi significativamente maior (48,8%) do que no grupo eDET ($p < 0,001$). Além disso, as taxas de gestação múltipla foram expressivamente inferiores no grupo eSET + SET (2,7%) quando comparado ao grupo eDET (30,4%; $p < 0,001$).

Conclusão Nosso estudo mostrou que a associação das estratégias de congelamento de todos os embriões com até duas eSETs sequenciais resultou em maiores taxas de sucesso do que uma DET com embriões descongelados, além de reduzir drasticamente a ocorrência de gestações múltiplas.

Palavras-chave

- ▶ transferência de embrião único
- ▶ criopreservação de todos os embriões
- ▶ gestação múltipla
- ▶ fertilização in vitro
- ▶ taxas de gravidez

Introduction

The ultimate goal of assisted reproduction techniques (ART) is to offer patients the highest chance of having a healthy live birth. However, multiple pregnancies, which carry an increased risk of complications for both fetuses and mothers, is yet a very common condition in ART. Since the first successful conception via in vitro fertilization (IVF) 40 years ago, advances in protocols have resulted in increasing success rates. Nowadays, in the era of personalized medicine, the practice of fixed protocols is becoming outdated and defining individualized parameters for each situation is now considered more appropriate for obtaining higher success rates, that is to say ongoing pregnancy rates (PRs), and fewer adverse effects, such as multiple pregnancies, of IVF.

Among these advances, the improvement in embryo culture, better embryo selection techniques, and excellent

results after embryos vitrification have allowed for better planning of cycles and embryo transfers, also allowing the transfer of a smaller number of embryos without impairment in the outcomes. The single embryo transfer (SET) is the ideal approach to reduce multiple pregnancies.¹ However, despite of the recommendations for a reduction in the number of embryos transferred,² the double embryo transfer (DET) is still the most common practice worldwide, with multiple pregnancies remaining the most important iatrogenic complication of ART.³

Efforts to stimulate SET were made, mainly based on studies demonstrating the transfer of two embryos in sequential SET cycles, with results in similar cumulative live birth rates compared with DET, and reduced multiple pregnancy rates.⁴ However, SET is preferentially practiced in the good prognosis couples⁵ or associated with preimplantation genetic testing for aneuploidy, which also advocates the

freeze-only strategy for most cases. The freeze-only strategy has been increasingly used, in which all available good-quality embryos are frozen, and transfers are delayed for a natural or hormone replacement cycle. This practice is supposed to allow for better synchrony between blastocyst and endometrium maturation, which could hypothetically improve the overall outcomes due to a temporal interaction between an implantation-competent blastocyst and a receptive endometrium.^{6,7} The main indication of the freeze-only strategy is for patients at the risk of ovarian hyperstimulation syndrome (OHSS)⁸ and those undergoing preimplantation genetic testing for aneuploidy.⁹ Despite some authors, who defend the superiority of frozen-embryo transfers' regimen as compared with the fresh embryo transfer strategy in both normal and high-responders,^{10,11} there is no consensus on the widespread use of the freeze-only strategy.¹²

Based on the perception that the combination of freeze-only strategy and SET is an efficient approach, we aimed in this study to evaluate retrospectively the outcomes of the real routine IVF practice in a cohort of patients undergoing the freeze-only strategy, who underwent consecutive elective SET. As reference, we compared the outcomes with patients who had the same characteristics but underwent DET.

Methods

Study Design

This is a retrospective cohort study evaluating freeze-only cycles performed as part of the routine care in a single assisted reproductive center. Written informed consent was obtained from all patients before treatment, consenting to the treatment procedures and to the use of their data in scientific publications with no patient identification.

This study is based on databank of anonymized data and according to local legislation it was exempt from approval by the Institutional Review Board and specific Informed Consent. The database included all IVF cycles performed between 2011 and 2019 at Monteleone Assisted Reproduction Center, São Paulo, Brazil.

The inclusion criteria were cycles of patients in which all embryos were cryopreserved (freeze-only cycles) and no fresh embryo transfers were placed. From 5156 cycles performed in the period of study, we selected 2725 freeze-only cycles. From those, we excluded cycles using donated oocytes, testicle sperm, embryo biopsy and more than 2 embryos transferred in the subsequent frozen-thawed embryo transfers (FET). Missing data were not a reason for case exclusion and all cycle analyzed had all essential data (associated to inclusion or exclusion criteria) and most of the additional information.

The study group included 209 elective SET (eSET), in which patients underwent a SET in their first FET and had at least one surplus embryo cryopreserved (eSET group). Among patients in the eSET group who did not become pregnant, 57 patients underwent a second frozen-thawed SET (eSET + SET). As a comparative group, we included 291 cycles in which two embryos were placed in the first FET and

had at least one surplus embryo cryopreserved composed the elective DET group (eDET group) (– Fig. 1).

IVF Protocol

All patients underwent ovarian stimulation and oocyte pickup according to routine medical criteria. Briefly, pituitary blockage was performed with a GnRH antagonist (Cetrotide, Merck, Darmstadt, Germany). Ovarian stimulation was accomplished using recombinant Follicle-Stimulating Hormone (rFSH, Gonal-F, Merck, Darmstadt, Germany), with 150 IU/day as the starting dose for women up to 35 years of age and 225 IU/day for women older than 35 years. The dose was adjusted according to ovarian response. Follicular maturation was triggered when at least two follicles reached a diameter of 18 mm by using a GnRH agonist (Gonapeptyl, Ferring, Saint-Prex, Switzerland). Oocyte retrieval was performed after 35 to 36 hours by transvaginal ultrasound-guided aspiration. All oocytes were fertilized by Intracytoplasmic Sperm Injection (ICSI)¹³ according to routine procedures; embryos were cultured using standard methods in a triple gas incubator (90% N₂, 5% O₂ and 6% CO₂) at 37°C until vitrification.

All good quality embryos were vitrified on day 3 (D3) or day 5 (D5) using the Vitrification Freeze kit (Irvine Scientific, Santa Ana, CA, USA) with a Cryotip device (Irvine Scientific, Santa Ana, CA, USA), following the manufacturer's instructions. For warming, a Vitrification Thaw kit (Irvine Scientific, Santa Ana, CA, USA) was used. Embryos were evaluated by morphological criteria on D3 and/or D5. The embryos on D3 were considered good quality when they presented 8 to 10 symmetric blastomeres, with no multinucleation, and a maximum fragmentation level of 20%.¹⁴ Blastocysts on D5 were considered good quality when they were expanded, with inner cell mass grade 3 or 4, and the trophectoderm was classified as A or B.¹⁵

For FET, endometrial preparation was conducted with 100 µg of oestradiol valerate (Estradot, Novartis, Basel, Switzerland) for 14 days plus 800 mg of vaginal micronized progesterone (Utrogestan, Farmoquímica, FQM, Rio de Janeiro, RJ, Brazil) beginning 5 days before the transfer. Patients had standard endometrium evaluations through ultrasonography, and no other endometrial evaluations or procedures were performed. Embryos were thawed and evaluated for survival and morphology. For embryos cryopreserved at the cleavage stage, they were thawed, evaluated for survival, cultured until blastocyst stage, evaluated for morphology, and transferred. For embryos cryopreserved at blastocyst stage, they were warmed, evaluated for survival and morphology, and transferred in the same day. A higher quality blastocyst was always preferentially transferred.

Data Collection and Statistical Analysis

The data were obtained from the clinical report forms and tabulated for this study. The groups were determined according to the number of embryos transferred (SET or DET). However, the choice for the number of embryos to be transferred was not controlled, as it was a shared decision

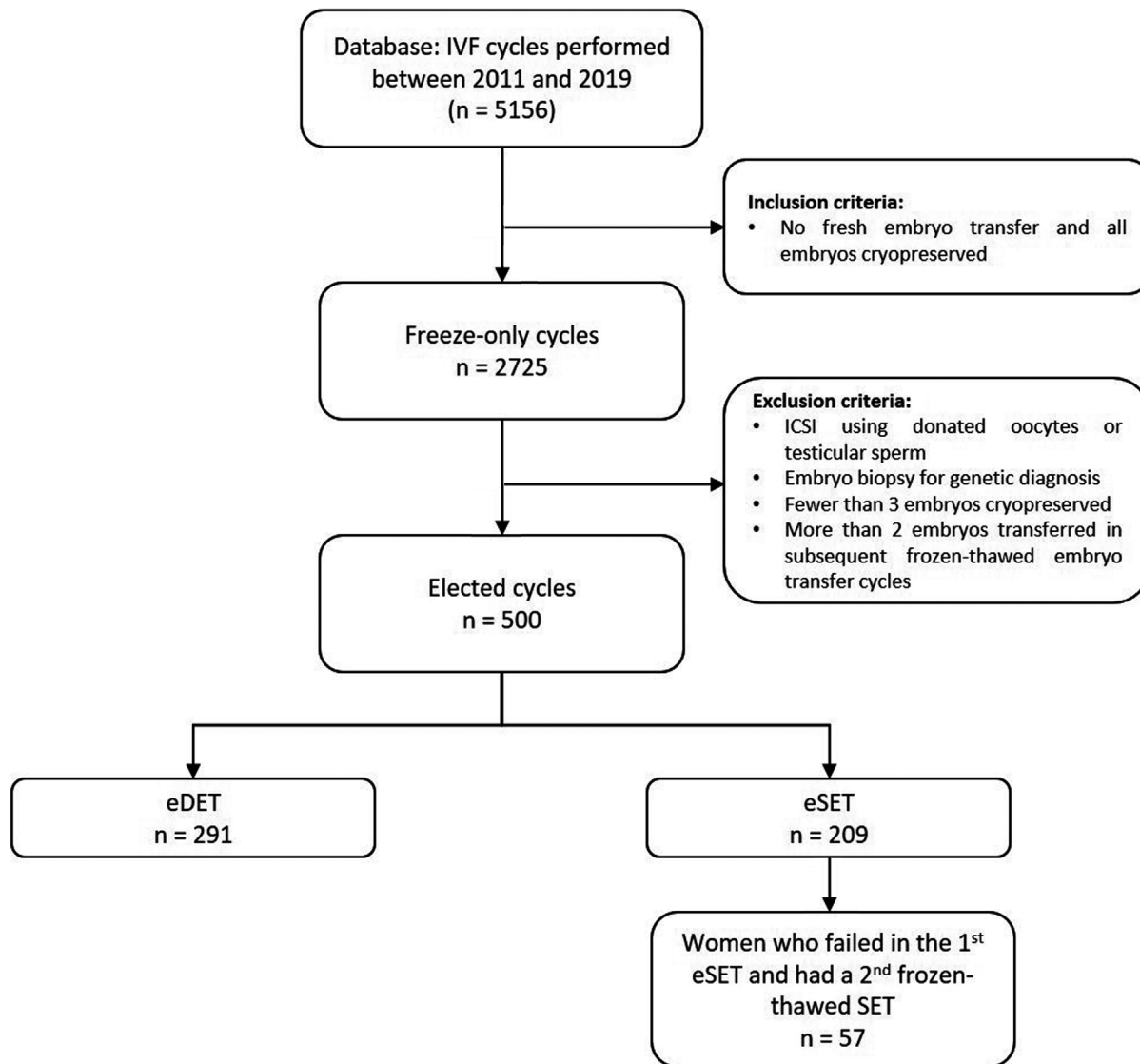


Fig. 1 Workflow of study design.

between the couple and an assistant doctor. The woman's age, number of previous failed cycles, infertility factor, embryos quality, and the couple's choices were the factors that guided the number of embryos to be transferred, as is routine in the clinical practice.

The primary endpoint was an ongoing pregnancy, defined by the presence of a gestational sac with a heartbeat at 2 weeks after biochemical confirmation of pregnancy with serum β -hCG measurement. The ongoing pregnancy rate (PR) was calculated as the number of patients presenting a gestational sac with a heartbeat divided by the number of patients with embryos transferred, after the first transfer. Additionally, for the calculation of the cumulative ongoing PR, considering the 2nd SET for patients who did not become pregnant in the 1st SET (eSET + SET), we used a formula previously described by Luke et al. (2015): cumulative ongoing PR was equal to [ongoing PR for the 1st SET + ongoing PR for the 2nd SET * (1 - ongoing PR for the 1st SET)]. This calculation assumes no contraindication during cycle 1 for

continuing into cycle 2, and estimates an outcome assuming that all patients who failed in the first cycle had a second SET.

The secondary outcomes evaluated in this study were multiple pregnancy rate (n° of patients with multiple gestational sacs divided by the total n° of patients with gestational sac), the implantation rate (IR) (n° of gestational sacs divided by the n° of embryos transferred) and miscarriage rate (n° of miscarriages divided by the n° of patients with gestational sac). Data analysis was performed using SPSS V.21 (IBM SPSS Software, USA). Normality distribution tests were performed, and patient demographic data were evaluated using descriptive statistics, including the means and frequencies. As data were normally distributed, parametric tests were used to compare means (Student *t*-test) of continuous variables. The Pearson chi-squared test was used to compare frequencies as appropriated. We considered *p*-values ≤ 0.05 to be statistically significant.

The sample power calculation was performed by using a two-tailed, two proportions calculation using the number of

Table 1 Demographic characteristics of patients and cycles included in the study

n	eSET	eDET	p
	209	291	
Age (years)	35.4 ± 3.9	34.9 ± 4.2	0.155
Body mass index (kg/m ²)	22.5 ± 2.9	23.1 ± 3.6	0.092
Infertility time (years)	2.5 ± 1.7	2.9 ± 2.2	0.053
Basal FSH (IU/mL)	6.3 ± 5.0	6.3 ± 3.2	0.959
Total gonadotropin dose administered (IU)	1.809.4 ± 372.2	1.869.9 ± 481.4	0.129
Number of collected oocytes	20.0 ± 11.5	17.0 ± 9.2	0.002
Number of collected MII oocytes	15.2 ± 8.5	13.3 ± 7.4	0.008
Number of cryopreserved embryos	9.1 ± 4.5	8.8 ± 4.5	0.381

Note: According to the Student t-test. Abbreviations: eDET, elective double-embryo transfer; eSET, elective single-embryo transfer; FSH, follicle-stimulating hormone; MII, metaphase II.

samples included in the study and cumulative ongoing PRs for eDET and eSET + SET groups. For the significance level (α) of 5%, the sample power (β) was 0.60.

Results

Most of the couples included in the study were undergoing their first or second IVF cycles (88.1%). The demographic characteristics of the patients/cycles included in the study are presented in **Table 1** and compared using the Student t-test.

For the first FET, we compared clinical outcomes between groups. The ongoing PRs and miscarriage rates were similar, while lower implantation and higher multiple PR rates were observed in the eDET group, as expected. The eSET group had two monozygotic twin pregnancies (2.7%), which is compatible with the incidence of twins in natural conception (**Table 2**).

In the eSET group, 135 women had their first transfer fail and 57 performed a second SET (eSET + SET, $n = 57$), resulting in 12 ongoing pregnancies (21.1%). Among the 78 remaining couples, 51 received two embryos in the second transfer with 18 ongoing pregnancies (35.3%). A total of 27 couples did not undergo a second transfer despite having embryos cryopreserved, resulting in a dropout rate of 20.0%. Our primary endpoint was to compare the clinical outcomes after the transfer of two embryos in one transfer cycle (eDET)

or in two sequentially eSETs. The cycles in which an eSET failed in the first transfer, with none or a DET in the second transfer could not be included in the calculations. Then, we calculated the estimated cumulative ongoing PRs of the eSET + SET subgroup, according to the previously described formula, which assumes that all patients who failed in the first eSET would have received a second frozen-thawed SET. We named that result as estimated cumulative ongoing PRs for eSET + SET group. The comparison showed that the cumulative ongoing PR is significantly higher (10% higher) when two SETs are performed compared with the DET group (**Fig. 2**).

Discussion

Aiming to decrease the rate of multiple pregnancies and its consequences in IVF cycles, reproductive medicine and IVF societies stimulate the use of SET procedures. In general, the reduced number of embryos transferred for a maximum of two in most cases had a great impact for decreasing high order multiple pregnancies, but the rate of twin pregnancies is still excessive and heterogeneous globally. Despite several countries and clinics having introduced SET in their routine, there are several barriers that hinder the implementation of that practice. The female age is the foremost demographical factor influencing the number of embryos transferred, due to societal pressure on older women to have children, longer duration of

Table 2 Clinical outcomes of the study groups

	eSET	eDET	p
Number of transfers	209	291	
Implantation rate (%)	44.4%	29.7%	< 0.001
Ongoing pregnancy rate (%)	74/209 (35.4%)	112/291 (38.5%)	0.497
Miscarriage rate (%)	20/94 (21.3%)	26/138 (18.8%)	0.648
Multiple pregnancies rate (%)	2/74 (2.7%)	34/112 (30.4%)	< 0.001

Note: According to the continuity correction chi-square test. Abbreviations: eDET, elective double-embryo transfer; eSET - elective single-embryo transfer.

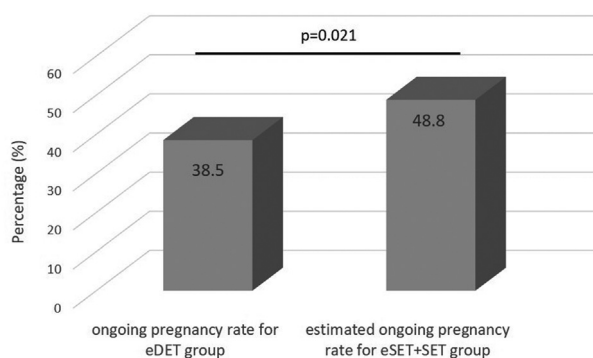


Fig. 2 Cumulative clinical pregnancy rate after the transfer of two embryos in one transfer (eDET group) and in two single embryo transfers (eSET + SET group). Abbreviations: eDET, elective double-embryo transfer; PR, pregnancy rate; SET, single-embryo transfer.

infertility, and the reducing pregnancy chances with their own oocytes. The number of embryos available for transfer and their morphological quality is a biological factor that also influences this decision. In another facet of ART, three environmental aspects are important to mention; first, the financial issues are an important barrier, in which the insurance or government coverage of treatments, associated to the perception of transferring more embryos bringing a higher chance of pregnancy, can influence the choice of the number of embryos to be transferred. Societal, religious, and cultural factors can also impact the SET choice, as can some couples' desire to have twins regardless of the risks. Finally, the highly competitive market and the commercialization of ART services, drives the desire of providers to show higher success rates, even at the risk of high rates of multiple pregnancies.¹⁶

On the other hand, the only efficient strategy to avoid multiple pregnancies in ART is SET. A randomized clinical trial (RCT) already showed the equivalence of two single embryo transfers compared with a double embryo transfer in different combinations almost 20 years ago. Thurin et al.¹⁷ demonstrated the equivalence of one fresh SET plus one frozen-thawed SET compared with a fresh DET, with a dramatic reduction in multiple pregnancy rates. Following that, several studies demonstrated similar outcomes,^{18,19} which in turn supports the recommendation of reproductive medicine societies to performing SETs.

Our study had a different outcome. We demonstrated that, besides the advantage of avoiding multiple gestation, two consecutive frozen-thawed SETs results in higher success rates than DET in one frozen-thawed cycle. The association of the freeze-only strategy with consecutive frozen-thawed SETs has not been extensively studied and most of the studies describe one SET in the fresh cycle and subsequent frozen-thawed ones. One retrospective study showed similar cumulative pregnancy and live birth rates after single and double frozen-thawed blastocyst transfers after a freeze-only strategy,²⁰ and another study evaluating the freeze-only strategy and SET in women with hypogonadotropic hypogonadism showed that SET is an effective strategy for decreasing the incidence of multiple conceptions while maintaining satisfactory live birth rates (50.5%).²¹

Corroborating our hypothesis of better clinical outcomes after a freeze-only strategy plus SET, the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology (ASRM/SART) recommended SET for patients with a good prognosis aged < 38 years, except in cases in which the patient had several previous cycle failures and for whom DET was suggested.⁵ Reinforcing the efficiency of the ASRM/SART recommendation, Eubanks et al.²² evaluated retrospective data about clinical PRs before and after the ASRM/SART guidelines were published in 2017, as their clinic policy is to transfer no more than the recommended number of embryos. The study assessed patients < 38 years old using their own eggs and without preimplantation genetic testing, before (mean of 1.3 embryos transferred per patient) and after (all single embryo transfers) guideline revision. The outcomes showed that SET was very efficient in this population, as the overall live birth rates were maintained at around 50% after the reduction in the number of embryos transferred, and the twin PR rates decreased from 14.2% to 2.5%.²²

The differential characteristic of our study, compared with previous publications is that we used a freeze-only strategy, in which all embryos were cryopreserved by vitrification and transferred in subsequent hormone replacement cycles in the blastocyst stage, independently of the patients' age. Our population is composed of mainly good prognosis patients, considering a mean of 9 embryos cryopreserved per patient. But we showed better outcomes by using the sequential SETs approach and can discuss several hypotheses that support this unprecedented result. Some of the most important variables associated with the embryo implantation potential which have been the focus of several studies are: the embryo quality evaluated using conventional morphology, time-lapse morphokinetics, or preimplantation genetic test,²³ as well as the endometrium status,²⁴ and embryo-endometrial synchrony²⁵

Studies have investigated progesterone action, endometrium gene, receptors, and protein expression based on data from the endometrial receptivity array.^{26,27} More recently, the endometrium microbiome and its association with embryo implantation have been studied by the same research group.²⁸ Although the association of endometrium gene expression or microbiome with the implantation rates is controversial in the literature,²⁹ it is clear that there is a variability in the endometrial condition between cycles according to the patient's clinical condition or changes in the treatment approach. These variations in the endometrium performance can support the greater chance of implantation when performing consecutive SETs compared with one DET, as we transfer embryos in different endometrial conditions after one previous failure.

In the case of embryo feature, the vitrification technique is able to maintain the embryo implantation potential,^{30,31} which, in turn, allows the performance of a freeze-only strategy and consecutive transfers in natural or hormone replacement cycles without impairment in the implantation potential. An extensive study evaluating more than 20,000 freeze-only cycles and FETs, in which all embryos transferred from that stimulation cycle were considered, demonstrated

that the mean cumulative live birth rate was 50.0%, and dependent on the number of oocytes collected and the patient's age, recommending the applicability of the freeze-only strategy for the general population.³² Besides that, the culture conditions, including time-lapse incubators and morphokinetic evaluation of embryos, preimplantation genetic test, and other add-ons can be applied to select embryos and encourage the practice of SET.³³

Considering the existence of variables that cannot be controlled in a clinical routine, and those inherent to the procedure that can be corrected in a subsequent cycle, it is reasonable to note that the transfer of embryos in separate events (consecutive SETs) will allow corrections, and produce a higher success rate than the transfer of two embryos in a single event. Our study confirmed the efficiency of the freeze-only strategy but, more importantly, we showed that consecutive SET is the better option for embryo transfer protocol and should be more extensively used. Owing to the retrospective nature of our study, we cannot exclude the possibility of residual interfering factors such as endometrium status or embryo ploidy, as these conditions were not evaluated in the cycles included in our study. A limitation of our study lies in the fact that not all patients who had a failed eSET in the 1st transfer proceeded to a 2nd SET cycle. Nevertheless, the calculation used in our study estimated the cumulative ongoing PRs as if all women who had a failed first SET had a second SET, confirming a clear advantage of SET over DET.

We must consider that the decision about the number of embryos to be transferred and their quality cannot be controlled, either. As a clinical routine, the number of embryos transferred is determined through a shared decision-making process between patients and doctors, after explaining the advantages and disadvantages of each procedure. Thus, the choice of the number of embryos to be transferred could have been influenced by the quality of the blastocysts available and the couple's preferences. Additionally, the percentage of couples undergoing their first or second cycle was a little higher in the eSET group (92.3%) than in the eDET group (85.1%), which can be another reason to choose DET for some couples. Although, it should be mentioned that our practice prioritizes transferring the best-quality frozen-thawed blastocysts available, all cycles included were elective (with at least one surplus frozen blastocyst), and the demographic characteristics of our study groups were similar, which made the comparisons possible.

Another point of our study that deserves attention is the similar ongoing pregnancy rates even after the first embryo transfer, while most studies show a higher pregnancy rate after DET when compared with SET. Most studies comparing the DET and SET strategies were performed in fresh cycles, which regards the condition of the endometrium after ovarian stimulation, or of FET after an unsuccessful fresh transfer, which means that the transferred embryo was not the first choice, and probably not the best quality one for that cycle. Our outcomes can be explained by the freeze-only strategy used in our study, and FET transferred the best quality embryo of the cohort in the hormone replacement cycle. Those outcomes can support the superiority of the freeze-all strategy even in cycles

without classic indications, such as risk of OHSS or genetic evaluation of embryos. It is important to highlight that we excluded cycles with genetic analysis of embryos, and we did not have endometrium evaluations other than ultrasonography; therefore, we are studying only the regular embryo and endometrium evaluations.

Conclusion

In summary, our study not only shows that eSET in freeze-only cycles maintains similar ongoing PRs to those of DET group after the first transfer, but also indicates that a second consecutive SET brings the best cost-benefit ratio, as it increases the success rates and decreases the rate of multiple pregnancies. Finally, several strategies can be used to avoid multiple pregnancies while keeping the satisfactory or desired success rates, and maybe it is time to consider that multiple embryo transfers should no longer be used in clinical practice. The freeze-only strategy and consecutive SETs can be an effective choice, as the one plus one approach is better than the two embryos transfer approach, leading to an increased chance of implantation and avoiding of multiple gestations.

Contributions

Pedro FM Peregrino: data acquisition and revising the article critically for important intellectual content. Tatiana CS Bonetti: conception and design, analysis and interpretation of data, drafting the article and revising critically for important intellectual content. Alecsandra P Gomes: data acquisition and revising the article critically for important intellectual content. Hamilton de Martin: data acquisition and revising the article critically for important intellectual content. José Maria Soares: revising the article critically for important intellectual content. Edmund C Baracat: revising the article critically for important intellectual content. Pedro AA Monteleone: conception and design; interpretation of data; and revising critically for important intellectual content.

Conflict of Interest

The authors have no conflict of interests to declare.

Acknowledgments

The authors gratefully acknowledge the contributions of the team from Centro de Reprodução Humana Monteleone, São Paulo, Brazil, for their excellent support with patients, procedures, and data collection.





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Does Obesity Aggravate Climacteric Symptoms in Postmenopausal Women?

A obesidade agrava os sintomas climatéricos em mulheres na pós-menopausa?

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Rev Bras Ginecol Obstet 2022;44(6):586–592.

Abstract

Objective To determine if there is a correlation between body mass index (BMI) and climacteric symptoms in postmenopausal women.

Methods The study sample was composed of 109 postmenopausal women with a mean age of 57 ± 8 years, mean body mass index (BMI) of 30 ± 6 kg/m², and 8 ± 8 years after menopause. For the assessment of the climacteric symptoms, the Blatt-Kupperman Index (BKI), the Menopause Rating Scale (MRS), and the Cervantes Scale (CS) were used. Data analysis was performed through the Chi-squared test, analysis of variance (ANOVA) with the Bonferroni post hoc test, and multiple linear regression. The level of significance adopted was of $p < 0.05$. The statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, United States) software, version 26.0.

Results The multiple linear regression showed a positive association ($p < 0.01$) between BMI values and menopause symptoms when adjusted for age and time after menopause in the 3 questionnaires used (BKI: $B = 0.432$; CS: $B = 304$; and MRS: $B = 302$). Regarding symptom scores, the obese women had higher mean scores ($p < 0.05$) when compared to eutrophic women (BKI = 28 ± 10 and 20 ± 10 ; and MRS = 20 ± 10 and 13 ± 7 , respectively). In the Chi-squared analysis, 28% of obese women had severe symptoms and 46% had moderate symptoms, while only 1% and 46% of eutrophic women had these same symptoms.

Conclusion There is an association between BMI and climacteric symptoms, and overweight or obese women have more intense and moderate symptoms than eutrophic women.

Keywords

- ▶ climacteric symptoms
- ▶ obesity
- ▶ overweight
- ▶ menopause

received
April 15, 2021
accepted
February 3, 2022

DOI <https://doi.org/10.1055/s-0042-1745789>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo Verificar se há correlação entre o índice de massa corporal e os sintomas do climatério em mulheres na pós-menopausa.

Métodos Participaram do estudo 109 mulheres na pós-menopausa, com idade média de 57 ± 8 anos, índice de massa corporal (IMC) médio de $30 \pm 6 \text{ kg/m}^2$ e 8 ± 8 anos após a menopausa. Para a avaliação dos sintomas climatéricos, foram utilizados os questionários específicos para essa população: Índice de Kupperman-Blatt (IKB), Menopause Rating Scale (MRS), e Escala de Cervantes (EC). A análise dos dados foi realizada por meio do teste do chi-quadrado, análise de variância (*analysis of variance*, ANOVA, em inglês) com o teste *post hoc* de Bonferroni e regressão linear múltipla. O nível de significância adotado foi $p < 0,05$. Todas as análises estatísticas foram realizadas no programa Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, Estados Unidos), versão 26.0.

Resultados A regressão linear múltipla mostrou associação positiva ($p < 0,01$) entre os valores do IMC e os sintomas do climatério quando ajustados pela idade e pelo tempo após a menopausa nos 3 questionários utilizados (IKB: $B = 0,432$; CE: $B = 304$; e MRS: $B = 302$). Quanto às pontuações dos sintomas, as mulheres com obesidade apresentaram médias maiores ($p < 0,05$) quando comparadas às mulheres eutróficas (IKB = 28 ± 10 e 20 ± 10 ; e MRS = 20 ± 10 e 13 ± 7). Na análise pelo chi-quadrado 28% das mulheres obesas apresentaram sintomas graves, e 46%, moderados, ao passo que apenas 1% e 46% das eutróficas apresentavam esses mesmos sintomas.

Conclusão Há uma associação entre IMC e sintomas climatéricos, e mulheres com sobrepeso ou obesidade apresentam sintomas mais intensos e moderados do que mulheres eutróficas.

Palavras-chave

- ▶ sintomas climatéricos
- ▶ obesidade
- ▶ sobrepeso
- ▶ menopausa

Introduction

With the increase in the life expectancy of women in Brazil, the fact that menopause occurs at the approximate age of 50 years results in a greater number of women living almost one-third of their lives in postmenopause.¹

The onset of symptoms is related to the tissues and organs that have estrogen receptors (α and β), and, in a situation of hypoestrogenism, clinical manifestations are present, with the most common being those related to genitourinary syndrome of menopause (GSM), osteoporosis, and vasomotor symptoms. Hot flashes, night sweats, and palpitations are vasomotor symptoms that affect 80% of women during the climacteric period, with 50% experiencing effects on quality of life due to the intensity and frequency of these symptoms.^{2,3}

The symptoms are due to multiple factors, which, in addition to low levels of estrogen, are related to the aging process and to psychosocial factors, and, according to several longitudinal population studies,^{4,5} ethnic, geographic, and individual factors also affect the prevalence and severity of symptoms. Therefore, not all changes (such as those regarding libido, mood, cognition, or weight gain) are specific to menopause, although they may be secondary to vasomotor symptoms and subsequent insomnia. Several diseases associated with menopause, such as obesity, coronary vascular disease, cancer of the reproductive organs, depression, and dementia may also occur.³

In addition to changes in the reproductive system, a lifestyle with increased physical inactivity, added to the

changes resulting from the aging process, leads to important changes in the body composition of women during this period, with a gradual reduction in metabolism and increases in body and fat mass, which may reach 0.7 kg per year.⁶⁻⁹

Physiological changes during the climacteric period occur not only due to ovarian failure, but also due to changes in hypothalamic and pituitary functioning.¹⁰ In addition, estrogen is a hormone that directly affects fat tissue, the inflammatory profile, and oxidative stress.¹¹ These changes resulting from the climacteric, specifically in postmenopause period, may represent a link between obesity and the climacteric period, implying an increase and distribution of body fat and possibly affecting the frequency and intensity of symptoms.

Saccomani et al.¹² analyzed the relationship between obesity and climacteric symptoms and found a positive relationship using the Menopause Rating Scale, however, all climacteric women were considered as a population, with no stratification according to menopause stage. In a study by Essa and Mahmoud,¹³ obese women were found to be 2.11 times more at risk of developing symptoms when compared to women with a normal body mass index (BMI); however, the authors assessed other correlated factors, such as chronic diseases and smoking, and analyzed the symptoms with instruments different from those used in the present study. The objective of the present study is to understand the relationship between the body mass index factor and climacteric symptoms, using three different questionnaires in a

group of women of the same post-menopausal climacteric stage.

Our hypothesis is that body mass (more specifically, BMI) affects the expression of climacteric symptoms, whose intensity and frequency in postmenopausal women will increase as the BMI increases. Therefore, the present study attempts to correlate BMI with climacteric symptoms in postmenopausal women.

Methods

The sample was composed of 109 postmenopausal women recruited through advertisements in traditional media (newspapers, radio and TV) and electronic media (social networks), with telephone contact available for those interested. After contacting the women and verifying if they met the inclusion criteria, interviews were scheduled to apply the questionnaires. Women aged between 50 and 70 years were included; the other inclusion criteria were amenorrhea for at least 12 months, no current use of hormone therapy or phytoestrogens, and non-smoking status.

The present is an observational, cross-sectional study conducted from March 2018 to March 2019 through interviews. Specific questionnaires were applied to assess the climacteric symptoms and anamnesis, including data on age, time after menopause (years), and weight and height (self-reported) in order to calculate the BMI. All assessments were previously scheduled, and the questionnaires were administered at the Laboratory of Cardiorespiratory and Metabolic Physiology (Laboratório de Fisiologia Cardiorrespiratória e Metabólica, LAFICAM, in Portuguese) of the School of Physical Education and Physical Therapy (Faculdade de Educação Física e Fisioterapia, FAEFI, in Portuguese) of Universidade Federal de Uberlândia (UFU), in the State of Minas Gerais, Brazil. The study was approved by the local Ethics Committee (CAEE: 12453719.1.0000.5152).

The climacteric symptoms were assessed using the version validated for Brazilian Portuguese of the Menopause Rating Scale (MRS) and the Cervantes Scale (CS).^{14,15} The Blatt-Kupperman Index (BKI), although not validated for the Brazilian population, showed reliability,¹⁶ and has been used in other studies¹⁷⁻¹⁹ with this population.

The BKI consists of eleven symptoms (vasomotor, paresthesia, insomnia, nervousness, melancholy, vertigo, weakness, arthralgia/myalgia, headache, palpitations, and tingling), to which different scores are attributed. The total score is classified as light (≤ 19), moderate (from 20 to 35) or intense (≥ 36).²⁰

The MRS consists of eleven questions that address psychological, somatic and urogenital domains. There are five possible answers for each question according to the intensity of the symptoms: none (0 points), mild (1 point), moderate (2 points), severe (3 points) and extremely severe (4 points). The total score can vary from zero to 44 points, and is classified as asymptomatic or scarce (0-4 points), mild (5-8 points), moderate (9-15 points) or severe (> 16 points).¹⁵

The CS is a questionnaire composed of 31 questions divided into 4 domains: menopause and health (15 items),

the psychic domain (9 items), couple relationships (3 items) and sexuality (4 items). For each question, there are 6 possible answers with scores from 0 to 5. In addition to a negative scale, the positive questions (4, 8, 13, 15, 20, 22, 26 and 30) have an inverted score for the total sum. The sum of the points can vary from 0 to 155, with 0 corresponding to the best quality of life in the climacteric period, and 155, the worst.¹⁴

The sample size was calculated according to the formula presented by Tabachnick and Fidell,²¹ which considers the number of explanatory variables to be included in the model ($n = 50 + 8m$ [m is the number of explanatory variables]; given that $m = 3$ in the present study, a minimum of 74 women should be recruited, and we recruited 109). To verify the association between BMI and climacteric symptoms, multiple linear regression was used, with climacteric symptoms as a dependent variable (total scores of the BKI, CS and MRS), and the BMI values, adjusted for years after menopause and age, as an independent variable.

A subanalysis was performed to verify the differences between the BMI classifications (eutrophic [n = 24], overweight [n = 39], and obese [n = 46]) in relation to the questionnaire classifications (MRS and BKI). One-way analysis of variance (ANOVA) with the Bonferroni post hoc test was performed. To verify the frequency of the symptoms, the Chi-squared test was used, and, to analyze the relationship between the questionnaires, the Spearman correlation was used. The level of significance adopted was $p < 0.05$. All analyses were performed using The Statistical Package for the Social Sciences (IBM SPS Statistics for Windows, IBM Corp., Armonk, New York, United States) software, version 26.0.

Results

The clinical data and the data regarding the symptoms are shown in ► **Table 1**. The volunteers (n = 109) were divided into 3 groups according to the BMI, as classified by the World Health Organization (WHO):²² eutrophic (n = 24), overweight (n = 39), and obese (n = 46). There were no

Table 1 Clinical characteristics and questionnaire scores according to the classification of the Body Mass Index (n = 109)

Clinical characteristics	Eutrophic (n = 24)	Overweight (n = 39)	Obese (n = 46)
Age (years)	52 ± 7	55 ± 9	57 ± 5
Time after menopause (years)	4 ± 7	6 ± 8	5 ± 8
Body mass (kg)	58 ± 6	69 ± 5	90 ± 12
Body Mass Index (kg/m ²)	22 ± 1	27 ± 1	34 ± 4
Score on the questionnaires			
Blatt-Kupperman Index	20 ± 10*	24 ± 8	28 ± 10
Cervantes Scale	44 ± 25	57 ± 23	58 ± 25
Menopause Rating Scale	13 ± 7*	18 ± 7	20 ± 10

Notes: One-way analysis of variance with the Bonferroni post hoc test; * $p < 0.05$: eutrophic versus obese.

differences in terms of mean age (52 ± 7 , 55 ± 9 , and 57 ± 5 years respectively) or mean time since amenorrhea (4 ± 7 , 6 ± 8 and 5 ± 8 years respectively) among the groups. The three questionnaires used assess the climacteric symptoms, and showed significant ($p < 0.01$), positive, and strong correlations ($r > 0.7$). Regarding the questionnaire scores, the eutrophic group showed fewer climacteric symptoms when compared to the obese group in the BKI ($p < 0.01$) and MRS ($p = 0.01$), but not in the CS ($p = 0.07$). There were no significant differences regarding the scores of the overweight women in any of the questionnaires when compared to the eutrophic or obese women.

► **Table 2** shows the frequency according to the classifications of each questionnaire and the BMI. For a better understanding of the analysis of the distribution among the questionnaires, in the MRS, which contains four classifications (asymptomatic, mild, moderate and severe), we grouped the asymptomatic and mild classifications as one. Since the CS has no classification, we chose not to present the distributions in order not to change the understanding of its score. The mild symptoms were significantly more frequent ($p < 0.01$) in eutrophic (50%) than overweight (26%) and obese (26%) subjects, and more severe in obese (28%) than overweight (5%) and eutrophic (4%) subjects, according to the BKI.

Multiple linear regression was used to verify whether the proposed models (including the dependent variables: BMI, age, and time after menopause) were able to predict changes in the symptoms in the three questionnaires used. The

results revealed that the models predict the severity of climacteric symptoms in 18%, 11% and 9% of the variations (r^2) of the BKI, CS and MRS respectively, and showed a moderate correlation (r values between 0.3 and 0.6). ► **Table 3** shows the regression results for the BKI. The BMI, even when adjusted for age and time after menopause, showed a significant association ($p < 0.01$) and greater impact on symptoms (Beta = 0.432).

► **Table 4** shows the regression results for the CS. Again, the BMI, even when adjusted for age and time after menopause, showed a significant association ($p < 0.01$) and greater impact symptoms (Beta = 0.304).

► **Table 5** shows the regression results for the MRS. Once more, the BMI, even when adjusted for age and time after menopause, showed a significant association ($p < 0.01$) and greater impact symptoms (Beta = 0.302).

Discussion

The present study was performed to verify the association between menopausal symptoms and body mass in postmenopausal women. The results showed that the frequency and intensity of symptoms increase as the BMI increases, with differences regarding eutrophic, overweight and obese statuses, relating that the change in classification according to body mass is already sufficient to affect the quality of life during the climacteric period.

Climacteric symptoms are the most common clinical manifestations during this period, and they are due to

Table 2 Distribution of eutrophic, overweight and obese Women according to climacteric symptoms (n = 109)

	Eutrophic (n = 24)		Overweight (n = 39)		Obese (n = 46)		p
	n	%	n	%	n	%	
<i>Blatt-Kupperman Index</i>							
Mild	12	50	10	26	12	26	< 0.01*
Moderate	11	46	27	69	21	46	
Severe	1	4	2	5	13	28	
<i>Menopause Rating Scale</i>							
Asymptomatic + mild	7	29	3	8	6	13	
Moderate	7	29	13	33	10	22	0.11
Severe	10	42	23	59	30	65	

Note: *Chi-squared $p < 0.05$.

Table 3 Significance of the multiple regression parameters of the Blatt-Kupperman Index variable

	Unstandardized coefficients		Standardized coefficients	t	Significance
	B	Standard error	Beta		
(Constant)	19.545	9.045		2.161	0.033
Body Mass Index	0.723	0.150	0.432	4.817	0.000
Age	-0.310	0.170	-0.237	-1.829	0.070
Time after menopause	0.199	0.159	0.160	1.250	0.214

t value: test for the statistical significance of each of the independent variables.

Table 4 Significance of the multiple regression parameters of the Cervantes Scale variable

	Unstandardized coefficients		Standardized coefficients	t	Significance
	B	Standard error	Beta		
(Constant)	68.949	23.614		2.920	0.004
Body Mass Index	1.271	0.392	0.304	3.243	0.002
Age	-0.999	0.443	-0.305	-2.255	0.026
Time after menopause	0.613	0.415	0.197	1.478	0.142

t value: test for the statistical significance of each of the independent variables.

Table 5 Significance of the multiple regression parameters of the Menopause Rating Scale variable

	Unstandardized coefficients		Standardized coefficients	t	Significance
	B	Standard error	Beta		
(Constant)	8.838	8.176		1.081	0.282
Body Mass Index	0.432	0.136	0.302	3.184	0.002
Age	-0.075	0.153	-0.067	-0.486	0.628
Time after menopause	0.070	0.144	0.066	0.489	0.626

t value: test for the statistical significance of each of the independent variables.

multiple factors, which, in addition to low levels of estrogen, are also related to the aging process and psychosocial factors. These symptoms affect approximately 80% of women, and 50% of this population undergoes impacts on quality of life due to their intensity and frequency.^{3,23} Therefore, tools that enable a complete analysis of these symptoms are necessary in order to recognize them. For this, we used three different but complementary questionnaires, which made it possible to understand not only the symptoms (MRS), but also the quality of life related to the climacteric period (CS) and based on the outpatient routine (BKI).

Saccomani et al.¹² used the MRS and found an average score of 10, but in a group of Brazilian women who were younger (with ages ranging from 45 to 60 years) and in another climacteric stage, which would justify the lower score obtained by them when compared to the mean scores of 17 found in the present study. In line with our findings, Ruan et al.²⁴ observed higher frequency and severity of symptoms among postmenopausal women (aged between 50 and 70 years) than among women in earlier climacteric stages, such as perimenopause. In addition, there may be an association between the onset of long-term symptoms and more visible effects of aging, such as, atrophy and vaginal dryness, thus generating more symptoms and, consequently, higher scores.²⁵

In the study by Yim et al.,²⁶ the variables of age, obesity and level of physical activity demonstrated an association with the severity of symptoms. The age factor seems to mainly affect sexual and vasomotor symptoms, while the obesity factor seems to be more related to physical and vasomotor symptoms. In the present study, we did not assess the level of physical activity, but studies^{17,27} have shown that active women have fewer symptoms than inactive women, and that after 10 weeks of moderate physical exercise, the climacteric symptoms can be reduced by up to 50%.

The results of the present study demonstrate that obesity, as well as overweight status, are important and significant factors in the increase in climacteric symptoms; and we found that, the higher the BMI, the higher the frequency and intensity of the symptoms. Adipose tissue, even in small amounts, can be pathogenic due to the adverse consequences of excessive fat mass and/or negative endocrinological activity, and it is associated with many metabolic diseases.²⁸ In a study involving Spanish women conducted by Fernández-Alonso et al.,²⁹ the presence of metabolic diseases seemed to be an aggravating factor for climacteric symptoms, as well as age and overweight status.

Considering the average increase of 0.7 kg/year in weight during the climacteric period⁹ and the growing projection of overweight women (from 29% to 53.9%) and obesity (8% to 20.7%) based on data from the last 35 years, attention, treatment and monitoring of this population is necessary since the first signs of uncontrolled body mass or overweight are observed, so that the condition does not worsen, as stated by Pereira and Lima³⁰ in a study with Brazilian women.

Postmenopausal women are at a higher risk of developing cancer and cardiometabolic diseases, and one of the influencing factors, in addition to lifestyle parameters (such as physical inactivity, unhealthy eating habits), is the reduction in the levels of estrogen, which is characteristic of menopause that can cause changes in energy expenditure and reduced leptin sensitivity.³¹ Estrogen is involved in the regulation of several physiological processes, and has receptors (α and β) in different organs and tissues. This activity affects the inflammatory profile, oxidative stress, acts directly on adipose tissue, and, more specifically, controls energy balance, adiposity and distribution of body fat, as well as the onset of climacteric symptoms.^{10,11}

Excess adiposity is considered an important factor that affects women's quality of life during menopause, and it has been associated with longer duration of menopause, higher incidence of general symptoms and higher prevalence of vasomotor symptoms.⁴ Obesity is related to autonomic imbalance, with greater chronic sympathetic activation and reduced parasympathetic activation, which could increase the presence of symptoms in this population. In addition, changes in thermoregulation and reduction in heat release occur due to the accumulation of adipose tissue.^{32,33}

Individual factors associated with obesity, such as low schooling and economic levels, poor general health and stressful events, also favor the onset and worsening of symptoms.^{4,34} Data from several longitudinal studies have shown that the prevalence of symptoms can also vary among countries due to ethnic, regional and climatic factors, such as increased or reduced exposure to sunlight. Consistent with this, African women appear to be affected by more persistent symptoms, European and Latin American women experience a higher prevalence of hot flashes and insomnia, while Scandinavian women are at an increased risk of suffering osteoporotic fractures, and women from warmer countries have a higher incidence of hot flashes and night sweats.^{4,35}

One of the main limitations of the present study is its small sample size, with different numbers of participants in each BMI subgroup. We did not assess the level of physical activity or socioeconomic aspects, since this was not the objective of the present work, but this might have complemented the results obtained and broadened the understanding of the influencing factors.

One of the strengths of the study is that we used three specific questionnaires that allowed a reliable evaluation of the data, with results that complement each other. In addition, another strong point is the stratification of the sample based on the climacteric stage, more specifically in the postmenopausal period. Since the stages of climacterium may present different patterns in the frequency and intensity of symptoms due to hormonal fluctuations, homogenizing the sample according to the same period after menopause makes it possible to understand the influence of obesity specifically for this population, under hormonal conditions as similar as possible.

Conclusion

Climacteric symptoms are related to BMI, and, in postmenopausal women, the gradual increase in BMI in turn increases the frequency and severity of the symptoms. Understanding this relationship can contribute to the development of public policies for the care of women during the climacteric.

Contributions

Juliene Costa: conceptualization, methodology, investigation, writing of the (original draft, and formal analysis. Raquel Rodrigues: investigation, writing of the original draft, review and editing, and data curation. Guilherme Puga: formal analysis, methodology, review and editing,

and data curation. Nádia Cheik: conceptualization, supervision, formal analysis, project administration, and review and editing.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the postgraduate grant.


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Main Complications during Pregnancy and Recommendations for Adequate Antenatal Care in Sickle Cell Disease: A Literature Review

Principais complicações durante a gestação e recomendações para o cuidado antenatal na doença falciforme: Revisão da literatura

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Rev Bras Ginecol Obstet 2022;44(6):593–601.

Abstract

Sickle cell disease (SCD) is the most common monogenic disease worldwide, with a variable prevalence in each continent. A single nucleotide substitution leads to an amino-acid change in the β -globin chain, altering the normal structure of hemoglobin, which is then called hemoglobin S inherited in homozygosity (HbSS) or double heterozygosity (HbSC, HbS β), and leads to chronic hemolysis, vaso-occlusion, inflammation, and endothelium activation. Pregnant women with SCD are at a higher risk of developing maternal and perinatal complications. We performed a narrative review of the literature considering SCD and pregnancy, the main clinical and obstetrical complications, the specific antenatal care, and the follow-up for maternal and fetal surveillance. Pregnant women with SCD are at a higher risk of developing clinical and obstetric complications such as pain episodes, pulmonary complications, infections, thromboembolic events, preeclampsia, and maternal death. Their newborns are also at an increased risk of developing neonatal complications: fetal growth restriction, preterm birth, stillbirth. Severe complications can occur in patients of any genotype. We concluded that SCD is a high-risk condition that increases maternal and perinatal morbidity and mortality. A multidisciplinary approach during pregnancy and the postpartum period is key to adequately diagnose and treat complications.

Keywords

- ▶ sickle cell disease
- ▶ maternal morbidity
- ▶ maternal mortality
- ▶ pregnancy

Resumo

Doença falciforme (DF) é a condição genética mais comum no mundo, com uma prevalência variável nos continentes. A substituição de um nucleotídeo muda um aminoácido na cadeia da β globina, e altera a estrutura normal da hemoglobina, que é

received
August 3, 2021
accepted
November 3, 2021
published online
February 9, 2022

DOI <https://doi.org/10.1055/s-0042-1742314>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave

- ▶ anemia falciforme
- ▶ morbidade materna
- ▶ mortalidade materna
- ▶ gestação

então chamada de hemoglobina S, e pode ser herdada em homozigose (HbSS) ou heterozigose (HbSC, HbS β), e leva a hemólise crônica, vaso-oclusão, inflamação, e ativação endotelial. Realizou-se uma revisão narrativa da literatura considerando doença falciforme e gestação, as complicações clínicas e obstétricas, o cuidado antenatal específico, e o seguimento para monitoramento materno e fetal. Gestantes com DF têm maior risco de desenvolver complicações clínicas e obstétricas, como crises dolorosas, complicações pulmonares, infecções, eventos tromboembólicos, pré-eclâmpsia, e morte materna. E seus recém-nascidos correm maior risco de desenvolver complicações neonatais: restrição de crescimento fetal, prematuridade e óbito fetal/neonatal. Complicações graves podem ocorrer em qualquer genótipo da doença. Concluiu-se que DF é uma condição de alto risco que aumenta a morbimortalidade materna e perinatal. Um seguimento com abordagem multidisciplinar na gestação e puerpério é fundamental para o diagnóstico e o tratamento das complicações.

Introduction

Sickle cell disease (SCD) is the most common monogenic recessive inherited disease worldwide, and it was first described more than a century ago.¹ Approximately 300 thousand children are born with the disease every year,²⁻⁴ and the prevalence of the mutated gene varies in each continent. In the Americas, the prevalence is of about 0.49 for every one thousand live births, 0.07 in Europe, 0.68 in South and Southeast Asia, and 10.68 in Africa.⁵ In Brazil, there are 2 million people carrying the sickle-cell gene mutation, and about 25 thousand to 50 thousand people with the homozygous form of the disease.⁶ The incidence in Brazil varies according to the state, from 1:650 live births in Bahia to 1:13,500 live births in Rio Grande do Sul.⁷

A single nucleotide substitution leading to a switch in a glutamic acid residue to a valine one in the β globin chain turns normal hemoglobin into a structurally-abnormal one, called hemoglobin S (HbS), which causes SCD and is associated to endothelium activation and chronic inflammation. Other genotypes include hemoglobinopathy SC (HbSC), when the mutated hemoglobin S is associated with hemoglobin C, and sickle beta thalassemia, when hemoglobin S is associated with thalassemia mutations in the β chain (HbS β).^{1,2,8,9} Those heterozygous forms may have better outcomes,^{10,11} although they are also associated with higher morbidity and mortality, especially during pregnancy and the postpartum period.

Complications in pregnancy include higher frequency of hypertensive disorders, (including preeclampsia), thromboembolic events, fetal demise, fetal growth restriction (FGR), preterm birth,¹² and a higher risk of maternal death.^{11,13} Also, sickle cell complications, such as pain episodes, acute chest syndrome, anemia, and infections^{14,15} are common in pregnant women,¹² and responsible for recurrent hospitalizations and morbidity.

Pathophysiology of Sickle Cell Disease

The polymerization of deoxyhemoglobin S upon exposure to low oxygen levels deforms the membrane of red blood cells,

which become elongated in the typical sickled shape, more adherent to endothelial cells, and less flexible.⁸ The same changes can also occur in reticulocytes.¹⁶ Red blood cell sickling shortens the lifespan of hemoglobins by removing them from circulation either by the reticuloendothelial system or intravascular hemolysis.⁸ The release of free hemoglobin from within red blood cells, along with sickling and cell adhesion to endothelial cells, leads to endothelial activation, generates cytokines, and activates the coagulation cascade in a systemic inflammatory response.¹⁷ Neutrophils and platelets are also activated, ultimately culminating in sickle cell vaso-occlusion,^{8,16} a hallmark of the disease, which is responsible for acute complications as well as end organ damage due to ischemia and inflammation.⁸ In the past 30 years, major advances in research have resulted in a better understanding of the pathophysiology of SCD, and earlier interventions during childhood, including the use of penicillin, vaccinations, screening and prevention of stroke, for example, have improved the quality of life of patients and have extended the life expectancy of people with SCD, enabling women to reach childbearing age¹⁸⁻²¹ and pursue pregnancy. Sickle cell disease is a chronic inflammatory condition, and pregnancy in such women is considered a high-risk condition^{14,22-26} that requires close follow up in specialized medical services with a multidisciplinary approach.

Clinical and Obstetric Complications in SCD

Several studies^{1,14,15} have reported maternal complications of SCD, including vaso-occlusive crises (VOCs, the most frequent cause of morbidity and hospitalization), infections (especially in the urinary tract), thromboembolic events (including deep venous thrombosis and stroke), pulmonary complications (the main cause of mortality), chronic renal failure, cesarian section, and maternal death. Fetal complications include FGR, low birth weight (LBW), prematurity, fetal distress during labor, and increased perinatal mortality.^{10,14,15,22,27} However, there is a great deal of variation among published reports regarding the

incidence of complications due to different study designs, country or world region of the studied cases, access to healthcare, and even the absence of statistical analysis to account for confounding variables.¹² A meta-analysis published in 2015¹⁰ compared maternal and perinatal outcomes among women with and without SCD. The study analyzed 26,349 women with SCD and compared them in groups according to the genotype (1,276 women with HbSS and 279 women with HbSC); however, the majority of SCD cases had no known genotype (24,794). The study reported an almost 18-fold increase in maternal mortality among women with SCD compared with non-SCD women, and a more than 2-fold risk of developing preeclampsia. No additional risk of developing eclampsia was found, except among those women with the HbSS genotype (an almost 5-fold risk). The authors¹⁰ also reported a small increase in the risk of undergoing cesarean section in all SCD groups, and a higher risk of having stillbirth in both studied genotypes. Neonatal death and premature birth were two-fold higher in the HbSS group only, and small for gestational age babies were more prevalent among SCD women than among the control group.¹⁰ A 2010 study²⁷ on mortality in SCD and the use of hydroxyurea (the first drug approved to treat SCD by increasing fetal hemoglobin production) showed a reduction in SCD complications such as painful episodes, blood transfusion, and acute chest syndrome, increasing the chance of patient survival from 65% to 86% in the from 65% to 86% in the treated group.²⁷ Although hydroxyurea is not approved for use in pregnancy, its use may be considered after pregnancy and breastfeeding in order to improve quality of life and reduce hospitalizations. Another study,²⁸ published in 2018, which evaluated adverse outcomes among patients with different SCD genotypes (HbSS, HbSC, and HbS β thalassemia), included 89 women and found that 52% were hospitalized during pregnancy for clinical or obstetrical complications. The main reasons for hospitalization were VOC (41%) and obstetric adverse events (22%), and most of them occurred in HbSS patients. However, the authors²⁸ did not find statistically significant differences among the SCD genotypes. Perinatal outcomes such as LBW, prematurity, preeclampsia, and stillbirth were more frequent in the HbSS and HbSC groups, with no significant difference among the SCD groups. Postpartum adverse outcomes (hemorrhage, infections, and thromboembolic events) were significantly more frequent among the HbS β thalassemia group (57%) compared with the HbSS (18%) and HbSC (13%) groups.²⁸ Another study,²⁹ with 62 SCD pregnancies, compared the complications within the 3 genotypes (HbSS, HbSC, and HbS β thalassemia). Urinary tract infection was the most common complication, with similar frequencies in the HbSS and HbSC groups (30% and 33% respectively). The second most prevalent complication was VOC, and it was more frequent among HbSC pregnancies (27%). Preeclampsia occurred in 11% of cases of HbSS, in 40% of cases of HbS β , and in 20% of HbSC pregnancies. Cesarean section was the delivery mode in 37%, 70%, and 40% of the cases in the HbSS, HbSC, and HbS β thalassemia groups respectively.

The rates of prematurity were of 41% in the HbSS group, and of 23% in the HbSC group, with no reported cases among the HbS β thalassemia group. Stillbirth only occurred among the HbSS group (11%), and no maternal deaths were reported in the study.²⁹ In Nigeria, a study²⁴ compared 50 HbSS women with normal controls, and the results showed a higher frequency of pregnancy-induced hypertension (28% in the HbSS group and 6% the in control group) and 32% of VOC in the SCD group. The authors²⁴ also found 16% of patients with FGR and no cases in the control group. Preterm delivery was also more frequent in the HbSS group (28% versus 10%). Overall, complications were significantly higher in the HbSS group, occurring in 92% of the women (versus 38% in the controls).²⁴ The high frequency of complications in SCD pregnancies corroborates the need for early diagnosis and surveillance to reduce morbidity and mortality. Maternal mortality ranges from 1% in a retrospective study conducted in the United States³⁰ to 9.2% in a Nigerian study.³¹ That discrepancy may be due to differences in the quality of care, including early diagnosis and treatment of complications, as well as under-reporting of cases. Near miss is a condition in which women survive a severe complication during pregnancy, childbirth, or within 42 days of the postpartum period. In Latin America, it is estimated there are 34 cases of near miss to every one thousand live births,³² and 15 cases of near miss for each maternal death.^{33,34} About a third of SCD pregnant women face a near miss event during pregnancy or the puerperal cycle, especially due to acute chest syndrome, a severe form of VOC affecting the lungs, and the leading cause of death in adult SCD patients.^{27,35} Unsurprisingly, SCD increases the possibility that a woman will experience a near miss event during pregnancy and/or the postpartum period. Despite the acute maternal severity of a near miss condition, this event is also associated with LBW and very low birth weight newborns, newborn admission to intensive care, stillbirth, early neonatal death, and long maternal hospital stays.^{32,36-38} Studies with SCD in pregnancy usually involve a small number of patients due to the relative rarity of the condition and the difficulties in the compilation of data. A summary of meta-analyses on SCD during pregnancy found in the PubMed, SciELO, and Embase databases is presented in **Table 1**.

Antenatal Care

Since SCD is a chronic systemic condition, pregnancy should ideally be planned in order to minimize possible complications. One main concern is regarding the use of medications for SCD during pregnancy and lactation. Common medications used in SCD management that should be discontinued before and during pregnancy include angiotensin-converting enzyme (ACE) inhibitors, iron chelators, and hydroxyurea. The use of hydroxyurea is not recommended, and women are advised to avoid conception up to 6 months after their last dose of hydroxyurea due to animal studies showing teratogenicity, and a few case reports of fetal growth abnormality and preterm birth. For more recently-approved SCD-specific therapies, the antioxidant amino acid L-glutamine is generally considered to

Table 1 Systematic Reviews on Sickle Cell Disease during Pregnancy

Author (year, country)	Study design	Number of studies and/or women	Outcomes	Conclusions
Oteng-Ntim et al. ¹⁰ (2015, United Kingdom)	Meta-analysis	26,349 SCD women	MM (RR: 18.51; 95%CI: 8.63–39.72) PE (RR: 2.06; 95%CI: 1.49–2.85) CS (RR: 1.27; 95%CI: 1.18–1.36) ND (RR: 2.68; 95%CI: 1.49–4.82)	Pregnant women with SCD have high risks of developing maternal and perinatal adverse outcomes; risks are greatest for those in low-income countries and for those with HbSS disease compared to HbSC
Boafor et al. ³⁷ (2016, Ghana, Nigeria, and United States)	Meta-analysis	- 9 studies	MM (OR: 10.91; 95%CI: 1.83–65.11; $p = 0.009$)	SCD increases the risk of adverse maternal and perinatal outcomes in low- and high-income countries
		- 12 studies	PE (OR: 2.05; 95%CI: 1.47–2.85; $p < 0.001$)	
		- 13 studies	CS (OR: 1.54; 95%CI: 1.27–1.87; $p < 0.001$)	
		- 6 studies	ND (OR: 2.71; 95%CI: 1.41–5.22; $p < 0.003$)	
		- 10 studies	FGR (OR: 2.69; 95%CI: 1.85–4.21; $p < 0.001$)	
		- 6 studies	Perinatal mortality (OR: 3.76; 95%CI: 2.34–6.06; $p < 0.001$)	
		- 11 studies	Prematurity (OR: 2.14; 95%CI: 1.56–2.95; $p < 0.001$)	
		- 9 studies	LBW (OR: 2.00; 95%CI: 1.42–2.83; $p < 0.001$)	
		- 10 studies	Stillbirth (OR: 4.05; 95%CI: 2.59–6.32; $p < 0.001$)	
- 6 studies	Infection (OR: 2.48; 95%CI: 1.23–5.01; $p = 0.011$)			
Inparaj et al. ³⁸ (2020, United Kingdom)	Meta-analysis	3,964 Patients	ACS/pneumonia (event rate: 6.46%; 95%CI: 4.66–8.25); Pulmonary thromboembolism (RR: 7.74; 95%CI: 4.65–12.89)	Strong association between SCD and maternal pulmonary complications

Abbreviations: 95%CI, 95% confidence interval; ACS, acute chest syndrome; CS, cesarian section; FGR, fetal growth restriction; LBW, low birth weight; MM, maternal mortality; ND, neonatal Death; OR, odds ratio; PE, preeclampsia; RR, risk ratio; SCD, sickle cell disease.

be safe, the antisickling agent voxelotor is safe through pregnancy but not recommended during lactation, and there are no data on the anti-adhesive monoclonal antibody crizanlizumab. Care for pregnancy in SCD patients must include specialized antenatal care, since complications can occur at early gestational ages. Pregnancy in SCD patients requires more frequent follow-up, including a multidisciplinary team^{22,26,39} with an obstetrician, with close fetal surveillance, hematological support, nutritional and psychological assessments, and an ultrasonographer experienced in materno-fetal medicine. It may

be convenient that appointments with the obstetrician take place at least monthly in the first and second trimesters, and more frequently after that, with individual assessment. It is paramount to check the immunization status and update it when necessary, taking into consideration that SCD patients require broader coverage for encapsulated bacteria (such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria*). Laboratory checks must include hemoglobin level, hemolytic markers (reticulocyte count and lactate dehydrogenase [LDH]), and screening for infections (especially urinary

tract infection and asymptomatic bacteriuria), more frequently than for a low-risk pregnancy. Anemia during pregnancy is defined by the World Health Organization (WHO) as a hemoglobin level below 11g/dL^{40,41} at any trimester of gestation. Maternal anemia is a common condition even for women with normal hemoglobin, especially during the last trimester of pregnancy, when the levels of iron need to be increased.⁴² When anemia presents in the first and second trimesters, it may contribute to LBW, prematurity, and neonatal complications.⁴²⁻⁴⁴ Chronic anemia is a very common feature of SCD, and it impacts patients since the beginning of pregnancy. However, it is important to assess if there are additional contributors to maternal anemia, such as nutritional deficiencies. Anemia can negatively affect fetal development, resulting in a growth-restricted fetus.⁴³⁻⁴⁶ The hemoglobin level of these patients can be very low, and the need for blood transfusion is common. Therefore, many studies have evaluated the benefits of prophylactic blood transfusion during pregnancy. Transfusion of red blood cells aims to improve the oxygen-carrying capacity. It can be performed through simple transfusion, when the goal is to achieve a certain level of hemoglobin, or exchange transfusion (manual or automated erythrocytapheresis),⁴⁷ when the aim is to decrease the levels of circulating HbS. In acute complications that lead to severe anemia, simple transfusion is usually the choice. Those transfusions aim to increase hemoglobin, taking it to levels closer to baseline while avoiding hyperviscosity and heart failure.⁸ Red blood cell transfusions can also be chronically used for stroke prevention, and acutely to treat acute chest syndrome or multiorgan failure.⁸ Exchange transfusion has been used during pregnancy to reduce the occurrence of complications, but there is no definitive evidence to indicate it to all patients. If red blood cell exchange is indicated in pregnancy, reasonable targets would be a level of HbS lower than 40%, with a level of hemoglobin of 10g/dL.⁴⁸ A meta-analysis published in 2015⁴⁹ concluded that prophylactic transfusion was associated with lower maternal mortality, VOCs, pulmonary complications, perinatal and neonatal mortality, and premature delivery, but no improvement in preeclampsia and FGR. Other studies reinforce the findings of lower maternal mortality⁵⁰ and VOCs^{50,51} with prophylactic transfusion. A 2007 Brazilian study⁵² found better fetal outcomes with fewer cases of FGR and preterm deliveries. Nevertheless, there is no consensus regarding the ideal hemoglobin level during pregnancy or the best moment to start transfusions in pregnant SCD patients. Some authors⁵⁰ recommend starting transfusions in the second trimester while others^{53,54} recommend an earlier start, in the first trimester. A more conservative approach is to transfuse pregnant patients who have severe anemia with Hb below 7g/dL, or any level of anemia if signs of impaired fetal growth or fetal distress are observed. To make this decision, providers should also consider that the more transfusions, the greater the risk of alloimmunization, which is of about 16% to 20% in this population.^{26,50} Alloimmunization can lead to lifetime difficulty to find compatible blood and delayed hemolytic transfusion reactions,⁵⁵ the latter sometimes manifesting with hyperhemolysis syndrome, a life-threatening situation in which hemoglobin levels drop to below pretransfusion levels.

Placental Findings in SCD

The placenta is an organ with an adapted surface for oxygen and nutrient exchange between the maternal and fetal circulations.⁵⁶ Studies on SCD^{57,58} have shown placental abnormalities such as syncytial knots, villous necrosis, congestion, deposits of sickle hemoglobin, and intravillous fibrin. Increased expression of proinflammatory genes in the placenta have been documented, suggesting that the organ is exposed to a proinflammatory environment and hypoxia,⁴⁶ and the imbalance in inflammatory substances could favor vaso-occlusive episodes and necrosis.^{48,57} Furthermore, abnormal placental size, location, and adhesion to the uterine wall have also been described in SCD pregnancies. The exact pathophysiology explaining how abnormalities in placental development can contribute to worse perinatal outcomes and complications in SCD is not yet fully understood. However, those abnormalities may increase the risk of uteroplacental insufficiency, leading to maternal and fetal adverse outcomes.⁴⁶

Fetal Surveillance and Risk of Fetal Growth Restriction

Fetal growth restriction occurs when the fetus does not reach its biological growth potential and is usually associated to placental insufficiency.⁵⁹ Those fetuses are at a higher risk of adverse outcomes in pregnancy, higher morbidity and mortality, and impaired neurological development,^{60,61} which makes recognition and appropriate follow-up of such cases essential. Statistical deviations from population-based reference growth curves define FGR.⁶² For fetal assessment, the ultrasound (US) scan is the preferred method to evaluate fetal wellbeing, as it can estimate fetal weight (which is especially important during the third trimester) and detect placental impairment with Doppler velocimetry; therefore, it should be part of the regular antenatal care. However, due to the heterogeneity among SCD patients, there is no specific recommended protocol for US follow up. We suggest performing US at least once during the first and the second trimesters, and then monthly until delivery. That seems like a reasonable approach if there is no major complication, and providers should consider shorter scan intervals if necessary. During the third trimester, closer follow-up with a two-week interval if there is early suspicion of fetal impairment is acceptable.

Diagnosis and Treatment of Complications during Pregnancy

The complications of SCD may have distinct presentations and should always be suspected based on patient's history and examination. The symptoms may mimic common pregnancy discomforts, delaying adequate healthcare. The most frequent complication is VOC, which is typically experienced as acute bone or joint pain that starts abruptly. Uncomplicated VOCs last for four to five days on average. The severity of the pain also varies widely, but severe pain often requires admission. The treatment of VOC is based on hydration,

analgesia, and treatment of the precipitating factors. Common triggers for VOC include dehydration, sudden changes in temperature (including but not limited to cold exposure), infections (including urinary tract infection, pneumonia, acute osteomyelitis etc.), delayed transfusion reactions, thromboembolic events, the acute phase of avascular necrosis, and emotional distress, but many VOCs will not have an identifiable trigger. Controlled fluid management should be enough to reduce blood viscosity, but must not be overdone to avoid acute pulmonary edema. There is no scientific evidence to recommend a specific type of intravenous fluid, and providers can freely choose to use normal saline, sodium chloride (NaCl) 0.45%, Ringer lactate solution, and others. Analgesia must include non-opioid and/or opioid analgesics, depending on the intensity of the pain.⁶³ The use of opioids during pregnancy increases the risk of neonatal complications, including withdrawal syndrome in the newborn, but should not be considered a contraindication to the use of opioids in this setting. Non-steroidal anti-inflammatory drugs are not recommended after 34 weeks gestation in order to avoid cardiac dysfunction with premature closure of the arterial canal. Transfusions should not be routinely indicated for VOCs, and should take into consideration if there is symptomatic anemia, and the potential risks associated with the procedure. Acute chest syndrome is a major complication characterized by a VOC with acute pain in the thoracic region associated with respiratory symptoms and fever, mostly associated with the finding of a new pulmonary opacity, and hypoxemia in severe cases. It is the main cause of death among adults with SCD.¹⁰ The treatment is symptomatic, with analgesia, fluid management, oxygen supplementation for oxygen saturation below 92%, and ventilatory support if necessary. Simple transfusion may be indicated in patients with severe anemia (Hb < 7g/dL), and red blood cell exchange transfusion must always be considered for severe cases with hypoxemia. Acute chest syndrome is indistinguishable from pneumonia; therefore, the use of empiric broad-spectrum antibiotics is indicated, antivirals should be considered, and consultation with an infectious disease's specialist is encouraged to discuss options during pregnancy. The association of SCD and pregnancy increases the risk of deep-vein thrombosis and pulmonary embolism, so a low threshold to indicate lung computed tomography (CT) angiography is encouraged for patients with signs and symptoms of acute chest syndrome. While preeclampsia is known to be more frequent in SCD patients, the diagnosis of severe preeclampsia with hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome may be challenging. Laboratory abnormalities caused by SCD delay the detection of hemolysis, since the levels of LDH and aspartate aminotransferase (AST) are increased by chronic hemolysis, and haptoglobin is already undetectable in SCD. In addition, HbSS patients may have a baseline elevated platelet count due to autosplenectomy, sometimes above 600 thousand, and HbSC or HbSβ patients often have splenomegaly, leading to mild to moderate chronic thrombocytopenia in the 80 thousand to the 150 thousand range. Young patients may already have some degree of microalbuminuria prior to pregnancy, so

early evaluation of the urinary sediment is encouraged as a baseline to help detect abnormal proteinuria later in pregnancy. Therefore, patients presenting with signs and symptoms suggestive of severe preeclampsia, such as headache and abdominal pain, should be carefully evaluated and monitored, and their laboratory evaluation must take into consideration their earlier results. We recommend keeping track of baseline urinalysis, LDH, liver enzymes, and platelet counts and throughout pregnancy to help the diagnosis of preeclampsia and HELLP syndrome in SCD patients. Sickle cell disease complications such as sickle hepatopathy and hepatic sequestration should be considered differential diagnoses, since they may also lead to an increase in the levels of liver enzymes and worsen the anemia.

Follow-up and Childbirth

Vaginal delivery is possible, so SCD should not be regarded as an indication for cesarian section. Labor may occur spontaneously or after induction in SCD pregnant patients. During labor, it is important to be mindful of the patient's hydration status, provide appropriate analgesia, since those women are more prone to vaso-occlusive events during stressful situations, and ensure close fetal monitoring. Since SCD is a chronic systemic condition, pregnancy in SCD patients should ideally be planned in order to minimize possible complications. Women of reproductive age and those in the postpartum period must be counseled about contraceptive options. According to the WHO, contraceptive methods containing only progesterone (the pill, injectable contraceptives, implants, or intrauterine devices) are category 1, meaning that the method can be used in any circumstance. Combined hormonal contraceptives and copper intrauterine devices are category 2, meaning that the method can generally be considered, but should take into account the

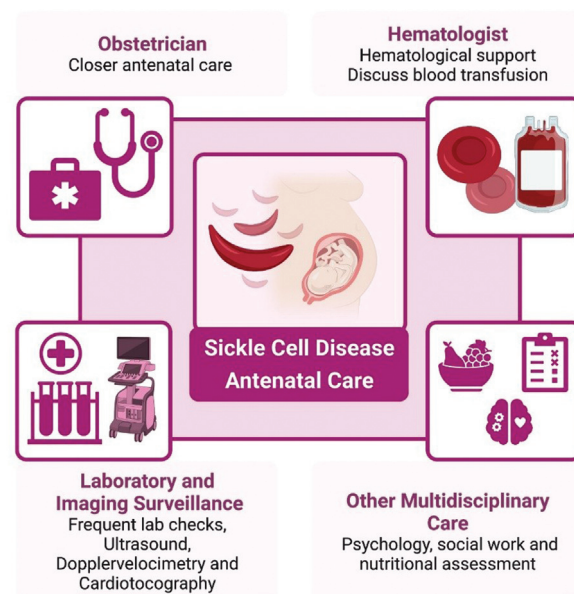


Fig. 1. Antenatal care of pregnant women with sickle cell disease (SCD).

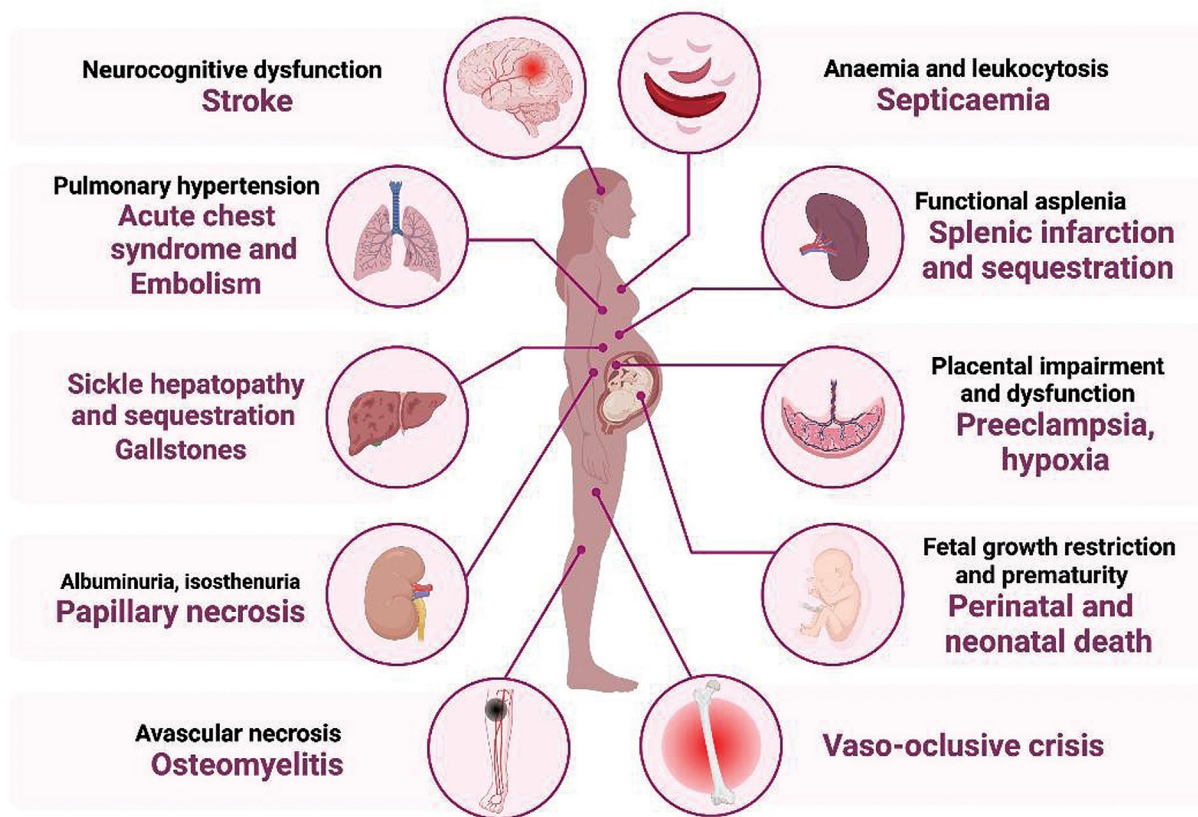


Fig. 2. Frequent complications in SCD.

individual risk of thromboembolic events, the history of menorrhagia, and patient preference.⁶⁴ Psychological and nutritional support should happen together with antenatal and postpartum care, as these patients have higher rates of hospitalization and are more prone to develop depressive episodes^{65,66} and chronic nutritional deficiency.⁶⁷ Sickle cell disease does not constitute a contraindication for breastfeeding, but the treatment with hydroxyurea is usually postponed until the patient is not breastfeeding. In addition, patients who were treated with blood transfusions during pregnancy should be evaluated for iron overload by their hematologist, particularly if chronically transfused. The indication for iron chelation therapy will depend on workup with serum ferritin, transferrin saturation, and liver magnetic resonance imaging. Low bone mineral density is a frequent complication of SCD,⁶⁸ even in women of childbearing age, and may remain undiagnosed for many years. Pregnancy and breastfeeding contribute to deplete calcium from the bones,⁶⁹ and we encourage providers to evaluate patients for osteopenia and osteoporosis with a dual-energy X-ray absorptiometry (DEXA) scan after they have finished breastfeeding, and verify vitamin D levels to provide supplementation if needed (► **Figures 1 and 2**).

Conclusion

Sickle cell disease is a complex chronic disorder with potential life-threatening complications during pregnancy. The management of pregnant SCD patients requires a multidis-

ciplinary approach to achieve favorable maternal and fetal outcomes, with accurate and timely diagnosis and treatment of its complications.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgements

The figures were created with the BioRender (BioRender, Toronto, ON, Canada) software.

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Coronavirus Disease 2019 Vaccination for Cancer Patients: Risk or Benefit?

Vacinação para COVID-19 em pacientes oncológicos: Risco ou benefício?

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Rev Bras Ginecol Obstet 2022;44(6):602–608.

Abstract

Objective The aim of the present study is to list the published clinical trials on coronavirus disease 2019 (COVID-19) vaccines, to describe the mechanism of action of the identified vaccines, and to identify protocols regarding safety, status, and prioritization of cancer patients for vaccination.

Methods This is a systematic review with a limited literature search conducted by an information specialist; key resources such as PubMed and websites of major cancer organizations were searched. The main search terms were *COVID-19*, *vaccination*, *cancer*, and *breast and gynecological cancers*.

Results Cancer patients infected with the new coronavirus are at high risk of complications and death, but we still know little about the risks and benefits of vaccination for COVID-19 in these patients. In an ideal scenario, all cancer patients should have their immunization status updated before beginning treatment, but this is not always possible.

Conclusion Patients with breast or gynecological cancers who are receiving treatment or are in the 5-year posttreatment period should be included in the priority group for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination.

Keywords

- ▶ cancer
- ▶ COVID-19
- ▶ vaccination
- ▶ protocols

Resumo

Palavras-chave

- ▶ câncer
- ▶ COVID-19
- ▶ vacinação
- ▶ protocolos

Objetivo O objetivo do presente estudo é listar os ensaios clínicos publicados sobre as vacinas para *coronavirus disease 2019* (COVID-19), descrever seus mecanismos de ação e descrever protocolos sobre segurança, status e priorização de pacientes oncológicos para vacinação.

Métodos Trata-se de uma revisão sistemática com uma pesquisa bibliográfica limitada conduzida por um especialista em informação; bases de dados como PubMed

received
February 15, 2021
accepted
February 3, 2022

DOI <https://doi.org/10.1055/s-0042-1745788>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

e sites das principais organizações de câncer foram pesquisados. Os principais termos de pesquisa foram *COVID-19*, *vacinação*, *câncer* e *câncer de mama e ginecológico*.

Resultados Pacientes com câncer infectados com o novo coronavírus têm alto risco de complicações e morte, mas ainda sabemos pouco sobre os riscos e benefícios da vacinação para COVID-19 nesses pacientes. Em um cenário ideal, todos os pacientes com câncer deveriam ter seu estado de imunização atualizado antes de iniciar o tratamento, mas nem sempre isso é possível.

Conclusão Pacientes com câncer de mama ou ginecológico em tratamento ou no período pós-tratamento de 5 anos devem ser incluídos no grupo prioritário para vacinação contra *severe acute respiratory syndrome coronavirus-2* (SARS-CoV-2.)

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China. On January 12, 2020, the World Health Organization (WHO) published a series of guidance documents on managing the outbreak caused by this novel virus. Subsequently, on January 30, 2020, the WHO Director-General declared the outbreak a public health emergency of international concern, at the highest level of alarm.¹

The new coronavirus is part of a family of viruses known since 1960; the virus is known for the crown-shaped spike proteins on its surface, which play a critical role in its infectivity. The new variant underwent a zoonotic spillover, becoming capable of infecting humans. This phenomenon is believed to have occurred in a Chinese fish market in the following pathway: from bats, via pangolins (mammals found in the tropical areas of Africa and Asia) as the probable intermediary, to humans.²

According to the WHO, the SARS-CoV-2 is currently responsible for more than 2 million deaths around the world, with approximately 100 million confirmed cases.³ More than a year after its emergence, there are no specific treatments to change its course. The global population had to adapt to the disease, medical services had to restructure themselves to continue treating chronic diseases, and COVID-19 became the main topic within all specialties as a new variable to be taken into account in any therapeutic plan.

In this context, vaccines emerged as the main weapon against the SARS-CoV-2 pandemic. Vaccines are already a global reality, and understanding the technologies used is essential for clinical practice and adequate patient management.

Types of Vaccines

Inactivated Virus

Inactivated virus technology has been successfully used in several vaccines, such as hepatitis A, polio, and influenza; these vaccines are produced from viral replication in cell cultures. The viruses are subsequently inactivated by chemical or physical agents that render them incapable of replication. This process reduces the immunogenicity of the

vaccine, making it necessary to use adjuvants and administer it in several doses to induce a robust immune response. The main commercialized vaccines of this type are CoronaVac, from Instituto Butantan, and Covaxin, from Bharat Biotech.^{4,5}

Recombinant Viral Vectors

Recombinant viral vector vaccines use viruses that are genetically modified to produce a specific protein. In the case of the SARS-CoV-2, the spike protein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor and allows the virus to enter the cell. Several vaccines use this approach, including the Oxford University/AstraZeneca vaccine, which uses a recombinant chimpanzee adenovirus (ChAd) as a vector; the Sputnik V vaccine, which uses two different types of recombinant adenoviruses (rAd5 and rAd26); and the Janssen vaccine, which is still undergoing clinical trials.^{7,8,26}

Messenger ribonucleic acid (mRNA) Vaccines

Messenger ribonucleic acid (mRNA) vaccines are the result of a new technology and acknowledged as one of the most promising vaccines. A strand of mRNA that encodes a specific antigen of the virus is used, and the body's cells use this information to produce this antigen, which is presented on the surface of the cells where it is recognized by the body as "no self", triggering an immune response mediated by the antibodies and T lymphocytes. This technology is being used in the Pfizer and Moderna vaccines.^{9,10} ▶ **Table 1** outlines the main vaccines that are being developed and/or distributed across the world, their characteristics, advantages, and disadvantages.

Methods

A systematic review with a limited literature search was conducted by an information specialist; key resources such as PubMed and websites of the major cancer organizations were searched. The main search terms were *COVID-19*, *vaccination*, *cancer*, and *breast and gynecological cancers*. The search was limited to the literature in English language and was conducted between January 20 and 26, 2021. The inclusion criteria were original articles from clinical trials of potential vaccines for COVID-19 and recommendations from

Table 1 Vaccines

Manufacturer	Technology/Platform	Name	Doses	Advantages	Disadvantages	Efficacy
Sinovac Research and Development Co., Ltd. ⁴	Inactivated virus	SARS-CoV-2 vaccine (inactivated) CoronaVac	Day 0 + 28	Safe for cancer patients Known technology Storage from 2 to 8°C	Low immunogenicity	50.36%
Bharat Biotech International Limited. ⁵	Inactivated virus	Whole-virion inactivated SARS-CoV-2 vaccine (BBV152)	Day 0 + 14	Known technology Easy storage	Low immunogenicity	Phase 3 in progress
AstraZeneca + University of Oxford. ⁶	Viral vector (non-replicating)	ChAdOx1-S - (AZD1222) (Covishield)	Day 0 + 28 or 3 months	Longer gap between doses. One dose protection		70.4%
Gamaleya Research Institute of Epidemiology and Microbiology, Russia. ⁷	Viral vector (non-replicating)	Sputnik V Gam-COVID-Vac (rAd26-S and rAd5-S)	rAd26-S given on day 0 and rAd5-S on day 21	Uses different vectors in two doses		91.6%
Janssen Pharmaceutical. ⁸	Viral vector (non-replicating)	Ad26.COV2.S	Day 0 or Day 0 + 56	Possibility of single dose, ongoing studies		Phase 3 in progress
Pfizer/BioNTech + Fosun Pharma. ⁹	RNA-based vaccine	BNT162 (3 LNP-mRNAs)	Day 0 + 21	Promising technology. Easy adaptation in case of viral mutation	Risk of accumulation in solid tumors due to the use of lipid capsule Storage at -70°C	95%
Moderna + National Institute of Allergy and Infectious Diseases (NIAID). ¹⁰	RNA-based vaccine	mRNA -1273	Day 0 + 28	Promising technology. Easy adaptation in case of viral mutation	Risk of accumulation in solid tumors due to the use of lipid capsule Storage at -20°C	94.1%

the main oncology societies. The exclusion criterion was articles that did not meet the inclusion criteria or had insufficient data.

Objectives

- To list the published clinical trials on COVID-19 vaccines, focusing on those that will be used in Brazil;
- To describe the mechanism of action of the identified vaccines with the aim of understanding their use in cancer patients;
- To identify protocols regarding safety, status, and prioritization of cancer patients for vaccination used by associations, organizations, and reference hospitals for the treatment of cancer patients.

Discussion

Due to the limited number of vaccine doses available, governments are selecting priority groups for vaccination according to the risk of infection and/or severity of the disease. One such group consists of patients with malignant tumors, including solid and hematological tumors, and those undergoing hematopoietic stem cell transplantation (HSCT), who are at a high risk of morbidity and mortality if infected with COVID-19.^{11,12}

Brazil is expected to register 625,000 new cancer cases for each year of the 2020/2022 triennium according to the Brazilian National Cancer Institute (INCA). Among these patients, those with breast and gynecological cancers (cervical, ovarian, and endometrial) stand out. According to the INCA's estimate for 2020, these tumors account for 44.8% of all malignant tumors in women. Due to their high incidence and the fact that the treatment includes surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted drugs, the patients and health professionals have concerns about the safety and effectiveness of vaccines against COVID-19.¹³

According to a retrospective cohort study conducted by the INCA, cancer patients infected with the new coronavirus are at a high risk of complications and death, probably due to increased clinical frailty and negative impact of immunosuppressive treatments: 14 to 19% of the patients without cancer versus 18 to 38% of the patients with cancer develop severe complications in the presence of COVID-19, indicating the increased likelihood of severe complications in cancer patients.¹⁴ Al-Quteimat and Amer¹⁵ found that cancer patients treated with surgery or chemotherapy 30 days before being diagnosed with COVID-19 have an increased risk of developing severe complications from the disease. In their meta-analysis, Zarifkar et al.¹⁶ showed that the risk of intra-hospital mortality among patients with both COVID-19 and cancer was five times higher than in the group of patients without cancer, which confirms the unfavorable disease course in this group of patients. Two other studies reported increased mortality by COVID-19 in cancer patients when adjusted for age and sex (hazard ratio, 1.4; 95% confidence interval, 1.0–2.0).^{17,18} Another study reported an increased risk of mortality among cancer patients under

50 years of age compared with non-cancer patients of the same age group (relative risk, 5.01; 95% confidence interval, 1.55–16.2).¹²

In an ideal scenario, all cancer patients should have their immunization status updated before beginning treatment. It is recommended that inactivated vaccines are administered 2 weeks before the beginning of treatment. Attenuated vaccines should be administered 4 weeks before treatment, not only for safety but also to ensure adequate production of immunoglobulins. However, immunization is often necessary while receiving immunosuppressive drugs. Inactivated vaccines do not present an increased risk of adverse events to immunosuppressed patients. Therefore, these vaccines should be administered, and a second dose may be needed after the treatment has ended to ensure an appropriate immune response. Attenuated vaccines (Bacillus Calmette-Guérin [BCG]; rotavirus; oral polio [OPV]; yellow fever; measles, mumps, and rubella/varicella [MMR/MMRV]; chickenpox; and herpes zoster) should not be given during immunodepression. In cases of moderate immunodepression, the physician responsible for the clinical and epidemiological evaluation determines whether yellow fever, MMR, MMRV, chickenpox, and herpes zoster vaccines should be administered. It is important to emphasize that the immunization of close contacts, family members, cohabitants, and health professionals responsible for the patient's care (according to the schedule for their age group) is essential to reduce the transmission of the virus to cancer patients.¹⁹

To date, there is no report of a live-attenuated virus vaccine available for use in Brazil. The Oxford University/AstraZeneca vaccine consists of an adenovirus vector that has no ability to replicate. CoronaVac is classified as an inactivated virus vaccine, and the Pfizer/BioNTech vaccine uses mRNA technology to stimulate immune response. Therefore, these vaccines should not pose a risk to immunocompromised patients, and, from the outset, the only specific contraindication would be hypersensitivity to any of the components of the vaccines.²⁰

However, the clinical trials that were conducted did not include cancer patients. Therefore, some issues should be addressed:

- Because RNA vaccines are delivered as lipid carriers, they can accumulate in solid tumor tissues. In addition, absorption of the material by these tumors may reduce the efficacy of this type of vaccine.²¹
- Patients in maintenance therapy (rituximab, tyrosine kinase inhibitors) may have reduced response to immunization.^{22–24}
- For patients undergoing chemotherapy, it is not yet known if immunization should be given at the time of cytotoxic drug administration or between cycles. The high variability of available regimens makes it difficult to determine the optimal timing, which remains controversial.^{22–24}
- Patients receiving checkpoint inhibitors may experience an exacerbated immune response, associated with an increased risk of adverse events. For safety, the vaccine

Table 2 Recommendations from the main associations and reference centers for the treatment of cancer patients

Protocol	Cytotoxic chemotherapy	Radiotherapy	Endocrine therapy	Targeted therapy	Corticoids	Immunotherapy	Surgery	Vaccination priority	Observations
AC Camargo Cancer Center. ²⁰	When blood counts have recovered to the maximum (end of the cycle). Avoid the day of chemotherapy treatment.		Cleared without restrictions.	Cleared without restrictions, provided blood counts are normal.		Cleared without restriction, provided blood counts are normal.			Information obtained from Pfizer-BioNTech and AstraZeneca-Oxford vaccines
National Comprehensive Cancer Network. ²²	Cleared without restrictions. There is no evidence of optimal timing of vaccination during treatment.	Cleared without restrictions	Cleared without restrictions (not a priority when used exclusively by non-metastatic patients)	Cleared without restrictions	May reduce the immune response to vaccination. It is recommended to delay vaccination.	Cleared without restrictions.	Do not vaccinate on the day of the surgery because the vaccine symptoms.	Yes. 1b/c priority group by CDC. Patients under endocrine therapy are not prioritized.	
Memorial Sloan Kettering Cancer Center. ²³	First dose between cycles, far apart from the nadir period, or after the end of the treatment if the latter is near completion.	Cleared without restrictions	Cleared without restrictions	Cleared without restrictions	Cleared without restrictions	If possible, 2 weeks before the start of therapy	Cleared without restrictions. Exceptions in cases of splenectomy	Yes. Prioritize by age not according to location or presence of metastasis.	Avoid immunotherapy or chemotherapy on 2nd or 3rd day after vaccination (period of increased risk vaccine side effects)
European Society for Medical Oncology. ²⁴	Cleared without restrictions. There is no evidence of the optimal timing of vaccination during treatment.					Potential reduction in vaccine effectiveness. The benefits outweigh the risk.		Yes, especially in patients with hematologic tumors (receiving chemotherapy or with active disease). Proteasome and CDK4/6 inhibitors should be used preferably at the end of the cycle, avoiding the day of chemotherapy treatment.	
Cancer Research UK. ²⁵	Optimal vaccination timing is before the start of the treatment. If treatment has already started, the patient should discuss the best timing for vaccination with the physician.	Cleared without restrictions.				Cleared without timing restrictions. Benefits are greater than costs.	Vaccination is recommended 2 weeks before surgery.		
MD Anderson Cancer Center. ²⁶	Cleared. However, the optimal timing for vaccination should be discussed with the physician.					Cleared. However, the optimal timing for vaccination should be discussed with the physician.	Vaccination is recommended 2 weeks after surgery	Yes. Increased COVID-19-related morbidity and mortality in cancer patients.	
Cancer Treatment Centers of America. ²⁷	Safe according to available data. Potential reduction in vaccine effectiveness during cancer treatment. A discussion with the physician is recommended.	Safe according to available data. Potential reduction in vaccine effectiveness.							Use of AstraZeneca Oxford vaccine is restricted in immunocompromised patients.
Sociedade Brasileira de Oncologia Clínica. ²⁸	Cleared, but should be given preferably before the start of the treatment.				Cleared. There is no evidence of the need for a second vaccine dose in immunosuppressed patients.	Cleared. Risk of interference with vaccine response and side effects.		Yes. Increased Covid-19-related morbidity and mortality in cancer patients.	

should be administered on the same day as the treatment, so that, if necessary, patients receive care and do not have to return to the healthcare service.^{22–24}

- Regarding patients who undergo surgery, it is difficult to distinguish between potential reactions to the vaccine and the organic response to the trauma caused by the surgery. It should be noted that a rise in temperature (38°C) is a common reaction to vaccination and may be confused with postsurgical infection. The recommendation is to perform the immunization approximately 2 weeks before any surgical procedure.^{22–24}
- Vaccination does not exclude the need for social distancing and precautionary measures on the part of the patient and cohabitants.^{22–24}

– **Table 2** outlines the recommendations on Sars-CoV-2 vaccines for each therapeutic modality of the main associations and reference centers for the treatment of cancer patients.

Conclusion

Although the evidence regarding the safety of Sars-CoV-2 vaccines in cancer patients is limited, the increased risk of morbidity and mortality of the disease in this group, the well-documented benefit of a vaccination plan for cancer patients, and the theoretical rationale of the mechanism of action of the vaccines already available are sufficient for prioritizing patients with breast or gynecological cancers who are receiving treatment or are in the 5-year posttreatment period for SARS-CoV-2 vaccination. Urgent and effective public policies are needed for this vulnerable group of patients; patients who remain disease free after 5 years should be included in their respective age group for vaccination prioritization. We emphasize that due to the scarcity of data, these recommendations may be modified as new evidence comes to light.

Conflict of Interests

The authors have no conflict of interests to declare.



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Pregnancy in Patients with Non-cirrhotic Portal Hypertension: A Literature Review

Gravidez em pacientes com hipertensão portal não cirrótica: Uma revisão da literatura

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Rev Bras Ginecol Obstet 2022;44(6):609–613.

Abstract

Keywords

- ▶ portal hypertension
- ▶ esophageal and gastric varices
- ▶ pregnancy outcomes
- ▶ EHPVO
- ▶ NCPF

Resumo

Palavras-chave

- ▶ hipertensão portal
- ▶ varizes esofágicas e gástricas
- ▶ resultados da gravidez
- ▶ EHPVO
- ▶ NCPF

Pregnancy in non-cirrhotic portal hypertension (NCPH) is an uncommon condition. Its management is challenging both to the obstetricians as well as to the gastroenterologists due to the lack of more extensive studies and standard clinical practice guidelines. These patients are at increased risk of portal hypertension (PTH) complications, especially variceal bleeding, and with an increased incidence of adverse maternal and fetal outcomes. Hence, a multidisciplinary approach is required for management of pregnancy in NCPH. This short review describes the different aspects of pregnancy with NCPH, emphasizing specific strategies for preventing and managing PTH from the preconceptional period to postpartum.

A gravidez na hipertensão portal não cirrótica (HPNC) é uma condição incomum. Seu manejo é desafiador tanto para os obstetras quanto para os gastroenterologistas devido à falta de estudos mais extensos e diretrizes de prática clínica padrão. Esses pacientes apresentam risco aumentado de complicações da hipertensão portal (PTH) especialmente sangramento por varizes e têm maior incidência de desfechos maternos e fetais adversos. Portanto uma abordagem multidisciplinar é necessária para o manejo da gravidez na NCPH. Esta breve revisão descreve os diferentes aspectos da gravidez com HPNC enfatizando estratégias específicas para prevenção e manejo do PTH desde o período pré-concepcional até o pós-parto.

Introduction

Portal hypertension (PHT) is defined as a pressure gradient of 3.5 mm Hg between the portal vein (PV) and inferior vena cava (IVC), which can be due to cirrhosis or have a non-cirrhotic etiology. Non-cirrhotic portal hypertension (NCPH)

is common in developing countries,¹ among which non-cirrhotic portal fibrosis (NCPF) and extrahepatic PV obstruction (EHPVO) are the two most common causes,¹ with other less common etiologies as enumerated in **Chart 1**.² Compared with patients with cirrhosis, NCPH is not associated with significant hepatic dysfunction. Hence, fertility in

received
October 5, 2021
accepted
March 3, 2022

DOI <https://doi.org/10.1055/s-0042-1748973>.
ISSN 0100-7203.

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Chart 1 Etiologies of non-cirrhotic portal hypertension (NCPH)

Pre-sinusoidal	Sinusoidal	Post-sinusoidal
<ul style="list-style-type: none"> o Portal vein obstruction o Porto-sinusoidal vascular disease (PSVD) o Schistosomiasis o Arteriovenous fistulas o Polycystic liver disease o Congenital hepatic fibrosis o Biliary diseases (primary biliary cirrhosis; primary sclerosing cholangitis) 	<ul style="list-style-type: none"> o Drug-induced o Acute fatty liver of pregnancy o Alcoholic liver damage o Non-alcoholic steatohepatitis o Viral hepatitis o Amyloidosis o Infiltrative diseases o Gaucher's disease o Visceral leishmaniasis 	<ul style="list-style-type: none"> o Budd-Chiari syndrome o Veno-occlusive disease o Primary vascular malignancies o Hypervitaminosis A o Epithelioid hemangioendothelioma and angiosarcoma

Source: Gioia et al. (2020).²

women with NCPH is usually normal compared with patients with cirrhosis. Association of NCPH in pregnancy is an infrequent scenario, but when it occurs, it can lead to a complex clinical situation due to associated PHT and risk of variceal bleed. There is a paucity of data with regard to the prevalence of NCPH in pregnant patients, and the majority of data reported are from India³⁻¹⁰ with few multicentric studies from Europe.^{11,12} As of yet, there are no definitive guidelines regarding the management of pregnancy in NCPH. Hence, this narrative review aims at summarizing the current data on pregnancy outcomes in patients with NCPH and the management of portal hypertension and its complications during pregnancy.

Methods

A literature search was conducted on PubMed using the dates of 1990 to 2021 with the following medical subject headings (MeSH) terms: *Hypertension, Portal* [Mesh] AND *Pregnancy* [Mesh]. There was no restriction regarding language as long as study outcomes are mentioned in the text. The search yielded a total of 249 results which were independently reviewed by two authors, and it was decided by consensus which articles to incorporate in this review. We also searched the bibliography of the included studies for any relevant

studies. The studies describing outcomes in patients with cirrhosis were excluded.

Hemodynamic Changes during Pregnancy

Pregnancy is associated with several changes in hemodynamic and physiological parameters due to the growing needs of the fetus. An increase in plasma volume by 40 to 50% is one of the first changes to occur. Increases in stroke volume and heart rate result in a 30 to 50% increase in maternal cardiac output. The effect of progesterone and placental bed development contributes to the reduced systemic vascular resistance.¹³ Consequently, these hemodynamic alterations lead to hyperdynamic circulation (→ Fig. 1)¹³ with widened pulse pressure, ultimately leading to the worsening of PTH and increased risk of variceal bleeding. So, the primary aim of the management of NCPH in pregnancy is to reduce PTH to prevent complications and improve maternal and fetal outcomes.

Pregnancy Outcomes

Maternal Outcomes

Variceal bleeding remains the most devastating complication of NCPH in pregnancy. Though variceal bleeding may occur at

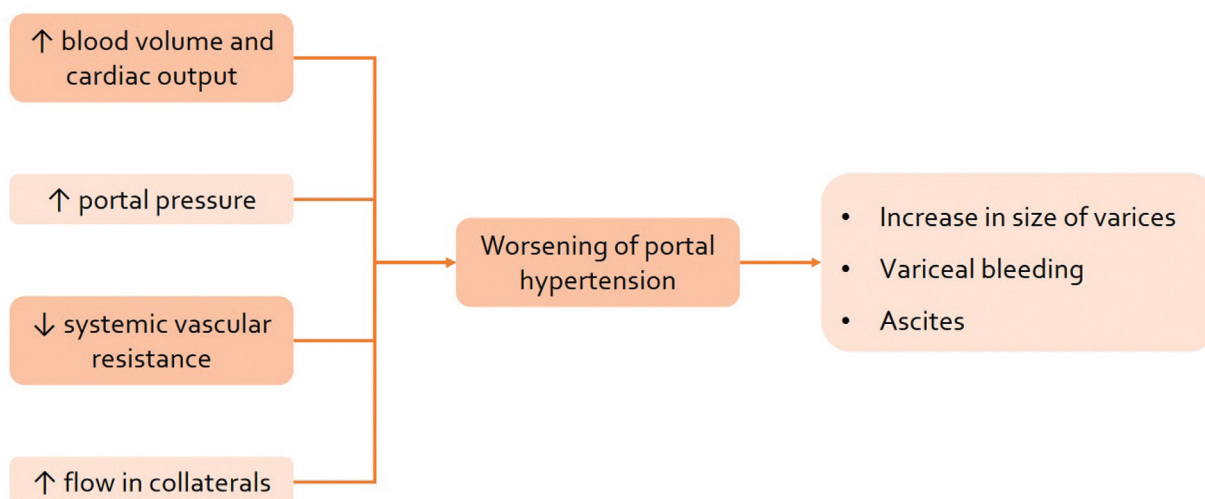


Fig. 1 Effect of pregnancy hemodynamics on portal hypertension. Source: López-Méndez and Avila-Escobedo (2006).¹³

any point during a pregnancy, it is most common during the second and third trimesters and during the second stage of labor. Studies have shown that variceal bleeding occurs in 4.3 to 34% of pregnancies.^{3-6,8-11} But pregnancies in which the PHT was diagnosed and managed prior to conception have lower variceal bleeding rates.^{6,9} Variceal bleeding during pregnancy has been associated with abortion, preterm labor, and maternal death.^{9,14} However, a recent study has shown comparable maternal and perinatal outcomes between patients who developed variceal bleeding and those who did not.⁵ This might be due to an improvement in endoscopic techniques and wider availability of endoscopic facilities. Pregnant patients with NCPH tolerate variceal bleeding better, with 2 to 6% mortality rates, compared with cirrhotics, in whom the mortality rate ranges from 18 to 50%.¹⁵ Ascites is uncommon in pregnant patients with NCPH compared with cirrhotic pregnant patients. However, ascites can still be seen in patients with non-cirrhotic PHT, with a reported incidence of 0.8 to 10% during pregnancy and usually disappear after delivery.^{3,4,9} Reported causes of maternal mortality include postpartum hemorrhage (PPH) and preeclampsia with hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome and disseminated intravascular coagulation.^{5,10} Rupture of splenic artery aneurysm is a rare but life-threatening complication that can occur in pregnancy with PHT caused by high estrogen levels, presence of splenomegaly, increased blood flow from pregnancy, and PHT.¹⁶ The risk of rupture is highest in the third trimester and is associated with a very high maternal and fetal mortality rate of up to 75% and 95%, respectively.¹⁶⁻¹⁸ Hence, screening for splenic artery aneurysms is recommended prior to conception with definitive endovascular or surgical management, if present.¹⁸

Fetal Outcomes

Pregnancy in NCPH is associated with adverse perinatal outcomes with increased rates of spontaneous abortion, premature delivery, small size for gestational age, stillbirth, and perinatal mortality. The reported incidence rate of spontaneous abortion in various studies is up to 23.8% of patients with NCPH.³⁻¹¹ Development of variceal bleeding during pregnancy in NCPH is well tolerated by the mother but poses a greater risk for the fetus. The incidence of preterm birth has been reported to be 10 to 37.5% in NCPH patients.^{4-7,9-12} Neonatal mortality is seen in up to 16% of pregnancies.⁴⁻¹¹

Management of Portal Hypertension in Pregnancy

Preconceptional Counselling

Detailed preconceptional counselling should be done for all women with NCPH. Patients should be oriented about the effect of pregnancy on PHT, the risk of complications during pregnancy, and the impact of drug therapy on the fetus. Patients should undergo a surveillance endoscopy prior to preconception for planning appropriate management of PHT. Prophylaxis for variceal bleeding can be achieved through

either endoscopic variceal ligation (EVL) or β -blockers. Prior history of variceal bleeding is a risk factor for bleeding during subsequent pregnancies.⁵ Hence, combination therapy with EVL and β -blocker is preferred for patients with varices and a previous history of variceal bleed.

Antenatal Management

If initial endoscopy was not performed preconceptionally and the patient presents for follow-up after conception, then endoscopy should be performed to assess the variceal status and plan further management. Despite limited studies on the safety of endoscopy in pregnant patients, it can be performed safely if the risk, benefit, and clinical indications are assessed carefully. As per the ACG guidelines on liver disease and pregnancy, the optimal time to screen for esophageal varices is in the second trimester, right after organogenesis has completed in the first trimester, and before delivery. Propofol is the preferred sedation for endoscopy due to its Food and Drug Administration (FDA) pregnancy category B. Meperidine can also be used but is less preferred due to pregnancy category C.¹⁹ Either EVL or β -blockers can be used for the control of varices. Non-selective β -blockers (propranolol, nadolol) and combined non-selective β -blockers with α 1-adrenergic receptor antagonist (carvedilol) are pregnancy category C drugs. The use of β -blocker in pregnancy has been associated with an increased risk of congenital malformations, fetal growth restriction, fetal bradycardia, and neonatal hypoglycemia.^{20,21} However, the benefit of using β -blocker outweighs the risk in patients with NCPH and should be continued in patients with large varices or small varices with red color signs (RCS). Patients with NCPH are also at risk for anemia, due to associated hypersplenism, and should be treated actively to reduce adverse outcomes like pre term labor and low birth weight. Hence, two weekly maternal and fetal monitoring with monthly hematological assessment is advised in these patients.¹⁴

Peripartum Management

Vaginal delivery is preferred, with a shorter second stage of labor, as repeated Valsalva maneuver leads to an increased risk of variceal bleeding. Forceps or vacuum extraction can be considered, if necessary, to shorten the second stage. Prophylactic shortening of the second stage of labor can be done to avoid overstraining by the mother. Multiple studies from India have reported using the vaginal mode of delivery in 50 to 84% of pregnant patients with NCPH.⁵⁻⁹ The current obstetric pain management relies mainly on neuraxial anesthesia (epidural, spinal, and combined spinal epidural techniques). Among these, epidural analgesia is the preferred option as it can also work if a lower segment caesarean section (LSCS) is required. Neuraxial analgesia can be safely administered if clinically indicated, with a very low risk of spinal epidural hematoma, if the platelet count is $> 70,000/\text{mm}^3$.²² There are no recommendations to perform a LSCS for all patients with PHT, and it should be reserved only for obstetric and fetal indications due to a higher risk of post-surgical bleeding in the setting of PHT. There are no studies that have compared the outcome of vaginal delivery versus

LSCS in PTH. Thrombocytopenia and anemia are common in patients with PHT and can be severe enough to require preprocedural transfusion. A platelet count of at least $50,000/\text{mm}^3$ is required to perform LSCS safely; hence, a platelet count below this level warrants transfusion before delivery.²³ Severe thrombocytopenia requiring platelet transfusion has been reported in 8.3 to 50% of patients.^{6,7,11}

Postpartum Management

Patients with PHT should be placed on strict postpartum monitoring due to an increased risk of PPH due to associated thrombocytopenia. Around 2.5 to 20% of patients with NCPH develop PPH.^{4-7,9-12} Postpartum hemorrhage management is the same as that of patients without PTH, including red blood cell units and platelet transfusion, oxytocin drip, and uterine artery embolization or surgery in case of failure of the above. There are no contraindications for breastfeeding in NCPH patients.

Management of Variceal Bleeding in Pregnancy

The management of variceal bleeding in pregnancy is the same as that of other patients, with pharmacological and endoscopic therapy being the mainstay of therapy. Preenoscopic preparation includes immediate resuscitation and hemodynamic stabilization of the pregnant patient. Octreotide (pregnancy category B) is the preferred vasoconstrictor agents in these patients, along with preprocedural antibiotics.¹⁹ Terlipressin is a category D drug, and it also causes increased uterine contractions, leading to reduced uterine blood flow. Hence, the use of terlipressin should be avoided.¹⁹ Endoscopic variceal ligation (EVL) is preferred over endoscopic sclerotherapy due to the lower risk of rebleeding and complications (ulceration, esophageal perforation, and stricture), with a higher rate of variceal eradication.²⁴ Gastric variceal bleeding can be managed with cyanoacrylate glue injection without any additional risk of complications.⁵ Development of variceal bleeding in a patient already on β -blocker warrants combination therapy with EVL and β -blocker for secondary prevention, although there are no direct studies available for pregnant patients.²⁵ **Fig. 2** summarizes the management of PHT and variceal bleeding in pregnancy.

Conclusion

Compared with patients with cirrhosis, women with NCPH have a better pregnancy outcome. Given the higher incidence of complications associated with PHT, these patients should be managed at a tertiary care level, with a multidisciplinary team including an obstetrician, hepatologist, anesthesiologist, and perinatologist. Variceal bleeding is associated with poor maternal and fetal outcomes; hence, effective control of PHT should be the primary aim of management as patients can still bleed even with NSBB therapy. Future studies are required to evaluate the role of primary prophylaxis with NSBB in patients with small varices as well as the role of combination therapy in secondary prophylaxis.

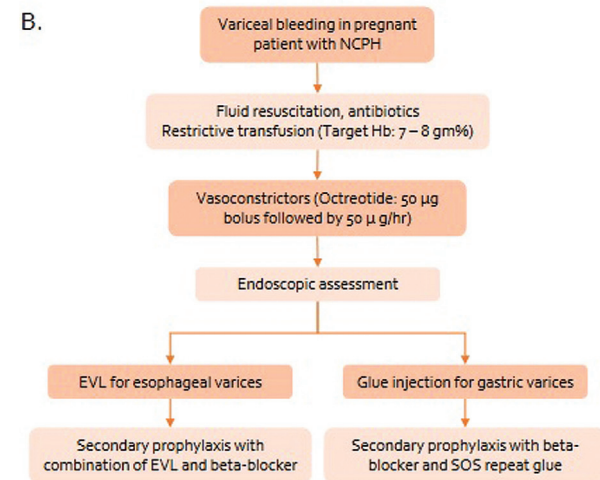
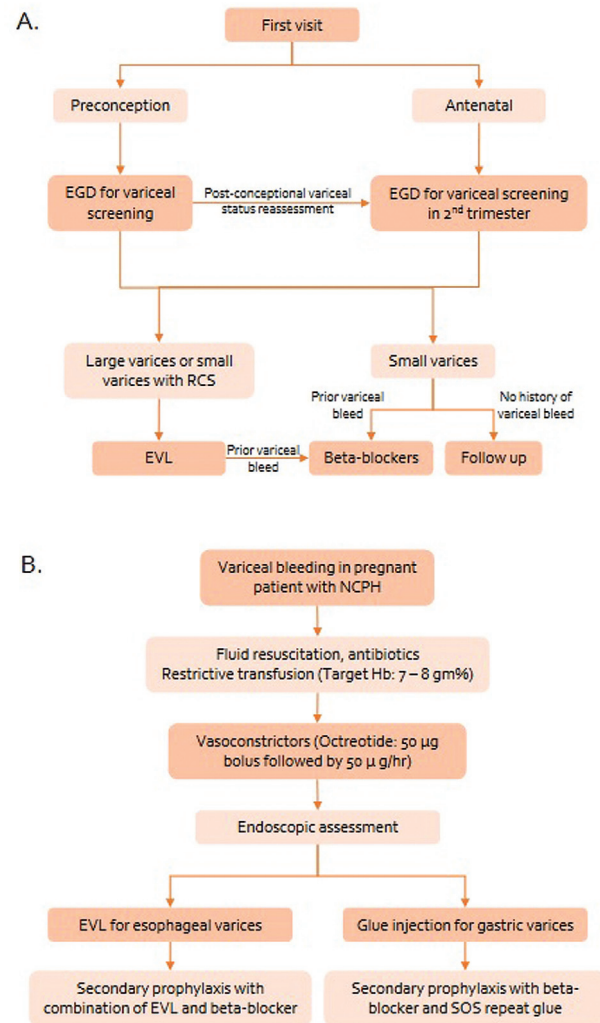


Fig. 2 (A) Management of portal hypertension in the preconception period and pregnancy, (B) Management of variceal bleeding in pregnancy.

Abbreviations: EGD, esophagogastroduodenoscopy; RCS, red color signs; EVL, endoscopic variceal ligation; NCPH, non-cirrhotic portal hypertension; Hb, hemoglobin.

Conflict of Interests

The authors have no conflict of interests to declare.

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The Correlation between *Chlamydia Trachomatis* and Female Infertility: A Systematic Review

A correlação entre clamídia trachomatis e infertilidade feminina: Uma revisão sistemática

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Rev Bras Ginecol Obstet 2022;44(6):614–620.

Abstract

The impact of *Chlamydia trachomatis* (CT) infection on female's fertility is not completely established yet, since the level of evidence associating these factors is still weak. Hence, the goal of the present review is to contribute to a better elucidation of this matter. The electronic database chosen was the Medline/PubMed, with the last survey on May 11, 2021. Publication date was used as a filter, with the previous 5 years having been selected. The following descriptors were used: *chlamydia trachomatis* AND *infertility*; *chlamydia trachomatis* AND *tubal alteration* AND *infertility*; *chlamydia* AND *low pregnancy rates*. From the 322 studies screened, 293 that failed to meet our eligibility criteria were excluded. Subsequently, we removed seven studies for not having the possible correlation between CT infections and female infertility as its main focus, and three for being about sexually transmitted infections (STIs) in general. Moreover, two studies designed as reviews were also excluded. Ergo, we included 17 studies in our qualitative analysis. The authors conducted research individually and analyzed carefully the studies selected. As we retrieved the information needed for our study through reading the texts, no contact was made with the authors of the studies selected. This systematic review corroborates the hypothesis that CT infection potentiates female infertility, as 76.47% of the included studies found a positive correlation between them. We conclude that there is an important association between CT infection and female infertility. Ergo, making CT screening part of the infertility investigation routine is relevant and has a reasonable justification.

Keywords

- ▶ chlamydia trachomatis
- ▶ infertility
- ▶ tubal factor infertility
- ▶ sexually transmitted diseases
- ▶ human reproduction

received
August 23, 2021
accepted after revision
January 27, 2022
published online
May 16, 2022

DOI <https://doi.org/10.1055/s-0042-1748023>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

O impacto da infecção por *Chlamydia trachomatis* (CT) na fertilidade feminina ainda não está completamente estabelecido, uma vez que o nível de evidência associando esses fatores ainda é insignificante. Assim, o objetivo desta revisão é contribuir para uma melhor elucidação deste assunto. A base de dados eletrônica escolhida foi a Medline/PubMed, com a última pesquisa em 11 de maio de 2021. Utilizou-se como filtro a data de publicação, sendo selecionados os 5 anos anteriores. Foram usados os seguintes descritores: *Chlamydia trachomatis* E infertility; *Chlamydia trachomatis* E tubal alteration E infertility; *Chlamydia* E low pregnancy rates. Dos 322 estudos selecionados, 293 que não atenderam aos nossos critérios de elegibilidade foram excluídos. Posteriormente, retiramos sete estudos por não terem como foco principal a possível correlação entre infecção por CT e infertilidade feminina e três por tratarem de infecções sexualmente transmissíveis (ISTs) em geral. Além disso, dois estudos concebidos como revisões também foram excluídos. Portanto, incluímos 17 estudos em nossa análise qualitativa. Os autores realizaram pesquisas individualmente e analisaram criteriosamente os estudos selecionados. Como obtivemos as informações necessárias para nosso estudo por meio da leitura dos textos, nenhum contato foi feito com os autores. Esta revisão sistemática corrobora a hipótese de que a infecção por CT potencializa a infertilidade feminina, pois 76,47% dos estudos incluídos encontraram correlação positiva entre eles. Concluímos que existe uma associação importante entre infecção por CT e infertilidade feminina. Portanto, tornar os procedimentos de triagem por CT parte da rotina de investigação de infertilidade é relevante e justificável.

Palavras-chave

- ▶ clamídia trachomatis
- ▶ infertilidade
- ▶ infertilidade tubária
- ▶ infecções sexualmente transmissíveis
- ▶ reprodução humana

Introduction

Chlamydia trachomatis (CT) infections represents, globally, the most prevalent sexually transmitted infection (STI) caused by bacteria, with 131 million new cases per year.^{1,2} *Chlamydia trachomatis*, which is an obligate intracellular parasite, can have a specific infectious potential to epithelial cells from male and female reproductive tracts. In symptomatic cases, men can present with urethritis, or, less commonly, epididymitis, and women, besides yellowish vaginal discharge, spontaneous bleeding, pain during sex or urination, and pelvic pain, may be led to pelvic inflammatory disease (PID).^{3,4} However, most women and 50% of men affected do not present many identifiable clinical symptoms, having an unnoticed infection.⁵ Therefore, the majority of infected individuals do not seek treatment, not only risking their sexual partners' health, but also worsening their condition, as the persistent presence of the pathogen evokes a chronic immune response, leading to an enhanced production of genital immune mediators, like interleukin (IL)-, IL-6 and gamma interferon, which increases the number of epithelial cells destroyed.^{5,6} This process is very dangerous, especially among women, once the manifestations and consequences are more damaging to their reproductive health than man's, a fact elucidated by the evidence that approximately 20% of women with chlamydial lower genital tract infection will develop PID, 4% develop chronic pelvic pain, 2% adverse pregnancy outcomes (chromosomal abnormalities, miscarriages, congenital malformations and stillbirth) and 3% infertility—probably due to scar formation and occlusion of the Fallopian tubes.⁷ The last possible consequence men-

tioned is defined as a couple's ineptitude to conceive after at least 12 months of regular unprotected intercourse and affects up to 15% of the reproductive-aged population.⁸ Even though this issue is widely recognized amidst the medical community as a secondary effect of female CT infection, the level of evidence corroborating the association is relatively weak.⁷ Thus, by doing a systematic review, we aim to contribute to the consolidation of this correlation.

Methods

The development of this study was based on the review writing methods of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.⁹

We included cohort studies, case-control studies, cross-sectional studies, and a letter, which were performed in the last 5 years and contained data about the correlation between infertility among reproductive-aged women and previous CT infection. Additionally, studies that compared the fertility rates between women with and without positive immunoglobulin G (IgG) for CT were admitted in this systematic review. There was no language restriction for the studies selection. Articles related to endocrine causes or just male infertility were excluded, as well as studies focused on STI in general or on different from CT. Additionally, we ruled out articles perceived as duplicates and reviews about the subject.

The electronic database chosen to carry out the search was the Medline/PubMed, with the last survey on May 11, 2021. The only filter used was the publication date, with the previous 5 years having been selected.

The authors conducted research individually. Subsequently, the studies obtained were carefully analyzed by them and, in case of disagreement, a consensus was used to decide whether the article would be included in the review or not. As we retrieved the information needed for our study through reading the texts, no contact has been made with the authors of the ones selected.

The research on the PubMed/Medline database was conducted using the following descriptors: (*chlamydia* [MeSH terms] OR *chlamydia* [all fields] OR *chlamydiae* [all fields] OR *chlamydias* [all fields]) AND (*infertile* [all fields] OR *infertilities* [all fields] OR *infertility* [MeSH terms] OR *infertility* [all fields] OR *infertile* [all fields] OR *infertility* [all fields]) AND (y_5 [filter]); (*chlamydia* [MeSH terms] OR *chlamydia* [all fields] OR *chlamydiae* [all fields] OR *chlamydias* [all fields]) AND (*tubal* [all fields] AND (*alter* [all fields] OR *altered* [all fields] OR *alteration* [all fields] OR *alterations* [all fields] OR *altered* [all fields] OR *altering* [all fields] OR *alters* [all fields]) AND (*infertile* [all fields] OR *infertilities* [all fields] OR *infertility* [MeSH terms] OR *infertility* [all fields] OR *infertile* [all fields] OR *infertility* [all fields])); (*chlamydia* [MeSH terms] OR *chlamydia* [all fields] OR *chlamydiae* [all fields] OR *chlamydias* [all fields]) AND (*low* [all fields] AND (*pregnancy* [MeSH terms] OR *pregnancy* [all fields] OR *pregnancies* [all fields] OR *pregnancy* [all fields]) AND *rates* [all fields]) AND (y_5 [filter]).

Firstly, in the identification phase, we found 325 studies through the database research and 2 by the references analyzed, leading us to 327 articles from which 5 were removed for being duplicates. Therefore, we had to screen 322 studies and, then, exclude 293 that failed to meet our eligibility criteria. So, in the eligibility phase, we assessed 29 articles. Finally, we removed seven studies for not having the possible correlation between CT infections and female infertility as the main focus, and three articles for being about STI in general. Moreover, two studies designed as reviews were ruled out too. Ergo, we included 17 studies in our qualitative synthesis.

Results

The flow diagram below (► Fig. 1), which is in line with the PRISMA methodology⁹, shows that we screened 322 publications from the existing literature in the Medline/Pubmed database. Subsequently, 305 manuscripts had to be removed in view of the following criteria: The data presented was not focused on the correlation between infertility among reproductive-aged women and previous CT infection or on the comparison of fertility rates of infected and not infected women; were related to endocrine or male causes of infertility; were focused on STI in general or just in others different from CT infection; were designed as reviews. Hence, 17 studies were included in our systematic review.

The findings of our research are summarized in **Chart 1**. As we can see, from the 17 manuscripts included, 8 were designed as cohort studies (including the regular, the retrospective and the longitudinal kind), 5 as case-control studies, 3 as cross-sectional studies and 1 as a letter- which was about

a cross-sectional hospital-based study. In relation to the screening of CT infection, the methods used were very diversified- 4 used polymerase chain reaction (PCR), 2 enzyme linked immunosorbent assay (ELISA), 2 CT serology, 1 nucleic acid amplification test (NAAT), 1 major outer membrane protein (MOMP) and 1 automated DNA extraction method. Also, some works used more than one strategy- 1 CT serology and PCR, 1 MOMP and ELISA, 1 CT serology and NAATs and 1 CSI-PCR, CT serology and/or self-reported infection. In 2 articles, however, the method of screening was not specified. The association between CT infection and female infertility, which is our main focus, was considered positive in 13.

Discussion

This systematic review corroborates the hypothesis that CT infection potentiates female infertility, as 76.47% of the included studies found a positive correlation between them. The results of the study conducted by Menon et al.,¹⁰ which included 239 women, indicate that up to half of subfertile women could have CT as a cause or contributing factor. This is also expressed in den Heijer et al.²³ finding that CT-positive women had approximately 70% higher chance of experiencing infertility. Davies et al.,¹² Ramadhani et al.,¹⁴ and Kayiira et al.,¹⁹ by presenting results that strengthen the discussed association, claim that policies of routine screening and interventions focused on preventing both first and repeated infections are extremely important in order to improve women's long-term reproductive health.^{12,14,19}

The type of female infertility more commonly associated with CT infection is tubal factor infertility (TFI), which occurs due to tubal occlusion (Toye et al., 1993).²⁷ According to Hoenderboom et al.,²² CT positivity represents a fourfold higher risk for TFI. In the study performed by van Door-emalen et al.,²⁶ it is observed that CT antibodies were significantly more common among the group with TFI compared to the group without it, respectively 41.9% and 9.6%.²⁶ Additionally, Rawre et al.¹¹ supported this correlation, once they observed that 56 out of the 75 women with TFI had had CT infection. Nevertheless, the mechanism behind this interconnection is still unclear.²⁷

If we imagine PID with severe adherences and significant tubal damage, it is easy to conclude that an anatomic cause harms fertility.^{28,29} However, there are some situations that do not visually present any alteration, which may suggest that there is also a molecular explanation. As CT is an intracellular pathogen that impairs the endothelium and the tubal muscle, probably it leads to an alteration in tubal motility and in endothelial cilia function.³⁰ This may explain the variations in intrauterine and tubal conformation, which presents areas of constrictions, which are observed during laparoscopy procedure, when a saline solution is inserted into the female reproductive tract. Even being fleeting there, CT facilitates the installation of other microorganisms in the female reproductive organs, causing a shift in its microbiota, with antigenic stimulus affecting the gametes and their

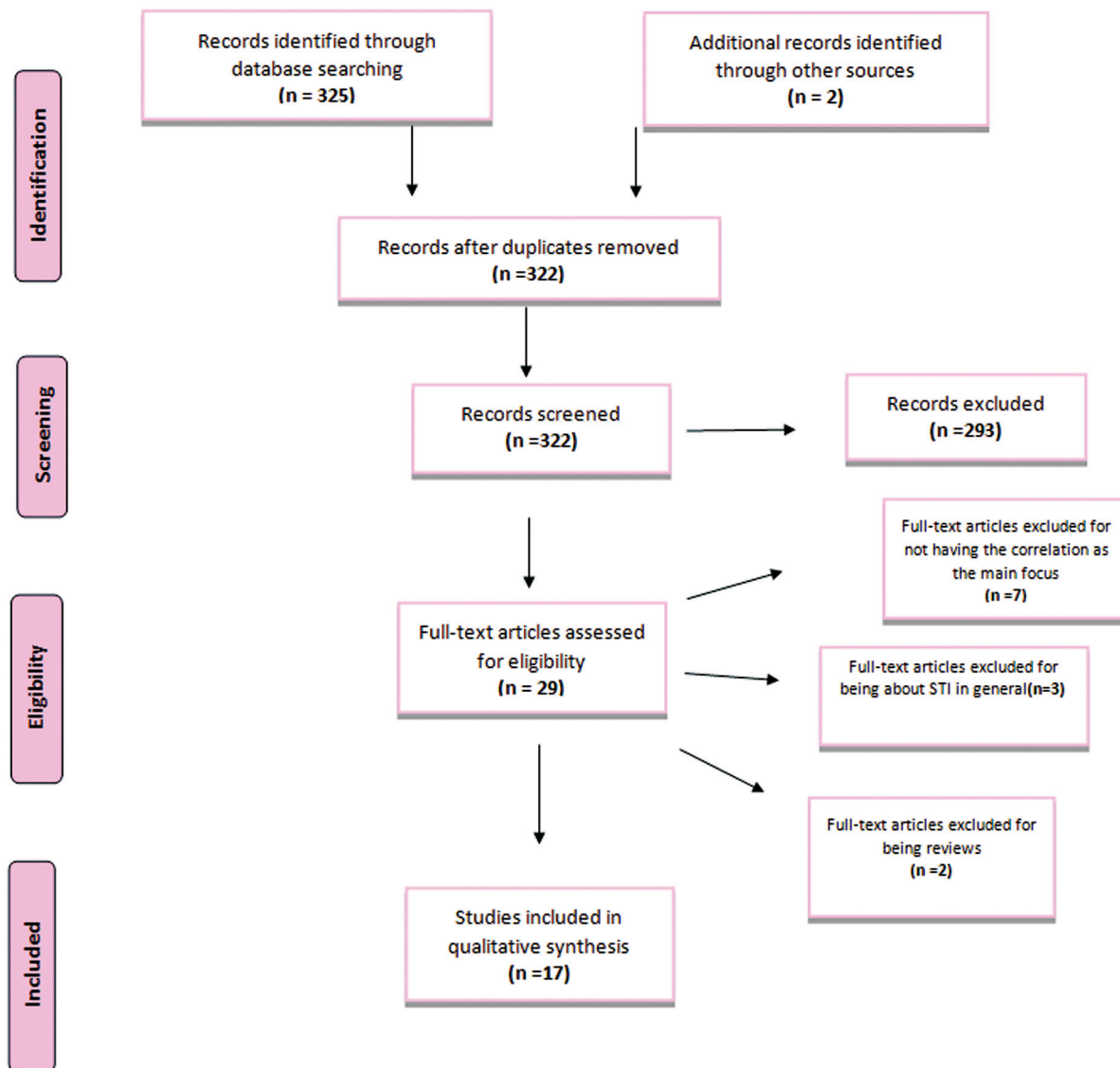


Fig. 1 PRISMA flow diagram.

conjunction.^{31–33} This immunological alteration can also explain the mild endometriosis in patients that previously presented CT infection, once the immunological imbalance caused might lead to the impossibility of an adequate action of the lymphocytes, allowing the maintenance of viable endometrial cells in the pelvic environment.³⁴ Thus, the CT infection and its associated mechanical and biochemical damage, as well as endometriosis, induce a modification in the female reproductive tract's environment, which becomes hostile to the gametes.

Concerning the four articles that denied the association between CT infection and female infertility, Rantsi et al.¹⁸ and Hoenderboom et al.²⁵ do affirm, however, that a longer time to conceive spontaneously was observed in women previously infected. This may indicate that past CT infection reduced the number of ciliated mucosal cells, leading to functional tubal damage and impairing the potential for pregnancy, even if it did not cause tubal occlusion. Joolayi et al.¹⁷ point out some limitations of its study, such as the low number of the study

population, the low number of women with secondary infertility, the short time of study, and the lack of real-time PCR.

We must mention that our review has two types of identified risks of bias—the publication and the selection bias. The first one is due to the fact that studies with a positive result have better chance of being published. Moreover, as we used only one database to find the articles, we might not have had access to articles on the subject published in other platforms, resulting in a selection bias. Also, there is a chance that we have not used all the proper keywords or that we failed to include in the review a useful study, which increases the last-mentioned type of bias.

Conclusion

Even though a consensus among doctors about the matter is not established yet, this systematic review emphasizes that there is an important association between previous CT infection and female infertility, once the majority of

Chart 1 Results

Author (year)	Design	Journal	Methods of CT screening	Number of participants	Association between CT infection and female infertility	Main results
Menon et al. (2016) ¹⁰	Cross-sectional study	Journal of Medical Microbiology	ELISA	239	Positive	Up to half of women who are subfertile in this population could have CT as a cause or contributing factor.
Rawre et al. (2016) ¹¹	Retrospective cohort study	APMIS	PCR	628	Positive	Significant association between rates of chlamydial infection and type of infertility, specially tubal factor infertility (74.7%; 56/75)
Davies et al. (2016) ¹²	Retrospective cohort study	The Lancet Infectious Diseases	Not specified	516,720	Positive	A positive CT test increased the risk of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility by at least 30%.
Dehghan Marvast et al. (2017) ¹³	Case-control study	Andrologia	CT serology and PCR	324	Negative	In contrast to other studies, this study did not support the relationship between CT infection and TFI.
Ramadhani et al. (2017) ¹⁴	Letter	Sexually Transmitted Infections	PCR	290	Positive	CT was more highly associated with primary infertility
Zhu et al. (2017) ¹⁵	Case-control study	Reproductive Health	PCR	30,760	Positive	The prevalence of CT in subfertile couples in this study was 3.15% and increased yearly from 2.45% in 2010 to 3.69% in 2014.
Begum et al. (2017) ¹⁶	Cohort study	Mymensingh Medical Journal	ELISA	69	Positive	This study shows that by laparoscopy, significant number of cases of tubal and pelvic pathology was diagnosed in the chlamydia trachomatis seropositive subfertile female
Joolayi et al. (2017) ¹⁷	Case-control study	International Journal of Reproductive BioMedicine	MOMP and ELISA	225	Negative	6 (6%) infertile and 2 (1.6%) fertile women were positive for IgM ($p = 0.21$). Also, PCR was positive for CT infection in 5 infertile (5%) and 2 fertile women (1.6%) ($p = 0.35$). We did not find any seropositive immunoglobulin G in both groups.
Rantsi et al. (2018) ¹⁸	Cohort study	American Journal of Reproductive Immunology	MOMP	96	Negative	The overall pregnancy rate or live birth rate did not differ by the presence of antibodies or CMI against CT. Time to spontaneous pregnancy was longer among CT positive women
Kayira et al. (2019) ¹⁹	Retrospective cohort study	Fertility Research and Practice	Are not specified	253	Positive	Exposure to current CT infection reduced chance of clinical pregnancy and a live birth after tubal flushing. Women with current CT infection had an increased risk of adverse events
Beyuo et al. (2019) ²⁰	Cross-sectional study	International Journal of Gynecology and Obstetrics	CT Serology	189	Positive	CT infection was present in 7.9% of women with suspected TFI, which was confirmed in 35% of them.
Al-Farraj and Moubayed (2019) ²¹	Case-control study	Saudi Journal of Biological Sciences	Automated DNA extraction method	200	Positive	The percentage positivity to infection was significantly more among the infertile group compared to the control group.
Hoenderboom et al. (2019) ²²	Cohort study	Sexually Transmitted Infections	PCR, CT serology and/or self-reported infection	13,498	Positive	This study adds to the evidence that chlamydia increases the risk for PID and TFI in women even if the infection was treated, ²⁹ but also

Chart 1 (Continued)

Author (year)	Design	Journal	Methods of CT screening	Number of participants	Association between CT infection and female infertility	Main results
den Heijer et al. (2019) ²³	Retrospective cohort study	Clinical Infectious Diseases	CT serology and NAATs	857,324	Positive	showed that incidence rates were small. Women who tested CT-positive had a substantially higher risk of experiencing female infertility (approximately 70%) than CT-negative women
Sukatendel et al. (2019) ²⁴	Cross-sectional study	Open Access Macedonian Journal of Medical Science	PCR	50	Positive	The proportion of CT infection in tubal abnormality in this study was 66.7%. It was obtained that there was a significant relationship between CT infection with tubal abnormality (non-patency tubal) with p -value < 0.005 ($p = 0.001$)
Hoenderboom et al. (2020) ²⁵	Longitudinal cohort study	Sexually Transmitted Diseases	NAATs	5,704	Negative	Overall pregnancy rates were not lower in chlamydia-positive women compared with chlamydia-negative women, but among women with a pregnancy intention, time to pregnancy was longer and pregnancy rates were lower in chlamydia-positive women.
van Dooremalen et al. (2020) ²⁶	Case-control study	Microorganisms	CT serology	891	Positive	CT antibodies were present significantly more often in the TFI+ compared to the TFI – group, respectively, 41.9% versus 9.6%

Abbreviations: CMI, cell-mediated immunity; CT, chlamydia trachomatis; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; PID, pelvic inflammatory disease; TFI, tubal factor infertility.

publications analyzed confirms it. Evidence of tubal damage is highly suggestive of impaired fertility as a secondary consequence of this parasite infection, but there is a need for further studies on the possible molecular causes. Finally, we believe that making CT screening part of the infertility investigation routine is extremely relevant and has a reasonable justification.

Conflict to Interests

The authors have no conflict of interests to declare.








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Breaking Bad News in Obstetrics and Gynecology: We Must Talk About It

Más noticias em obstetrícia e ginecologia: Devemos falar sobre isso

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Rev Bras Ginecol Obstet 2022;44(6):621–628.

Abstract

Breaking bad news is common in obstetrics and gynecology (ob-gyn). However, it is difficult, and few doctors receive training on how to deal with this situation. This narrative review aims to gather, analyze, and synthesize part of the knowledge on the area, focused on Ob-Gyn. Among the 16 selected articles, two are randomized controlled intervention studies, and most studies refer to obstetrics. The results found by us pointed out that simulation, feedback/debriefing, lectures, and protocols could improve doctors' performance in communicating bad news. For patients, the context and how the information is transmitted seem to impact more than the content of the news. Ob-Gyn doctors could benefit from specific protocols and education, given the specialty's particularities. There is a lack of evidence about the most effective way to conduct such training. Finding validated ways to quantify and classify studies' results in the area, which would allow for the objective analysis of outcomes, is one of the biggest challenges concerning this topic.

Keywords

- ▶ communication
- ▶ bad news
- ▶ obstetrics
- ▶ gynecology
- ▶ medical education

Resumo

Dar más noticias é comum em obstetrícia e ginecologia. Porém, é difícil e poucos médicos recebem treinamento sobre como lidar com essa situação. Esta revisão narrativa tem como objetivo reunir, analisar e sintetizar parte do conhecimento sobre a área, com foco na obstetrícia. Dentre os 16 artigos selecionados, dois são estudos de intervenção randomizados e controlados, e a maioria dos estudos refere-se à obstetrícia. Os resultados encontrados ressaltaram que simulação, feedback/entrevistas, palestras e protocolos podem melhorar o desempenho dos médicos na comunicação

received
June 16, 2021
accepted
November 3, 2021

DOI <https://doi.org/10.1055/s-0042-1742316>.
ISSN 0100-7203.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave

- comunicação
- más notícias
- obstetria
- ginecologia
- educação médica

de más notícias. Para os pacientes, o contexto e como as informações são transmitidas parecem ter maior impacto do que o conteúdo das notícias. Os obstetras e ginecologistas poderiam se beneficiar de cursos e protocolos específicos, dadas as particularidades da especialidade. Faltam evidências sobre a forma mais eficaz de realizar esse treinamento. Encontrar formas validadas de quantificar e classificar os resultados dos estudos na área, permitindo uma análise objetiva dos resultados, é um dos maiores desafios neste tema.

Introduction

“Bad news” is generally defined as any information that negatively impacts the life or vision of the future of those who receive it, according to their perspective.^{1,2} Due to this subjectivity, diagnoses with different degrees of complexity may be considered bad news. In addition to the impact caused by the content of the news itself, how communication occurs directly influences patient’s ability to face the diagnosis. This communication is also an important aspect of the doctor-patient relationship, and influences the patient’s satisfaction with the service provided.¹⁻³ Therefore, the way doctor-patient communication occurs can be more harmful than the diagnosis itself.⁴

Most physicians consider it an arduous task to transmit bad news, and the majority does not receive formal training for it in college, medical residency, or specialization programs.^{1,4,5} It is believed that this ability is acquired in daily practice, throughout the individual’s own practice, or by observing more experienced professionals. However, this is not corroborated by the literature, and the lack of adequate training is an important cause of the great stress that health professionals experience while transmitting bad news, which negatively impacts doctor-patient communication.^{1,4-6} This stress may aggravate the occurrence of burnout syndrome among medical professionals.³

The setting up, perception, invitation, knowledge, emotions, strategy and summary (SPIKES) protocol, created in the 1990s, aims to assist oncologists in breaking bad news by suggesting a strategy in the communication process.^{2,5} This protocol is increasingly used and adapted for different areas, including obstetrics and gynecology (ob-gyn).

Specific literature on breaking bad news is scarce, although it has expanded in recent years.⁵ Specifically in Ob-Gyn, the numbers are even smaller despite the recurrence of this type of communication in the area, which may involve pregnancy loss, fetal malformations, maternal complications during pregnancy, neoplasms, infertility, sexually transmitted infections, and any other diagnoses that negatively impact the patient’s life. The present narrative review aims to gather, analyze, and synthesize part of the existing knowledge about breaking bad news in Ob-Gyn, which are specialties with many particularities.

Methods

For this narrative review, we searched for publication in the databases PubMed, Scielo, Medline via Ovid, and Portal de Periódicos CAPES between April 2020 and February 2021, using the descriptors *breaking bad news obstetric*, *breaking bad news gynecology*, *breaking bad news*, *health communication*, *bad news obstetrics*, *bad news gynecology*, *SPIKES protocol obstetrics*, *SPIKES protocol gynecology*, *SPIKES protocol* and their Portuguese equivalents.

A total of 32 articles were selected and reviewed (► **Fig. 1**). Sixteen studies met the following inclusion criteria: belonging to the medical literature, specifically regarding ob-gyn and their subspecialties, being written in English or Portuguese, and focusing on breaking bad news. The exclusion criteria removed 16 articles, due to the following reasons: were related to ob-gyn but not in the medical field; mentioned “breaking bad news” but not as the focus of the study; were not associated with ob-gyn; were related to bad news in ob-gyn but did not focus on medical communication.

The 16 articles selected for this review are described in ► **Table 1**. Two of them were randomized controlled intervention studies. Opinion articles, narrative reviews, surveys, and a case study form the other publications included. Most refer to obstetrics.

Results/Discussion**Specific aspects of Gynecology and Obstetrics**

Breaking bad news in the context of ob-gyn has some particularities. The occurrence of adverse events during pregnancy or childbirth destroys the expectation and frustrates plans made about the supposedly healthy child to be born.⁷⁻¹¹ Pregnancy losses are considered one of the most stressful events in adulthood, and can trigger grief reactions. Mothers who experience fetal death are more likely to experience complicated and prolonged grief, which can last for more than a year.^{7,10} Feelings of guilt, anxiety, eating disorders, and shame are additional reactions experienced by parents who suffer pregnancy losses.^{9,10} From the perspective of health professionals, communicating fetal death is one of the most difficult duties, especially at the beginning of their careers.^{7,11}

When receiving bad news, the patient’s anxiety is greater when she does not expect something adverse to happen.⁹

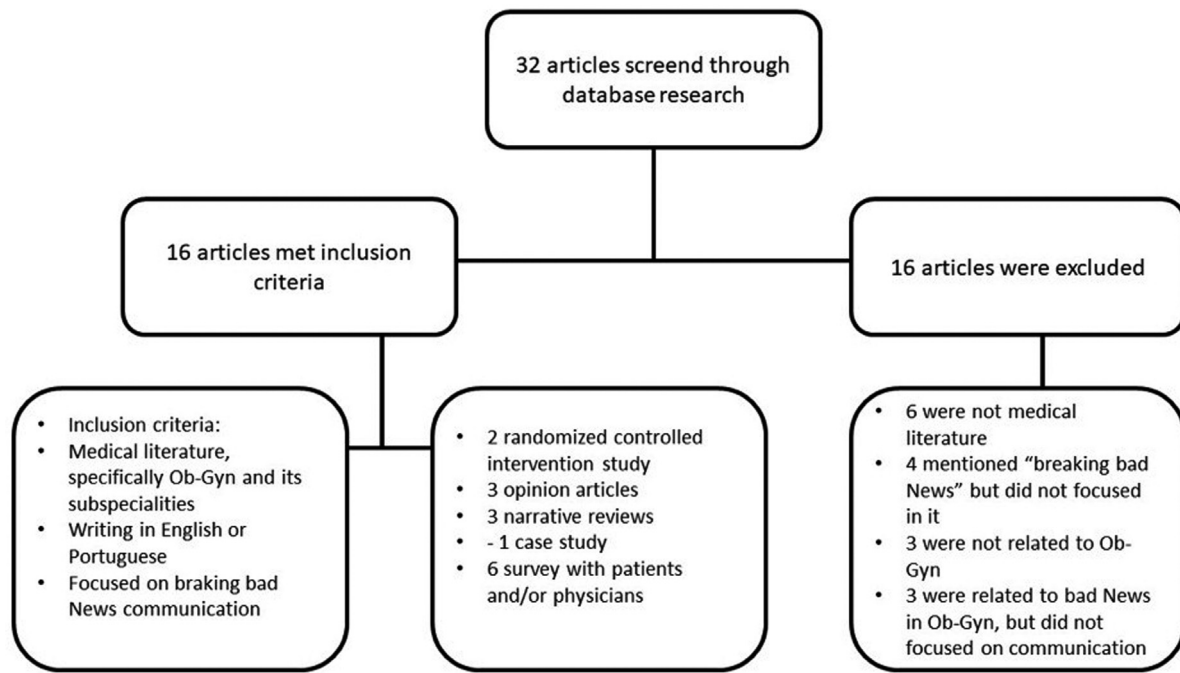


Fig. 1 Flowchart: selection process for the article.

This happens, for example, during ultrasound exams, as some women ignore its real purposes and consider it to be only a source of entertainment, a moment of personification of the fetus, and materialization of pregnancy expectations.^{9,12} The literature suggests patient education about ultrasound purposes, both by the requesting physician and by the examiner, as an attempt to avoid this situation.⁹ It is also important that the sonographer informs, when suitable, that they will perform the exam in silence and then discuss the findings with the patient, because unexpected silence may increase anxiety since the patient might think that something wrong with the test, even if it is not.^{9,12,13}

Additionally, regarding obstetrics—unlike other areas—the patient is no longer a single individual, but becomes the mother-fetus binomial and, when present, the partner is also considered as part of the “patient.” Thus, both parents should be present when the bad news is given for the first time, so that the mourning can start simultaneously. It is important that the doctor be aware that parents usually have different reactions when receiving bad news and it is their duty to understand and comfort both.^{7,12}

This perspective of the patient as more than one individual is also observed in reproductive medicine, where the couple is the patient, which can make it even more difficult to transmit negative news.^{14,15} Receiving an infertility diagnosis brings patients the feeling of frustration of an entire life plan, and has negative impacts on self-esteem, sexuality, and the couple’s relationship. It also creates feelings of shame and guilt. Leone et al.¹⁴ further claim that receiving a diagnosis of infertility may have the same psychological burden as receiving a breast cancer diagnosis. Also, in human reproduc-

tion, bad news may occur repeatedly and might have to be transmitted several times, with each treatment failure, for example.^{14,15}

When concerning gynecological cancer diagnosis, most of the time, it is announced by physicians who are not specialists in oncology, reinforcing the importance of improving communication skills for medical professionals of all areas.¹⁶ Another rare and specific situation in ob-gyn is the communication of cancer diagnosis during a pregnancy, because situations like this contrast the extremes of life: possible terminality *versus* the development of a new infant. The approach of these patients requires a multidisciplinary team, and communication must be done by a trained, preferably more experienced, professional.¹⁷

What are the Patients’ Perspectives?

The doctor’s lack of preparation to transmit bad news affects the patient. According to studies, the negative memories they have of the moment they received bad news are related to the report’s content itself and the doctor’s lack of skills for communication.^{7,9,11} How the information is transmitted is one factor that influences how traumatic this event will be for the patient.¹⁸ Patient satisfaction with medical care is based mainly on the doctor-patient relationship, which is greatly influenced by the physician’s communication skills.¹⁹ Dissatisfaction with this topic is an important cause of complaints and lawsuits against doctors and health care institutions.^{14,19,20} In line with this, Kuroki et al.¹⁶ and Alkazaleh et al.¹⁸ showed that the patient’s degree of satisfaction with communicating bad news was not completely related to the severity of the malignant neoplasm or fetal malformations, respectively, but to the physicians’ attitudes.^{16,18}

Table 1 Articles selected for the review

Author and year of publication	Area	Comments
Setubal et al. 2018 ⁷	Obstetrics	Randomized controlled intervention study. Case simulation of perinatal loss: a resident physician should inform the occurrence to a simulated patient (the parent), followed by instant feedback from the actor, and both moments are filmed. The participants were then randomly allocated to the intervention group (video review + training using the SPIKES protocol) or the control group (without training). A similar simulation was then performed and analyzed, with the actor blind to the intervention.
Karkowsky et al. (2016) ⁸	Obstetrics	Randomized controlled intervention study. Doctors underwent simulation of reporting a fetal death and care plan for the case, followed by immediate performance evaluation from the actor, the examiner, and themselves. After, they were divided randomly into two intervention groups: 1) a lecture about breaking bad news; 2) a debriefing session with the examiner. A new simulation was then performed, with different actors and examiners, blind to the intervention type, followed by further analysis. Six months after training, the researchers would contact the participants to assess the level of knowledge retention.
Guerra et al. (2011) ⁹	Fetal medicine	Opinion article
Lim et al. (2011) ¹⁰	Obstetrics	Opinion article
Nuzum et al. (2017) ¹¹	Obstetrics	An in-depth qualitative study based on interviews with grieving parents about their memories and insights regarding the moment they received a fetal death diagnosis.
Greiner and Conklin (2015) ¹²	Obstetrics ultrasonography	Narrative review
Romm (2002) ¹³	Gynecology and obstetrics	This article presents doctors' and patients' perceptions about the impact in communication skills produced by lectures given by patients to doctors, reporting their experiences in receiving bad news.
Leone et al. (2017) ¹⁴	Reproductive medicine	Doctors formed discussion groups to share their own experiences in communicating bad news and discuss the SPIKES protocol's applicability in the reproductive medicine area.
Lalos (1999) ¹⁵	Reproductive medicine	Opinion article
Kuroki et al. (2013) ¹⁶	Gynecologic oncology	Survey about patients' satisfaction regarding several aspects presented or not when they received bad news.
Zanetti-Dällenbach et al. (2006) ¹⁷	Mastology/ Obstetrics	Case study
Alkazaleh et al. (2003) ¹⁸	Obstetrics ultrasonography	Survey about patients' perception of the moment they received bad news and their preferences for such a situation.
Cockburn and Walters (1999) ¹⁹	Gynecology and obstetrics	Narrative review
Karkowsky and Chazotte (2013) ²⁰	Gynecology and obstetrics	Narrative review
Setubal et al. (2017) ²¹	Obstetrics	Physicians' (participants) perception of the training on communicating bad news reported by Setubal et al. (2018). ⁷
Johnson et al. (2019) ²²	Obstetrics ultrasonography	Analysis of a questionnaire applied to sonographers about training in breaking bad news, burnout syndrome, and psychological well-being.

When receiving bad news, patients may experience the grief reactions: denial, anger, negotiation/bargaining, depression, and acceptance.^{9,12,15} These emotions, added to anxiety, tension, and the amount of new information provided, can compromise the patient's assimilation of the content, which would cause them to forget up to two-thirds of the information given.^{9,19} Therefore, physicians should communicate bad news while respecting the patient's time to assimilate it, and repeat information if necessary.⁹ The use of excessively technical language also impairs assimilation and should be avoided.^{9,19}

Strategies to improve the patient's understanding of their health status include scheduling return visits, reviewing the content at the end of the appointment, offering help to inform anyone the patient wishes, and providing written materials containing information about the diagnosis.^{9,12,17,19} The presence of a companion also helps with the transmission of information, as having another individual to hear and remember the news, can give the patient time to process their emotions, and comfort them.⁹

Of the articles chosen for our analysis, 4 focused on patients' perception of the moment they received bad news from the attending physician (► **Table 1**). Kuroki et al.¹⁶ showed, with statistical significance, that the patients were more satisfied when they received the information in person during meetings lasting more than 10 minutes, set in a private, quiet, and comfortable environment, free of interruptions. When communication was patient-centered—that is, when patients were able to ask questions, and the doctor took into consideration the patients' needs and previous knowledge about their clinical condition—the satisfaction was higher.¹⁶

The other factors related to medical behavior that also positively impacted patient satisfaction were: being contacted later by the doctor for new explanations, sensing that the doctor is not nervous when giving the information, recognizing correct use of body language by the doctor.¹⁶ Adding to that, follow-up medical visits was also identified by Leone et al.¹⁴ as a factor that increases patient satisfaction. The adequate use of body language is reinforced by Guerra et al.⁹ and Greiner and Conklin.¹² How much the patient trusts the physician also interferes with satisfaction levels.¹⁶

In the study by Romm,¹³ patients also point out the aspects identified by Kuroki et al.,¹⁶ listed above, as crucial for proper communication of bad news, and added: providing information also in writing; allowing the presence of a companion, if it is the patient's wish; and passing the news as soon as possible, as long as it is not by text message or while the patient is at work.^{13,16} Regarding the physician's demonstration of empathy, patients dislike expressions like: "I know what you are going through" or "I know how you feel," unless the professional has experienced a similar situation themselves.¹³ The last point is reinforced in the review by Greiner and Conklin.¹² However, hearing from doctors that they are "very sorry for what the patient is going through" was considered desirable by the participants. Finally, patients pointed out that it was fundamental that the physician delivered the news entirely and in detail without

ending the patient's hopes. For this, they suggest doctors do not provide statistical data unless they are requested to do so.¹³ Cockburn and Walters¹⁹ reinforced the importance of maintaining the patient's hopes and advise doctors to encourage them to express themselves emotionally and to ask questions.

Alkazaleh et al.¹⁸ applied questionnaires to women who received the diagnoses of fetal malformations during an obstetric ultrasound. The results showed that patients consider the quality of the information the most important aspect when communicating bad news; this includes clarity of language, time to ask questions, receiving written information, and data about the care plan. In agreement with the previously mentioned studies, other points considered as positive were: how quickly they are informed about the diagnosis; the opportunity to have a companion; patient-centered communication; doctors' empathy; and a private environment when receiving the news.¹⁸ This last aspect is also reinforced by Cockburn and Walters.¹⁹

In agreement with Kuroki et al.,¹⁶ who showed no relationship between the specific aspects of the tumor and the degree of satisfaction with care, Alkazaleh et al.¹⁸ reported that the severity of the fetal malformation diagnosed did not impact the patient's satisfaction.^{16,18}

Nuzum et al.¹¹ collected data from interviews with grieving parents about their perception of the moment they received fetal death diagnosis. They reinforce the importance of adequate language used, the sensitivity from the doctor, and proper environment. Additionally, physicians' use of "diversionary techniques"—for example, omitting the news while waiting for a second opinion—was considered a negative attitude during communication.

The literature brings other points that improve transmission of bad news. For example, in the context of obstetric ultrasound, Guerra et al.⁹ recommends for the patient to be dressed, sitting at the same height and facing the doctor; eye contact is of great importance when receiving the news. Besides, in case of severe ultrasound findings, it is advisable to leave the patient and her companion alone in the room for some time after breaking the news, so they are free to express themselves.⁹

How to Improve Medical Training?

Among the reviewed articles, several reinforce the impact of the doctors' lack of preparation for communicating bad news through academic and professional life.^{7,9,19,20} Setubal et al.²¹ highlight the deficiency of this type of training in ob-gyn residences. Negative feelings experienced by physicians while communicating bad news make the task even more complicated, and excessive stress during this moment can be a risk factor for burnout syndrome among medical professionals.^{7,8,20–22} It is mistakenly believed that the practice and observation of more experienced colleagues breaking bad news could provide adequate training for this situation, but this training method allows for reproduction and perpetuation of errors.^{7,12,19,21}

Appropriate strategies for communicating bad news can be taught, just like other medical skills, and many doctors

recognize the importance of such training.^{8,19–21} Adequate preparation can prevent emotional damage for both doctors and patients.^{13,21} There is a lack of evidence in the literature about the most effective way to teach communication of bad news and how to keep this training up to date.^{16,20}

Setubal et al.⁷ showed that simulation activities followed by immediate feedback—and, in the intervention group, also a lecture on the SPIKES protocol—were able to increase ob-gyn and pediatrics residents' performance in breaking bad news. The benefit of the simulation followed by feedback or debriefing is also recognized by Karkowsky et al.⁸ and Leone et al.¹⁴ However, this method may require financial and human resources not available in all institutions.²¹

When assessing the perception of resident physicians participating in the study, most were satisfied with the methods applied and would recommend the training to a colleague.⁷ Almost all of the participants noticed an improvement in their skills and knowledge on how to deliver bad news, and believed that training would improve their practice. There was a consensus on recognizing the SPIKES protocol's great value to systematize bad news communication in clinical practice.²¹

In a similar randomized controlled study, Karkowsky et al.⁸ showed that the self-perception of ob-gyn doctors about their performance in communicating bad news improved after a simulated situation of breaking bad news, followed by a lecture on the topic or an individual debriefing session with a specialist, and then a new simulation. The individual perception of improvement was greater in the debriefing group, as the individuals who underwent debriefing appeared to have slightly greater improvement in verbal and non-verbal communication skills. Finally, when analyzing the ability to retain the knowledge learned after 6 months

of the intervention, the results were satisfactory in both groups. Romm¹³ also used a lecture as an attempt to enhance doctors' communication abilities and participants reported an improvement in recognizing key points when transmitting bad news.

In contradiction to the majority of the other articles, a survey performed by Johnson et al.,²² with sonographers from the United Kingdom, showed that the majority had received some training for communicating bad news. Lectures and discussion groups were the most common teaching methods. However, the preferred learning methods chosen by the professionals were observation of clinical practice and patient feedback. There was no correlation between receiving training on breaking bad news and the professional's psychological well-being or the occurrence of burnout syndrome. Still, training was associated with lower occurrence of loss of motivation toward the job.²²

Finally, Leone et al.¹⁴ concluded that the SPIKES protocol might benefit reproductive medicine doctors by reducing stress associated with communicating bad news. This protocol is also useful in other subspecialties of ob-gyn, as doctors consider dealing with the patient's emotions one of the most challenging steps.^{7,10,12,19}

In Brazil, communication skills and the ability of communicating bad news are part of the Professionalism Axis of the Competency Framework in Gynecology and Obstetrics, which was approved by the National Commission for Medical Residency (CNRM-MEC) as the official reference for training in this specialty. Therefore, all medical residency programs must offer the necessary training in these skills, as well as evaluate their acquisition by resident physicians.²³

Communicating negative news is part of the routine of Ob-Gyn. However, formal training for this skill is not yet part

Table 2 DOs and DON'Ts in communicating bad news in gynecology and obstetrics

Breaking bad news in Ob-gyn

DOs

Follow the SPIKES protocol, adapting it to ob-gyn reality.

Study and practice “communicating bad news” as any other medical professional should.

Try to guarantee the patient's privacy and an environment free of interruptions when breaking bad news.

The communication must be patient-centered.

Express empathy and hope.

Review the information with the patient and offer written material about it.

In obstetrics, consider both the parents and the fetus as the patient. Work with a multidisciplinary team whenever possible.

DON'Ts

Avoid expressions like “I know what you are going through” or “I know how you feel,” unless you have gone through a similar situation.

Avoid excessively technical language.

Do not provide static data unless you are requested to do so.

Do not omit, minimize, or delay the information, if the patient desires to hear it.

Do not communicate bad news through impersonal means, such as voice/text messages.

Abbreviation: Ob-gyn, obstetrics and gynecology.

of several residency programs and is equally deficient in medical school.^{5,7,8,11} There is a belief that doctors learn how to break bad news in daily practice, or by observing more experienced doctors perform such a task. However, the literature shows no difference in this ability when comparing medical students, residents, and specialists.^{1,5-7,11,19,21} Additionally, learning by observation favors the perpetuation of errors.⁷ This highlights the importance of implementing formal training in communicating bad news in medical education, given the negative impacts caused by poor communication. The principle of *primum non nocere* should not be forgotten.⁹ Although physicians cannot modify the content of negative news, they can improve their communication skills.¹¹ Unfortunately, there is still no evidence of the most effective way to conduct such training.¹

Initially designed for oncology, the SPIKES protocol has been used in several medical specialties, as well as in medical school, for training medical professionals on how to break bad news to patients.^{2,3,5,20} The strategies proposed by this protocol seem to be suitable for ob-gyn, resulting in the improvement of the professionals' performance and a greater personal satisfaction while communicating bad news to patients.^{7,10,11,14,21} However, ob-gyn has several particularities, and may benefit from specific protocols.^{8,20} In obstetrics and ultrasound, for example, the diagnosis and communication occur almost simultaneously, and there is no time to prepare the environment or for doctors to prepare themselves, which would be the first stage of the SPIKES protocol.^{9,20} Another particular aspect of the ob-gyn specialty is that the patient is often a couple, requiring different approaches for each of the individuals involved.^{9,14,15} The key points of the present review are collected on ► **Table 2**.

While protocols and training about how to break bad news can improve the physician's ability and decrease anxiety, this will never be never easy. It is an unwanted situation, both for doctors and patients, and it is made harder by the unpredictability of the patients' reactions to highly stressful situations.^{14,21}

Despite analyzing only part of the existing studies on the subject, this review shows that the communication of bad news is very recurrent and particular in ob-gyn, and the lack of preparation for such a situation is harmful to doctors and patients. It might be hard to produce robust evidence on the matter because of the absence of objective results to be analyzed, as the results achieved with improving communication are mostly subjective. Undoubtedly, finding validated instruments to quantify and classify such findings to allow a statistical and objective analysis of outcomes is one of the biggest challenges in the area.

Conflict of Interests

The authors have no conflict of interests to declare.



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Has the COVID-19 Pandemic Affected the Epidemiology of Syphilis in Brazil?

A pandemia da COVID-19 afetou a epidemiologia de sífilis no Brasil?

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Rev Bras Ginecol Obstet 2022;44(6):629–630.

Dear Editor,

Syphilis is a sexually-transmitted infection (STI) identified as a public health problem in Brazil and worldwide.¹ According to the World Health Organization (WHO),² in 2016, 6.3 million cases of the disease were diagnosed worldwide, with an estimated global prevalence of 0.5%. In Brazil, the disease has come to be considered an epidemic due to the significant increase in the number of cases in recent years.³

Syphilis is a disease of compulsory notification throughout the Brazilian territory. Data from the Ministry of Health indicate that, between 2010 and 2018, the incidence of syphilis in pregnant women increased from 3.5 to 21.4 cases per thousand live births. Regarding congenital syphilis, there was an increase from 2.4 to 9.0 cases per thousand live births.⁴

In 2020, the problem of syphilis became even more serious due to the emergence of the coronavirus disease 2019 (COVID-19) pandemic, which changed the epidemiology of STIs worldwide. Some studies^{5–8} performed in countries in Europe, Asia, North America, and the Caribbean have observed a reduction in the number of people diagnosed with syphilis during the pandemic, and this decrease was one of the consequences of social distancing measures and limited access to health services during this period. Moreover, Furlam et al.⁹ reported that the COVID-19 pandemic generated a reduction in the number of syphilis diagnosis and treatment procedures in Brazil, in addition to the weakening of the relationship between users and the health system in the country. In this sense, it is essential to analyze how this context influenced the epidemiology of syphilis throughout Brazil.

We analyzed data from the Brazilian Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação, SINAN, in the Portuguese acronym)¹⁰ of the Ministry of Health related to syphilis in pregnant women, and we observed a reduction of ~ 1.1% in the total number of reported cases across Brazil between 2019 and 2020 (before and during the COVID-19 pandemic respectively). The Southern, Northeastern and Northern regions followed the national trend, showing reductions of around 5.3%, 4.7% and 0.5% respectively, of reported cases when comparing 2019 and 2020. On the other hand, in the same period, the Southeastern region showed an increase of 1.5% in reported cases, while in the Midwestern region there was stability (– **Table 1**).

Table 1 Reported cases of gestational syphilis and congenital syphilis in Brazil according to geographic region

Region	Reported cases of syphilis in pregnant women		Reported cases of congenital syphilis	
	2019	2020	2019	2020
Northern	6,120	6,092	2,232	1,808
Northeastern	13,197	12,585	6,523	6,232
Southeastern	28,113	28,558	10,869	9,883
Southern	9,486	8,987	3,267	2,973
Midwestern	5,180	5,180	1,464	1,240
Brazil	62,084	61,402	24,355	22,136

published online
May 24, 2022

DOI <https://doi.org/10.1055/s-0042-1748024>.
ISSN 0100-7203.

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Data on congenital syphilis available on SINAN were also analyzed. We found a 9.2% reduction in reported cases of this condition between 2019 and 2020. Also, in the same period, all regions showed the same trend of reduction in reported cases, with the Northern and Midwestern being the regions that showed the highest rates of reduction (Northern: 19%, Midwestern: 15.4%, Southeastern: 9.1%, Southern: 9%, and Northeastern: 4.5%) (► **Table 1**).¹⁰

Therefore, it has been noted that until 2019 the rates of syphilis in pregnant women and congenital syphilis showed a constant increase. However, from 2020 onwards, simultaneously with the emergence of the COVID-19 pandemic, these rates showed a downward trend. In this regard, we suggest that researchers develop more in-depth and systematized investigations that make it possible to understand the influence of the pandemic on the epidemiology of these infections in Brazil, so that it is possible to define whether the reduction is a consequence of social distancing measures and limited access to health services, or if it results from the effectiveness of disease-control strategies in the country.

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Human papillomavirus vaccination for adult women

Number 6 - June 2022

DOI: <https://doi.org/10.1055/s-0042-1751331>

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

Key points:

- Update obstetrician–gynecologists about human papillomavirus (HPV) vaccination for adult women with Febrasgo position about this matter.
- Emphasize there is a generation of women who reached adulthood without HPV vaccination opportunity and highlight benefits provided by vaccine immunization.
- Address epidemiological and immunological aspects of HPV infection and available vaccines.
- Assess the susceptibility of unvaccinated adult women to oncogenic types of HPV and to lesions caused by HPV.
- Assess the difference in susceptibility to recurrence and reinfections after treatment of HPV-associated lesions among vaccinated adult women compared to unvaccinated adult women.
- Provide knowledge of best evidence for HPV vaccination among adult women and collaborate for an updated clinical practice.

Recommendations:

- Consider vaccination even in adult women with previous HPV infection history, as the natural infection does not seem to offer sufficient immunity to prevent new infections occurrence by the same viral type, unlike the immunogenicity induced by HPV vaccines.
- Consider most adult women have negative serological and molecular tests for the viral types included in vaccines.
- Consider second HPV infection peak in the woman's fifth decade of life.
- Consider adult women without vaccination coverage as still at risk for acquisition of HPV and for developing HPV lesions throughout their lives.
- Consider evidence of recurrences and / or reinfections risk reduction after vaccination of patients with previous lesions caused by HPV and who have already been treated.
- Consider adult women can benefit from individual protection even they are not eligible for vaccination in official programs based on population studies.
- Therefore, we endorse that adult women without HPV vaccination in adolescence, with or without a history of previous infection, may have protection benefits if immunized. In young women (up to 30 years old), these benefits are significant and were demonstrated in several publications. Therefore, this should be part of the medical prescription. However, there is also individual protection for women aged up to 45 years or more who may still be at risk of new infections. This information must be shared by their gynecologists.

Background

Human papillomavirus (HPV) infection is very prevalent. It occurs early, most of the times after onset of sexual activity. Among diseases associated with HPV infection, cervical cancer stands out. It continues to affect many women worldwide, especially in developing countries like Brazil, even though screening programs are effective when organized. The knowledge about genetic structure of different HPV types and the tech-

nological evolution provided vaccines development to prevent infection by oncogenic and non oncogenic HPV types.

Since 2007, HPV vaccines have been administered to adolescents in Immunization Programs around the world. They promote prevention of HPV cervical cancer and clinical lesions. In this target group, mainly between 9 and 12 years old, there is no concerns about vaccine safety and effectiveness. ^(1,2)

In Brazil, the National Program for Immunization (Programa Nacional de Imunizações, or PNI) implemented HPV vaccination in 2014, but vaccination coverage is still low. Currently, there are generations of adult women who have not benefited from HPV vaccination. The aim of this analysis was to present the main scientific evidence in vaccine indication for these women, especially after 25 years old. The PNI covers 9-14-year-old girls. In 2021, the MS/PNI extended the vaccination age for women with HIV, transplant recipients and cancer patients, from 9 to 45 years.⁽³⁾ The Technical Immunization Advisory Board (CTAI) at a meeting on May 30, 2022, decided to also expand to men with HIV, transplanted and oncological (First meeting of Technical Advisory Board on Immunizations-CTAI, May 30 and 31, 2022, Brasilia DF, oral communication).

As for non-vaccinated young women (up to 26 years old), although they are outside PNI, there is no further scientific discussion, as they have an obvious benefit and vaccination should be indicated.^(1,2)

What is the prevalence of HPV infection?

Human Papillomavirus (HPV) infection is the sexually transmitted virus with higher incidence worldwide.

It is estimated that about 600 million people are infected with HPV globally and that 80% of the sexually active population becomes HPV infected during a lifetime. The first peak of incidence occurs during the second decade of life and the second peak during the fifth and sixth decade of life. While the first peak is related to onset of sexual activity, the second can be explained by new exposure or immunity loss. The immunity against HPV infections in adult women is much lower than the immunity against HPV in adolescents.⁽⁴⁻⁶⁾

The relevance of HPV infection was consolidated when its association with cervical cancer was proven. It has been considered as the cause of all cases. The presence of HPV oncogenic DNA was found in 99.7% of cases of cervical cancer. It is the largest cause and effect relationship between an agent and cancer in humans. Several studies have shown that persistent HPV infection is the main risk factor for cervical intraepithelial neoplasia (CIN) and cervical cancer in young and adult females.⁽⁴⁻⁷⁾

There is increasing estimate of cervical cancer incidence in countries where there is no organized screening. Despite the availability of vaccines, the last few years estimative are around 530 thousand new cases and 275 thousand deaths annually. In Brazil, the Brazilian National Cancer Institute (INCA) estimates 16,710 new cases for the next years (2020-2022).⁽⁴⁻⁸⁾

It is important to note that women remain at HPV infection risk throughout their lives, even though the highest contamination rates are in the young population group. Contamination rates are up to 25% over five

years in women between 30 and 44 years old. In addition, persistent HPV infection is the main risk factor for CIN and cervical cancer for every age group.⁽⁶⁻⁹⁾

Does immunity develop after natural HPV infection?

Women exposed to HPV infection developed immunity after clearing this infection. This was the subject of several discussions regarding the protective ability for the same viral type. A pioneer study carried out in Costa Rica analyzed 10,049 women. It was observed that the incidence of HPV infection in seropositive women for a certain virus type was similar to seronegative women. This indicate inefficiency of the naturally acquired immunity in protecting against new infection or recurrence. This study evidenced that humoral immunity after natural infection may not prevent new infections, because antibodies levels produced are, generally, low and fall rapidly. They may even be negative.⁽¹⁰⁾ For this reason, adult women previously infected in previous years may not be protected against new infections, including the same viral type.

What is the clinical value of HPV vaccination for adult women?

Although vaccines were developed for prophylactic use in adolescents before exposure to HPV infections, data show a low adolescent number completing the immunization schedule recommended by PNI in Brazil. On the other hand, studies show that vaccines are effective in adult population even after onset of sexual activity. Besides, a considerable proportion of women did not have active infection due to the types of HPV contained in the vaccine after maturity.⁽⁶⁻¹²⁾

Literature also shows evidence of a reduction in relapses with vaccines administration even in patients with previous lesions triggered by HPV and who have already been treated. Although relapses are low (3%-7%), these numbers can decrease by 60% to 80% after vaccination.^(13,14) A recent meta-analysis demonstrated the benefits of vaccinating women undergoing excisional treatment for cervical cancer precursor lesions, corroborating some previous studies.⁽¹⁵⁾

About 99.6% of sexually active women up to 45 years old would benefit from HPV vaccines. Studies analyzed the viral infection presence of vaccine virus types in groups of women aged 16 to 23 and 24 to 45 years-old or more women. It was found that most women were seronegative or positive for only one of the viral types studied regardless of age.⁽¹¹⁻¹⁶⁾

The recommended vaccination for women up to 30 years old aims to rescue who have not been properly vaccinated between 9 and 14 years old. The decision must be shared between the physician and 30 to 45-year-old women. It should be recognized that

some not adequately vaccinated women may be at risk for new HPV infections and this age group may benefit from vaccination. Logically, the vaccine utility with the coming-of-age will depend on the person's exposure risk to new infections. The HPV types 6, 11, 16 and 18 vaccine is not licensed for use in women aged > 45 years.⁽²⁾

A recent cohort study in Sweden showed that HPV vaccination with quadrivalent vaccine was associated with a significant decrease of invasive cervical cancer risk among girls and women aged 10 to 30 at the population level.⁽¹⁷⁾

Is the vaccine safe in adult female?

There is no record of serious adverse events related to vaccination in any age group. Several regulatory agencies evaluate its safety globally. The HPV vaccines confirm, in practice, an excellent safety profile consistent with initial HPV vaccines trials. Therefore, there is no contraindication to vaccinate women aged up to 45 years or older (depending on the vaccine), since the vaccines are immunogenic and safe for various age groups. They must be individualized for each patient.^(2-6,18-20)

What are the additional benefits of adult female HPV vaccination?

Besides many adolescents did not receive HPV vaccination at the appropriate time, as discussed, most women seen by gynecologists are above the age limit recommended in the immunization schedule. Therefore, not missing the opportunity to indicate vaccination and avoid HPV infection complications is a fundamental point of the gynecologist care. Even for women who had high-grade precursor lesions and were treated, several studies showed that vaccination after treatment can decrease relapses. It is known that women who have developed HPV lesions have cofactors that facilitate viral action. As these cofactors tend to remain, it may result in pathologies elsewhere. Thus, women with precursor lesions are theoretically at greater risk for other related lesions. In that fashion, vaccination would have a more accurate indication.^(12-14,19,20)

Does the vaccine confer immunogenicity in adult female?

Antibody response, i.e. immunogenicity in women aged between 24 and 45 years was compared to immunological data of women aged 16 to 23 years, and these were comparable for the HPV-16 type and slightly smaller for HPV-6, 11 and 18. Furthermore, in a study, viral types contained in the vaccine were comparable to those observed at month 48 (end of baseline study), indicating no subsequent reduction in titers between four and six years after vaccination.^(12-19,21,22)

Should vaccination in adult women be systematic?

Studies show that vaccination of women aged 30 to 45 years is less effective when compared to vaccination in adolescents and young women (up to 30 years old), especially when DNA-HPV status is ignored or positive. This does not justify the systematic recommendation or calling protocol for vaccination. The woman must be evaluated individually.⁽¹⁷⁻²³⁾

Final remarks

The reduction in diseases caused by HPV is causally related to high HPV vaccination coverage among the target groups (children and adolescents). The vaccine is routinely administered before virus exposure.

If universal coverage is available, it will be possible to substantially decrease morbidity and mortality of diseases attributed to HPV worldwide. This could provide a breakthrough in global public health. The school-based vaccination program was suspended years ago. Its return may increase adolescent vaccination coverage. Therefore, it will no longer be necessary to discuss adult female vaccination in the future. Stimulating wide vaccination of adolescents is a fundamental point in primary health care that must not be overlooked. However, we must not miss the opportunity to indicate vaccination for adult women who have not benefited from vaccination as teenagers, especially in countries with lower than expected vaccination rates. This can provide clear benefits as shown by studies. It is important to note that the HPV vaccine administration, at any age, does not replace health promotion actions. Cervical cancer screening should be maintained according to the age group. HPV vaccine and cervical cancer screening are complementary methods to protect women from developing genital cancer. Some fundamental points regarding vaccination still need to be better elucidated among gynecologists and health professionals.

Among them, the indication of vaccination stands out, regardless of whether there is any suspicion or evidence of active HPV infection. In addition, vaccination can be recommended after the treatment of high-grade cervical lesions. It has benefits in reducing relapses, although these are extremely low. Concluding about HPV vaccination in adult women who have not been previously vaccinated, there is no discussion about vaccinating them routinely up to 30 years old, as the benefits have already been demonstrated, and gynecologists should be aware of vaccine prescription. National programs around the world recommend calling these women up for vaccinations. However, data demonstrate there are also benefits in vaccinating women aged up to 45 years or more. These women must be evaluated individually, and the indication must

be shared with them. The benefit of vaccinating with the coming-of-age depends on the risk of exposure to new infections.

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Conflict of interest: none to declare.

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BR-HPV-00656 PRODUCED IN MAY/2022 VALID FOR 2 YEARS

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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.

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- 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;
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- Title page;
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Title Page

- Title of the manuscript in English with a maximum of 18 words;
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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](http://www.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.

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*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.**

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