ISSN 0100-7203
eISSN 1806-9339

RBGO Gynecology & Obstetrics

Revista Brasileira de Ginecologia e Obstetrícia
Number 1 • Volume 43 • Pages 1–80 • January 2021

febrasgo
Federação Brasileira das Associações de Ginecologia e Obstetrícia

OPEN ACCESS

Thieme

ISSN 0100-7203

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Editor in Chief

Marcos Felipe Silva de Sá
Universidade de São Paulo, Ribeirão Preto, SP, Brazil

Former Editors

Jean Claude Nahoum
Rio de Janeiro, RJ (1979–1989)
Clarice do Amaral Ferreira
Rio de Janeiro, RJ (1989–1994)
Sérgio Pereira da Cunha
Ribeirão Preto, SP (1994–1997)
Jurandyr Moreira de Andrade
Ribeirão Preto, SP, Brazil (1997–2015)

Associated Editors

Agnaldo Lopes da Silva Filho
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Alessandra Cristina Marcolin
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Ana Katherine da Silveira Gonçalves
Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
Andréa da Rocha Tristão
Universidade Estadual Paulista "Júlio de Mesquite Filho", Botucatu, SP, Brazil
Angélica Nogueira Rodrigues
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Antonio Rodrigues Braga Neto
Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Conrado Milani Coutinho
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Corintio Mariani Neto
Universidade Cidade de São Paulo, São Paulo, SP, Brazil
Cristina Laguna Benetti Pinto
Universidade Estadual de Campinas, Campinas, SP, Brazil
Daniel Guimarães Tiezzi
Universidade de São Paulo,Ribeirão Preto, SP, Brazil
Diama Bhadra Andrade Peixoto do Vale
Universidade Estadual de Campinas, Campinas, SP, Brazil
Eddie Fernando Candido Murta
Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brazil
Edward Araujo Júnior
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Elaine Christine Dantas Moisés
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Eliana Aguiar Petri Nahas
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil
Fabrício da Silva Costa
Monash University, Melbourne, Victoria, Australia
Fernanda Garanhani de Castro Surita
Universidade Estadual de Campinas, Campinas, SP, Brazil
Fernando Marcos dos Reis
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Gabriel Costa Osanan
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Gustavo Salata Romão
Universidade de Ribeirão Preto, Ribeirão Preto, SP, Brazil
Helena von Eye Corleta
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Ilza Maria Urbano Monteiro
Universidade Estadual de Campinas, Campinas, SP, Brazil
João Paulo Souza
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
José Carlos Peraçoli
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil
José Geraldo Lopes Ramos
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
José Guilherme Cecatti
Universidade de São Paulo, Campinas, SP, Brazil
José Maria Soares Júnior
Universidade de São Paulo, São Paulo, SP, Brazil
Julio Cesar Rosa e Silva
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Lucia Alves da Silva Lara
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Lucia Helena Simões da Costa Paiva
Universidade Estadual de Campinas, Campinas, SP, Brazil
Luiz Carlos Zeferino
Universidade Estadual de Campinas, Campinas, SP, Brazil
Luiz Gustavo Oliveira Brito
Universidade de São Paulo, Campinas, SP, Brazil
Marcos Nakamura Pereira
Instituto Fernandes Figueira, Rio de Janeiro, RJ, Brazil
Maria Celeste Osório Wender
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Maria Laura Costa do Nascimento
Universidade Estadual de Campinas, Campinas, SP, Brazil
Melânia Maria Ramos de Amorim
Universidade Federal de Campina Grande, Campina Grande, PB, Brazil
Mila de Moura Behar Pontremoli Salcedo
Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil
Omero Benedicto Poli Neto
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Patrícia El Beitune
Universidade Federal de Ciências da Saúde de Porto Alegre, RS, Brazil
Paula Andrea de Albuquerque Salles Navarro
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Renato Moretti-Marques
Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
Ricardo Carvalho Cavalli
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Ricardo Mello Marinho
Faculdade Ciências Médicas de Minas Gerais, Belo Horizonte, MG, Brazil
Rosana Maria dos Reis
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Rosiane Mattar
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Rodrigo de Aquino Castro
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Silvana Maria Quintana
Universidade de São Paulo, Ribeirão Preto, SP, Brazil

Editorial Board

Sophie Françoise Mauricette Derchain
Universidade Estadual de Campinas, Campinas, SP, Brazil
Alex Sandro Rolland de Souza
Instituto de Medicina Integral Prof. Fernando Figueira, Recife, PE, Brazil
Ana Carolina Japur de Sá Rosa e Silva
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Aurélio Antônio Ribeiro da Costa
Universidade de Pernambuco, Recife, PE, Brazil
Belmiro Gonçalves Pereira
Universidade Estadual de Campinas, Campinas, SP, Brazil
Carlos Augusto Alencar Junior
Universidade Federal do Ceará, Fortaleza, CE, Brazil
Carlos Grandi
Universidad de Buenos Aires, Buenos Aires, Argentina
Cesar Cabello dos Santos
Universidade Estadual de Campinas, Campinas, SP, Brazil
Délio Marques Conde
Hospital Materno Infantil de Goiânia, Goiânia, GO, Brazil
Dick Oepkes
University of Leiden, Leiden, The Netherlands
Dino Roberto Soares de Lorenzi
Universidade de Caxias do Sul, Caxias do Sul, RS, Brazil
Diogo de Matos Graça Ayres de Campos
Universidade do Porto, Porto, Portugal
Eduardo Pandolfi Passos
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Edmund Chada Baracat
Universidade de São Paulo, São Paulo, SP, Brazil
Eliana Martorano Amaral
Universidade Estadual de Campinas, Campinas, SP, Brazil
Francisco Edson Lucena Feitosa
Universidade Federal do Ceará, Fortaleza, CE, Brazil
George Condous
Nepean Hospital in West Sydney, Sidney, Australia
Giuseppe Rizzo
Università degli Studi di Roma "Tor Vergata", Roma, Italy
Gutemberg Leão de Almeida Filho
Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Iracema de Mattos Paranhos Calderon
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil
João Luiz Pinto e Silva
Universidade Estadual de Campinas, Campinas, SP, Brazil
João Paulo Dias de Souza
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
João Sabino Lahorgue da Cunha Filho
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
José Carlos Peraçoli
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil
José Juvenal Linhares
Universidade Federal do Ceará, Campus de Sobral, Fortaleza, CE, Brazil
Joshua Vogel
Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland
Juvenal Soares Dias-da-Costa
Universidade Federal de Pelotas, Pelotas, RS, Brazil
Laudelino Marques Lopes
University of Western Ontario, London, Ontario, Canada
Luciano Marcondes Machado Nardozza
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Luis Otávio Zanatta Sarian
Universidade Estadual de Campinas, Campinas, SP, Brazil
Luiz Claudio Santos Thuler
Instituto Nacional do Câncer, Rio de Janeiro, RJ, Brazil
Luiz Henrique Gebrim
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Manoel J. B. Castello Girão,
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Marcelo Zugaib
Universidade de São Paulo, São Paulo, SP, Brazil
Marcos Desidério Ricci
Universidade de São Paulo, São Paulo, SP, Brazil
Maria de Lourdes Brizot
Universidade de São Paulo, São Paulo, SP, Brazil
Marilza Vieira Cunha Rudge
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil
Newton Sergio de Carvalho
Universidade Federal do Paraná, Curitiba, PR, Brazil
Nuno Henrique Malhoa Migueis Clode
Faculdade de Medicina de Lisboa, Lisboa, Portugal
Olímpio Barbosa Moraes Filho
Universidade de Pernambuco, Recife, PE, Brazil
Paulo Roberto Nassar de Carvalho
Instituto Fernandes Figueira-Fiocruz, Rio de Janeiro, RJ, Brazil
Renato Augusto Moreira de Sá
Universidade Federal Fluminense, Niterói, RJ, Brazil
Rintaro Mori
National Center for Child Health and Development, Tokyo, Japan
Roberto Eduardo Bittar
Universidade de São Paulo, São Paulo, SP, Brazil
Rosane Ribeiro Figueiredo Alves
Universidade Federal de Goiás, Goiânia, GO, Brazil
Roseli Mieko Yamamoto Nomura
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Rossana Pulcinelli Vieira Francisco
Universidade de São Paulo, São Paulo, SP, Brazil
Ruffo de Freitas Junior
Universidade Federal de Goiás, Goiânia, GO, Brazil
Sabas Carlos Vieira
Universidade Federal do Piauí, Teresina, PI, Brazil
Sebastião Freitas de Medeiros
Universidade Federal do Mato Grosso, Cuiabá, MT, Brazil
Selmo Geber
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Silvia Daher
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Shaun Patrick Brennecke
University of Melbourne Parkville, Victoria, Australia
Técia Maria de Oliveira Maranhão
Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
Toshiyuki Hata
University Graduate School of Medicine, Kagawa, Japan
Wellington de Paula Martins
Universidade de São Paulo, Ribeirão Preto, SP, Brazil

Editorial Office

Bruno Henrique Sena Ferreira

Editorial Production

Thieme Medical Publishers

ISSN 0100-7203

Federação Brasileira das Associações de Ginecologia e Obstetrícia

Brazilian Federation of Gynecology and Obstetrics Associations

Society Board (2020–2024)

President
Agnaldo Lopes da Silva Filho (MG)

Administrative Director
Sérgio Podgaec (SP)

Scientific Director
César Eduardo Fernandes (SP)

Financial Director
Olímpio B. de Moraes Filho (PE)

Professional Status Defence
Maria Celeste Osório Wender (RS)

Vice-president of North Region
Ricardo de Almeida Quintairos (PA)

Vice-president of Northeast Region
Carlos Augusto Pires C. Lino (BA)

Vice-president of Middle West Region
Marta Franco Finotti (GO)

Vice-president of Southeast Region
Marcelo Zugaib (SP)

Vice-president of South Region
Almir Antônio Urbanetz (PR)

Presidency and Executive Staff

Av. Brigadeiro Luís Antônio, 3421 - Sala 903 -
Jardim Paulista, São Paulo, SP, Brazil
CEP: 01401-001
Phone.: (+55 11) 5573-4919
www.febrasgo.org.br
presidencia@febrasgo.org.br

RBGO Editorial Office

editorial.office@febrasgo.org.br

Volume 43, Number 1/2021

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Editorial

1 Call to Eliminate Cervical Cancer in the Next Decade with a Focus on Brazil
Walquíria Quida Salles Pereira Primo, Neila Maria de Góis Speck, Cecilia Maria Roteli-Martins, César Eduardo Fernandes, and Agnaldo Lopes da Silva Filho

Original Articles

Obstetrics/High Risk Pregnancy

3 Peripartum Hysterectomies over a Fifteen-year Period
Alessandra Dorigon, Sérgio Hofmeister Martins-Costa, and José Geraldo Lopes Ramos

9 Is it Possible to Predict Massive Bleeding in Nulliparous Women with Placenta Previa?
Gokcen Orgul, Sule Goncu Ayhan, Gulhan Cetinkaya Saracoglu, and Aykan Yucel

14 Intercultural Childbirth: Impact on the Maternal Health of the Ecuadorian Kichwa and Mestizo People of the Otavalo Region
Susana Eulalia Dueñas Matute, Edson Zangiacomi Martinez, and Eduardo Antônio Donadi

20 Agreement Analysis between Sonographic Estimates and Birth Weight, by the WHO and Intergrowth-21st Tables, in Newborns of Diabetic Mothers
Marcus Vinícius Rodrigues de Souza, Lívia Pinto e Fróes, Pedro Afonso Cortez, Márcio Weissheimer Lauria, Regina Amélia Lopes de Aguiar, and Kamilla Maria Araújo Brandão Rajão

Endometriosis/Human Reproduction and Assisted Fertilization

28 The Graduated Embryo Score of Embryos from Infertile Women with and without Peritoneal Endometriosis
Juliana Caran, Vanessa Krebs Genro, Carlos Augusto Bastos de Souza, and João Sabino Cunha-Filho

Gynecological Endoscopy/Oncology

35 Residual Disease after Operative Hysteroscopy in Patients with Endometrioid Endometrial Cancer Associated with Polyps
Marcelo Simonsen, Henrique Mantoan, Carlos Chaves Faloppa, Lillian Yuri Kumagai, Levon Badiglian Filho, Andrea Guerreiro Machado, Najla Mohamed Tayfour, and Glauco Baiocchi

41 Efficacy of Endometrial Cancer Follow-up Protocols: Time to Change?
Amina Lubrano, Virginia Benito, Beatriz Pinar, Fernando Molano, and Laureano Leon

Surgery

46 Mid- to Long-Term Magnetic Resonance Imaging Results of Two Prolapse Surgeries for Apical Defect: A Secondary Analysis of a Randomized Controlled Trial
Luiz Carlos Santos Junior, Luiz Gustavo Oliveira Brito, Edilson Benedito de Castro, Sergio Dertkigil, and Cassia Raquel Teatin Juliato

Thieme Revinter Publicações Ltda

online www.thieme-connect.com/products

Review Article

54 COVID-19: Uncertainties from Conception to Birth

Bruno Ramalho de Carvalho, Karina de Sá Adami, Walusa Assad Gonçalves-Ferri, Marise Samama, Rui Alberto Ferriani, and Alessandra Cristina Marcolin

Clinical Consensus Recommendation

61 Pre-eclampsia: Universal Screening or Universal Prevention for Low and Middle-Income Settings?

Leandro Gustavo De Oliveira, Angélica Lemos Debs Diniz, Caio Antônio de Campos Prado, Edson Vieira Da Cunha Filho, Francisco Lázaro Pereira De Souza, Henri Augusto Korkes, José Geraldo Ramos, Maria Laura Costa, Mário Dias Corrêa Junior, Nelson Sass, Ricardo De Carvalho Cavalli, Sérgio Hofmeister De Almeida Martins-Costa, and José Carlos Peraçoli

Case Report

66 Does Big Mean Evil? Giant, but Benign Uterine Leiomyoma: Case Report and Review of the Literature

Luiz Gustavo Oliveira Brito, Natalia Lysei Ueno, and Maira Rossmann Machado

Letter to the Editor

72 Psychological Follow-up During Prenatal Care of Pregnant Women: Insights During the covid-19 pandemic

Magda Spinello Consul Da Silva, Edward Araujo Júnior, and Julio Elito Júnior

Febrasgo Statement

74 Good practices for ultrasound examinations in gynecology and obstetrics during the COVID-19 pandemic

Fernando Maia Peixoto Filho, Adriana Gualda Garrido, Anselmo Verlangieri Carmo, Eduardo Becker Júnior, Guilherme de Castro Rezende, Heron Werner Junior, Joffre Amin Junior, Jorge Roberto Di Tommaso Leão, Luciano Marcondes Machado Nardozza, Luiz Eduardo Machado, Manoel Alfredo Curvelo Sarno, Patricia El Beitune, Pedro Pires Ferreira Neto, Sergio Kobayashi, and Fabricio da Silva Costa

Complementary material is available online at www.rbgo.org.br.

© 2021. Thieme. All rights reserved. *RBGO Gynecology and Obstetrics/Revista Brasileiro de Ginecologia e Obstetrícia* is published monthly by Thieme-Revinter Publicações Ltda., Rua do Matoso, 170, Rio de Janeiro 20270-135, Brazil.

Editorial comments should be sent to **journals@thieme.com**. Articles may be submitted to this journal on an open-access basis. For further information, please send an e-mail to openaccess@thieme.com. The content of this journal is available online at **www.thieme-connect.com/products**. Visit our Web site at **www.thieme.com** and the direct link to this journal at **www.rbgo.com.br.**

Revista Brasileiro de Ginecologia e Obstetrícia is an official publication of the Federação Brasileira das Associações de Ginecologia e Obstetrícia (Brazilian Federation of Association of Gynecology and Obstetrics, Febrasgo), It is listed in Isi - Web of Science, Web of Knowledge (*Emerging*), MEDLINE / PubMed, Index Medicus, Scopus (Sci Verse), SCImago, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde, Index Medicus Latino Americano), and Portal de Periódicos Capes (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior). Thieme Medical Publishers is a member of the CrossRef initiative.

ISSN 0100-7203

Some of the product names, patents, and registered designs referred to in this publication are in fact registered trade marks or proprietary names even though specifi c reference to this fact is not always made in the text. Therefore, the appearance of a name without designation as proprietary is not to be construed as a representation by the Publisher that it is in the public domain.

All rights, including the rights of publication, distribution, and sales, as well as the right to translation, are reserved. No part of this work covered by the copyrights hereon may be reproduced or copied in any form or by any means—graphic, electronic, or mechanical, including photocopying, recording, taping, or information and retrieval systems—without written permission of the Publisher.

Important Note: Medical knowledge is ever-changing. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may be required. The authors and editors of the material herein have consulted sources believed to be reliable in their efforts to provide information that is complete and in accord with the standards accepted at the time of publication. However, in view of the possibility of human error by the authors, editors, or publisher of the work herein, or changes in medical knowledge, neither the authors, editors, or publisher, nor any other party who has been involved in the preparation of this work, warrants that the information contained here in is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from use of such information. Because of rapid advances in the medical sciences, independent verification of diagnoses and drug dosages should be made. Readers are encouraged to confirm the information contained herein with other sources. For example, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this publication is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this journal does not constitute a guarantee or endorsement of the quality or value of such product or of claims made by its manufacturer.

Editorial

Call to Eliminate Cervical Cancer in the Next Decade with a Focus on Brazil

Walquíria Quida Salles Pereira Primo[1] Neila Maria de Góis Speck[2] Cecilia Maria Roteli-Martins[3] César Eduardo Fernandes[3] Agnaldo Lopes da Silva Filho[4]

[1] Universidade de Brasília, Brasília, DF, Brazil
[2] Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil
[3] Faculdade de Medicina do ABC, Santo André, SP, Brazil
[4] Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

Rev Bras Ginecol Obstet 2021;43(1):1–2.

At the 73rd General Assembly, in 2020, the World Health Organization (WHO) approved the adoption of the "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem," based on the guarantee of the three following pillars: 1) that 90% of girls up to 15 years of age receive the vaccine against human papillomavirus (HPV); 2) that 70% of women perform a screening with HPV testing at 35 and 45 years old; and 3) that 90% of women identified with precursor lesions or invasive cancer receive treatment.[1]

Cervical cancer is a preventable, curable disease with high morbidity and mortality among women in countries without organized prevention programs, like Brazil. Globally, more than 570,000 new cases emerge annually, and more than 311,000 women die each year. According to the WHO, most of these deaths occur in countries with low development rates. In Brazil, cervical cancer ranks 3rd among malignant neoplasms in women, with 15.43 cases per 100,000 women per year, and 4th in mortality.[1,2]

In global actions of screening for this type of cancer in women aged 25 to 64 years, testing is performed in an organized way, with cervicovaginal oncotic cytology and triennial interval covering 70% of this population, thus resulting in a significant reduction in mortality, with figures under 2 deaths per 100,000 women a year. However, the sensitivity of cytology has been questioned, and the screening with HPV testing has shown greater accuracy. In the WHO's commitment to eliminate cervical cancer, the proposal of screening with HPV testing of 70% of women at 2 points in time, at the ages of 35 and 45 years, will reduce the mortality by about a third.

In Brazil, screening is not organized in the public system and is done exclusively by oncotic cytology in an opportunistic way. The screening guidelines published in 2016 by the Ministry of Health recommend the oncotic cytology examination at a 3-year interval for women aged 25 to 64 years old who had 2 previous normal results. Considering a target population of 50 million women and a 3-year interval, the screening would reach 17 million women a year. Data from the National Health Service (SUS, in the Portuguese acronym) show that 10 million women outside of the target population are screened a year. According to the publication by Costa et al. (2015)[3] on data regarding oncotic cytology exams collected by the Ministry of Health in the years 2012 to 2013:

- Coverage is below 70%;
- 50% of women are screened annually;
- 10% of women are screened every 3 years;
- 20% of screenings are performed in women under 25 years and even under 20 years of age.

The HPV vaccines are highly effective, promote a significant decrease in HPV infections and, consequently, in neoplastic cervical lesions. However, in Brazil, vaccination coverage has been below what is necessary for effective action in the coming decades. The reasons explaining the low coverage are mainly the logistical barriers of access and lack of continuous education of the population.

Address for correspondence
Walquíria Quida Salles Pereira Primo, UnB – Universidade de Brasília, Asa Norte, 70910-900, Brasília, DF, Brazil
(e-mail: walquiriaprimo@gmail.com).

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

DOI https://doi.org/10.1055/s-0041-1722939.
ISSN 0100-7203.

In 2014, the National Immunization Program (NIP) introduced the quadrivalent vaccine for girls aged 9 to 14 years old on a 2-dose schedule at a 6-month interval. In 2017, the program also included 11 to 14 years old boys on a 2-dose schedule. For the first dose, in the first year of implementation, coverage was above 80%. For the second dose, when the government transferred vaccination from the school environment to health facilities, there was a significant drop in coverage. In subsequent years, coverage has continued dropping, reflecting the little interest during this important time of pandemic. The insufficient coverage for boys demonstrates the need for strategies by professionals, educators, and parents to expand the reach of vaccination programs.

In the state of Amazonas, where the incidence of cervical cancer is 50/100,000 women, coverage is currently insufficient for both girls and boys at all ages. In 2014, the goal of covering the first dose of HPV vaccines was achieved in just 3 months, but experience has shown that vaccinating adolescents against HPV outside the school environment makes the goal of eradicating cervical cancer in the next decade more difficult.

In 2020, from January to July, mortality from invasive cervical cancer was between 25 and 30 deaths per month (1 death every 24 hours) across the state of Amazonas, and vaccine coverage fell to concerning levels. The government of Amazonas suspended treatment procedures due to the pandemic, and a major impact on mortality is expected in the coming months.

Cervical cancer is an important public health problem in Brazil and worldwide, even though it is a preventable neoplasm with the adoption of primary prevention (HPV vaccine) and secondary prevention (screening tests) measures that have proven efficacy and effectiveness. Cervical cancer is a preventable disease that if diagnosed early, has a high cure rate. Adequate treatment without delays is an important prognostic factor that has already been proven in numerous studies.

Invasive cervical cancers are usually treated with surgery or radiation combined with chemotherapy. The choice of the best therapeutic option depends on the clinical stage of the tumor, age, reproductive history, general condition of the patient, and conditions available at the local health service. In Brazil, $\sim$ 80% of women diagnosed with invasive disease are in an advanced stage and are, thus, ineligible for surgery, thereby requiring radiotherapy and chemotherapy as treatment and generating an enormous social and financial cost.[4]

The consequence of socioeconomic and cultural characteristics found in Brazil is a scenario in which factors related to poverty and development coexist. Thus, the access to screening and diagnosis services and timely treatments is severely compromised. Consequently, limitations of access to health services not only prevent poor women from being diagnosed, but also deprive them from having adequate and sufficient treatment in time to obtain a cure. In Brazil, this type of cancer occurs predominantly in non-white women (62.7%) with low educational level (62.1%), reinforcing that this neoplasia is not only a health issue but also a social problem.[5]

The Brazilian public health system serves 75.32% of cancer patients, that is, $\sim$ 448,959 cancer cases were treated in the public health system in 2016. The period between diagnosis and the 1st treatment was longer than 60 days in 58.0% of cases, and early deaths occurred in 11% of them.[5] Note that radiotherapy plays an important role as an adjuvant or exclusive treatment, especially in cervical cancer, depending on the extent of the disease, and in Brazil there is only 50.8% of the necessary amount of radiotherapy treatment equipment.[6]

Regarding deaths, almost 9 out of 10 deaths from cervical cancer occur in less developed regions, where the risk of dying from cervical cancer before the age of 75 is 3 times higher. We highlight the preventable deaths of young women —at the peak of their working lives and many of whom are head of their household—if they are treated properly.

The purpose of this call is to focus attention on the serious health problem of cervical cancer, which, being asymptomatic in the early stages, is unable to mobilize the public opinion effectively in order that the tools available for its eradication are applied.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 World Health Organization. Launch of the global strategy to accelerate the elimination of cervical cancer [Internet]. 2020 [cited 2020 Sep 12]. Available from: https://www.who.int/news-room/events/detail/2020/11/17/default-calendar/launch-of-the-global-strategy-to-accelerate-the-elimination-of-cervical-cancer

2 Ministério da Saúde Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil [Internet]. Rio de JaneiroInca2019 [cited 2020 Aug 20]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf

3 Costa RFA, Longatto-Filho A, Pinheiro C, Zeferino LC, Fregnani JH. Historical analysis of the Brazilian Cervical Cancer Screening Program from 2006 to 2013: a time for reflection. PLoS One. 2015;10(09):e0138945. Doi: 10.1371/journal.pone.0138945

4 Mascarello KC, Silva NF, Piske MT, Viana KCG, Zandonade E, Amorim MHC. Perfil sociodemográfico e clínico de mulheres com câncer de colo de útero associado ao estadiamento inicial. Rev Bras Cancerol. 2012;58(03):417–426

5 Gynecological cancer panorama in Brazil. JCO Global Oncol. 2020; 6:1617–1630

6 Mendez LC, Moraes FY, Fernandes GDS, Weltman E. Cancer deaths due to lack of universal access to radiotherapy in the Brazilian Public Health System. Clin Oncol (R Coll Radiol). 2018;30(01): e29–e36. Doi: 10.1016/j.clon.2017.09.003

Peripartum Hysterectomies over a Fifteen-year Period

Histerectomias periparto ao longo de um período de quinze anos

Alessandra Dorigon[1] Sérgio Hofmeister Martins-Costa[1,2] José Geraldo Lopes Ramos[1,2]

[1] Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
[2] Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Address for correspondence José Geraldo Lopes Ramos, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Escritório 1125, Porto Alegre, RS, 90035-903, Brazil (e-mail: jramos@hcpa.edu.br).

Rev Bras Ginecol Obstet 2021;43(1):3–8.

Abstract

Objective To determine the indications and outcomes of peripartum hysterectomies performed at Hospital de Clínicas de Porto Alegre (a university hospital in Southern Brazil) during the past 15 years, and to analyze the clinical characteristics of the women submitted to this procedure.

Methods A cross-sectional study of 47 peripartum hysterectomies from 2005 to 2019.

Results The peripartum hysterectomies performed in our hospital were indicated mainly due to placenta accreta or suspicion thereof (44.7% of the cases), puerperal hemorrhage without placenta accreta (27.7%), and infection (25.5%). Total hysterectomies accounted for 63.8% of the cases, and we found no difference between total versus subtotal hysterectomies in the studied outcomes. Most hysterectomies were performed within 24 hours after delivery, and they were associated with placenta accreta, placenta previa, and older maternal age.

Conclusion Most (66.0%) patients were admitted to the intensive care unit (ICU). Those who did not need it were significantly older, and had more placenta accreta, placenta previa, or previous Cesarean delivery.

Keywords

- puerperal hysterectomy
- postpartum hemorrhage
- placenta accreta
- placenta previa

Resumo

Objetivo Determinar as indicações e os desfechos das histerectomias periparto realizadas no Hospital de Clínicas de Porto Alegre nos últimos 15 anos, bem como analisar as características clínicas das mulheres submetidas a esse procedimento.

Métodos Estudo transversal de 47 histerectomias periparto realizadas no período de 2005 a 2019.

Resultados Em nosso hospital, as histerectomias periparto foram indicadas principalmente por acretismo placentário ou sua suspeita (44,7% dos casos), hemorragia puerperal sem acretismo placentário (27,7%), e infecção (25,5%). Histerectomias totais corresponderam a 63,8% dos casos, e não encontramos diferença entre histerectomia total e subtotal para os desfechos estudados. A maioria das histerectomias foi realizada dentro de 24 horas após o parto, o que estava associado a acretismo placentário, placenta prévia, e idade materna mais avançada.

Conclusão A maioria (66,0%) das mulheres necessitou de internação em unidade de terapia intensiva (UTI); aquelas que não necessitaram eram significativamente mais velhas, e tinham mais acretismo placentário, placenta prévia, ou cesárea prévia.

Palavras-chave

- histerectomia puerperal
- hemorragia pós-parto
- placenta acreta
- placenta prévia

received
April 1, 2020
accepted
September 30, 2020

DOI https://doi.org/10.1055/s-0040-1721354.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Introduction

In the history of Obstetrics, Horatio Storer performed the first hysterectomy on a gravid uterus in a live woman in 1869 due to a hemorrhage caused by a uterine tumor.[1] The role of peripartum hysterectomy has changed ever since. In the 20th century, it was even indicated as a procedure for sterilization.[2]

Currently, peripartum hysterectomy is performed mainly in cases of abnormal placentation (predominantly placenta accreta) or life-threatening hemorrhage.[3–5] A meta-analysis[3] of 128 studies from low- to high-income countries estimated a weighted average of 0.9 peripartum hysterectomies per 1,000 births, and a maternal mortality rate of 5.2% after this procedure.

Both primary or repeat Cesarean sections are significantly associated with an increased risk of peripartum hysterectomy, not only due to abnormal placentation, but also due to uterine atony.[6–9] Other risk factors are placenta previa (which is significantly associated with an increased likelihood of placenta accreta), advanced maternal age, twin pregnancy, chorioamnionitis, and puerperal infections.[3,7,8,10–12]

Women undergoing peripartum hysterectomy are at risk of postoperative complications, such as admission to the intensive care unit (ICU), blood transfusion, bladder and ureteral injury, reoperation, and wound complications.[3,5,13–15]

The objective of the present study was to analyze the peripartum hysterectomies performed at Hospital de Clínicas de Porto Alegre in the past 15 years to provide an evaluation of their main indications at our hospital. We also aimed to analyze the clinical characteristics of the patients submitted to this procedure.

Methods

The present cross-sectional study used retrospective data from the electronic health records stored in the database of Hospital de Clínicas de Porto Alegre from January 2005 (when the electronic health records were effectively implemented in our hospital) until August 2019 (final date of the search data). All 47 hysterectomies performed during this period due to pregnancy or puerperal complications were included. We chose to analyze some obstetric near-miss factors related to hysterectomy indications: hysterectomy time (up to 24 hours), admission to the ICU, use of antibiotics, type of hysterectomy (subtotal or total), and need of red-blood-cell transfusion. The prophylactic use of antibiotics was not considered, as it is part of the Cesarean-section protocol. Only the use of antibiotics in the postpartum period was considered. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software. The Student *t*-test was used for the continuous variables, and the Fisher exact test, for the categorical variables. Values of $p < 0.05$ were considered statistically significant. The present study was registered at Plataforma Brasil, the Brazilian unified database of research records involving human beings. Ethics approval was granted by the Ethics Committee of Hospital de Clínicas de Porto Alegre. The authors signed a data-confidentiality agreement.

Results

The present study identified 47 cases of hysterectomies performed due to complications during pregnancy or the puerperium in the period from 2005 to 2019 in our hospital. Considering that 54,617 births occurred in this period, we estimate a rate of 0.87 peripartum hysterectomies per 1,000 births.

Maternal characteristics and previous and current pregnancy complications are shown in ►**Table 1**. The mean maternal age was 31.2 years, the mean BMI was of 30.9 kg/m^2, and 59.6% of the patients had a previous Cesarean section. In the current pregnancy, the most frequent complications were intrauterine infection and/or puerperal infection and placenta accreta (44.7% and 42.6% of the cases respectively). Placenta previa was present in 27.7% of the patients.

►**Table 2** shows the indications for Cesarean section and peripartum hysterectomy and the maternal and fetal outcomes. In total, 74.5% of the deliveries were by Cesarean section, and its main indication was placenta previa. The most frequent cause of hysterectomy was placenta accreta or suspicion thereof (44.7% of peripartum hysterectomies), followed by postpartum hemorrhage without placenta accreta or suspicion (27.7%) and puerperal infection (25.5%). In addition, 63.8% of the hysterectomies were total, and 66.0% were performed within 24 hours

Table 1 Maternal characteristics and previous and current pregnancy complications

Maternal characteristics and previous and current pregnancy complications	n	Mean (standard deviation) or % (n)
Maternal age (years)	47	31.2 (6.3)
Previous cesarean section	47	59.6% (28)
Maternal weight (kg)	46	81.1 (16.3)
Maternal Body Mass Index (kg/m^2)	46	30.9 (6.0)
History of previous postpartum hemorrhage	47	8.5% (4)
Placenta previa in the current pregnancy	47	27.7% (13)
Placenta accreta in the current pregnancy	47	42.6% (20)
Preterm labor in the current pregnancy	47	19.1% (9)
Prelabor rupture of membranes in the current pregnancy	47	10.6% (5)
Cephalopelvic disproportion in the current pregnancy	47	8.5% (4)
Postpartum hemorrhage in the current pregnancy	47	55.3% (26)
Intrauterine infection and/or puerperal infection	47	44.7% (21)
Urinary tract infection in the current pregnancy	47	29.8% (14)

Table 2 Indications for Cesarean delivery and for peripartum hysterectomy and maternal and fetal outcomes

Indications for Cesarean delivery and for peripartum hysterectomy and maternal and fetal outcomes	n	Mean (standard deviation) or % (n)
Cesarean delivery in the current pregnancy	47	74.5% (35)
Indication for cesarean delivery		
Placenta previa	35	37.1% (13)
Fetal distress	35	17.1% (6)
Cephalopelvic disproportion	35	11.4% (4)
Placenta accreta or suspicion thereof with no placenta previa	35	11.4% (4)
Cause of peripartum hysterectomy		
Placenta accreta or suspicion thereof	47	44.7% (21)
Postpartum hemorrhage with no placenta accreta nor suspicion thereof	47	27.7% (13)
Puerperal infection and suspicion thereof	47	25.5% (12)
Uterine rupture	47	2.1% (1)
Total hysterectomy	47	63.8% (30)
Hysterectomy within 24 hours after delivery	47	66.0% (31)
Antibiotic therapy during delivery or hysterectomy hospitalizations or in the postpartum period	47	59.6% (28)
Transfusion of red blood cells	47	76.6% (36)
Intensive care admission	47	66.0% (31)
Gestational age at delivery (weeks)	47	37.2 (3.2)
Male newborn	45	35.6% (16)
Birth weight (kg)	45	2.876 (0.686)

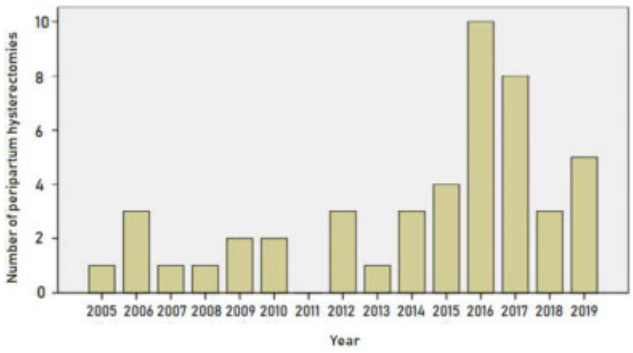

Fig. 1 Timeline of peripartum hysterectomies.

after delivery. Most patients required red-blood-cell transfusion and admission to the ICU (76.6% and 66.0% respectively). The mean gestational age at delivery was 37.2 weeks.

►**Fig. 1** shows the annual distribution of peripartum hysterectomies in our hospital from 2005 to 2019. There was a peak in the number of hysterectomies in 2016 and 2017, and a subsequent reduction in 2018.

►**Table 3** compares peripartum hysterectomy within 24 hours after delivery with hysterectomy performed more than 24 hours after delivery. Earlier hysterectomy was associated with older maternal age (33.3 versus 27.1 years; $p = 0.001$), placenta accreta (54.8% versus 18.8%; $p = 0.029$), and placenta previa (38.7% versus 6.3%; $p = 0.036$). Premature rupture of membranes was less common in cases of earlier peripartum hysterectomy (3.2% versus 25.0%; $p = 0.040$).

►**Table 4** shows that patients who were not admitted to the ICU were significantly older (33.3 versus 30.1 years; $p = 0.045$), had a higher prevalence of placenta accreta (62.5% versus 32.3%; $p =$. 065), of placenta previa (50.0% versus 16.1%; $p = 0.020$), and of previous Cesarean section (87.5% versus 45.2%; $p = 0.006$).

We compared the use of postpartum antibiotics during the hospitalization with patients who did not use antibiotic therapy. We can see that the women treated with antibiotics were younger (29.5 versus 33.7 years; $p = 0.024$) and had preterm labor more frequently, but that was not statistically significant (28.6% versus 5.3%; $p = 0.064$). We

Table 3 Peripartum hysterectomy within 24 hours after delivery

	Hysterectomy after 24h after delivery		Hysterectomy within 24h after delivery		*p-value*
	n	Mean (standard deviation) or % (n)	n	Mean (standard deviation) or % (n)	
Previous Cesarean section	16	43.8% (7)	31	67.7% (21)	0.131
History of previous postpartum hemorrhage	16	0% (0)	31	12.9% (4)	0.284
Placenta previa	16	6.3% (1)	31	38.7% (12)	0.036
Placenta accreta	16	18.8% (3)	31	54.8% (17)	0.029
Prelabor rupture of membranes	16	25.0% (4)	31	3.2% (1)	0.040
Preterm labor	16	31.3% (5)	31	12.9% (4)	0.239
Cephalopelvic disproportion	16	12.5% (2)	31	6.5% (2)	0.597
Maternal age (years)	16	27.1 (6.6)	31	33.3 (5.1)	0.001
Maternal Body Mass Index (kg/m^2)	15	30.5 (6.2)	31	31.1 (6.0)	0.742
Gestational age at delivery (weeks)	16	37.3 (3.7)	31	37.1 (3.0)	0.835
Birth weight (kg)	14	3.068 (0.768)	31	2.790 (0.640)	0.212

Table 4 Admission to the intensive care unit (ICU)

	NO ICU ADMISSION		ICU ADMISSION		*p-value*
	n	Mean (standard deviation) or % (n)	n	Mean (standard deviation) or % (n)	
Previous Cesarean section	16	87.5% (14)	31	45.2% (14)	0.006
History of previous postpartum hemorrhage	16	12.5% (2)	31	6.5% (2)	0.597
Placenta previa	16	50.0% (8)	31	16.1% (5)	0.020
Placenta accreta	16	62.5% (10)	31	32.3% (10)	0.065
Prelabor rupture of membranes	16	12.5% (2)	31	9.7% (3)	1.000
Preterm labor	16	18.8% (3)	31	19.4% (6)	1.000
Cephalopelvic disproportion	16	0% (0)	31	12.9% (4)	0.284
Maternal age (years)	16	33.3 (3.5)	31	30.1 (7.2)	0.045
Maternal Body Mass Index (kg/m^2)	16	30.8 (6.9)	30	31.0 (5.6)	0.894
Gestational age at delivery (weeks)	16	36.8 (2.5)	31	37.4 (3.6)	0.595
Birth weight (kg)	16	2.650 (0.493)	29	3.001 (0.751)	0.101

found no statistically significant difference between total and subtotal hysterectomy for the clinical factors analyzed. Blood transfusion was not associated with any of these factors either.

Discussion

In the present study, we found that the rate of peripartum hysterectomies was of 0.87 per 1,000 births. This number is very similar to the weighted average peripartum hysterectomy of 0.9 per 1,000 births provided by the aforementioned meta-analysis,[3] although still above many estimates from high-income countries.[3–5]

The main cause of peripartum hysterectomy in the present study – placenta accreta or suspicion thereof – was responsible for 44.7% of the cases. Although our hospital is a referral center for these patients, this finding is consistent with systematic reviews that report placental abnormalities as the most common indication, followed by uterine atony and other causes, such as uterine rupture and infection (including chorioamnionitis and endometritis).[3–5] However, the fact that 25.5% of our peripartum hysterectomies are due to infection contrasts with most other series, in which it accounts for 2% or less of hysterectomies.[3–5,16]

In the present study, 74.5% of deliveries were Cesarean sections, and their main indication was placenta previa. This may be related both to the increased risk of peripartum hysterectomy after primary or repeat Cesarean section, and to the strong association between placenta previa and placenta accreta.[6–9,11,12] At Hospital de Clínicas de Porto Alegre, the rate of Cesarean section in the same period was of 34.2%.

Total hysterectomy represented 63.8% of the hysterectomies performed in our patients. The proportion of total versus subtotal hysterectomies varies in different studies.

Two systematic reviews reported rates of 51.1%[3] and 52.2%[5] of total hysterectomies, but large series[14] have also reported higher proportions. In addition, in the present study there was no significant difference between total and subtotal hysterectomy for the analyzed outcomes. The comparison between the two techniques produced controversial results, and, while some series of studies found statistically significant differences[14], others did not.[13,17]

Blood transfusion and ICU admission were necessary for 76.6% and 66.0% of the patients respectively. According to systematic reviews and other studies, many patients undergoing peripartum hysterectomy require blood transfusion and ICU admission.[3,5,13–15]

We observed that the use of antibiotic therapy during the hospitalization was associated with premature labor, which was 5.4 times more frequent in women treated with antibiotics (28.6% versus 5.3%), although the *p*-value was not statistically significant (0.064). Inflammation and infection are part of the pathogenesis of premature labor, which possibly explains a greater need for antibiotics in this group of patients. Another discussion point would be if the use of antepartum antibiotic therapy could select infecting bacteria in the postpartum period.

The finding that hysterectomy more than 24 hours after birth was associated with premature rupture of membranes may have been biased by a small number of cases in each group (4 after 24 hours versus 1 within 24 hours). On the other hand, the association of hysterectomy performed in the first 24 hours after delivery with placenta accreta, placenta previa and more advanced maternal age is expected. Many cases of placenta accreta in the present series were suspected before birth, leading to early intervention. Some were even preprogrammed.

In addition, women in the present series who were not admitted to the ICU were also significantly older and more likely to have placenta previa or undergo Cesarean section. Although the difference was not statistically significant ($p = 0.065$), 62.5% of these patients had placenta accreta versus 32.3% of those who were admitted to the ICU. The prenatal suspicion of cases of placenta accreta in the present series enabled the adoption of special measures, possibly reducing maternal morbidity. When placenta accreta is suspected, the care of a multidisciplinary team and not attempting placenta removal both improve the results.[18–20] In addition, placenta previa, advanced maternal age and Cesarean section are associated with placenta accreta.[11,12]

There were two maternal deaths in the present series, one due to hemorrhagic shock and the other due to septic shock. The mortality rate for peripartum hysterectomies was of 4.3%, which is lower than the 5.2% estimate of a meta-analysis[3] of 128 studies from different countries (11.9% in low- and middle-to-low-income countries, compared with 2.5% in high- and middle-to-high-income countries).

Conclusion

We found an expressive association between peripartum hysterectomy and placenta previa and placenta accreta, which was an important factor in the indication of hysterectomy. This situation has been advancing in Brazil in recent years because of the excessive performance of Cesarean sections.

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

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

References

1 Durfee RB. Evolution of cesarean hysterectomy. Clin Obstet Gynecol. 1969;12(03):575–589. Doi: 10.1097/00003081-196909000-00002
2 Davis ME. Complete cesarean hysterectomy; a logical advance in modern obstetric surgery. Am J Obstet Gynecol. 1951;62(04): 838–853. Doi: 10.1016/0002-9378(51)90174-3
3 van den Akker T, Brobbel C, Dekkers OM, Bloemenkamp KW. Prevalence, indications, risk indicators, and outcomes of emergency peripartum hysterectomy worldwide: a systematic review and meta-analysis. Obstet Gynecol. 2016;128(06):1281–1294. Doi: 10.1097/AOG.0000000000001736
4 de la Cruz CZ, Thompson EL, O'Rourke K, Nembhard WN. Cesarean section and the risk of emergency peripartum hysterectomy in high-income countries: a systematic review. Arch Gynecol Obstet. 2015;292(06):1201–1215. Doi: 10.1007/s00404-015-3790-2
5 Rossi AC, Lee RH, Chmait RH. Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systematic review. Obstet Gynecol. 2010;115(03):637–644. Doi: 10.1097/AOG.0b013e3181cfc007
6 Bateman BT, Mhyre JM, Callaghan WM, Kuklina EV. Peripartum hysterectomy in the United States: nationwide 14 year experience. Am J Obstet Gynecol. 2012;206(01):63.e1–63.e8. Doi: 10.1016/j.ajog.2011.07.030
7 Whiteman MK, Kuklina E, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, Marchbanks PA. Incidence and determinants of peripartum hysterectomy. Obstet Gynecol. 2006;108(06):1486–1492. Doi: 10.1097/01.AOG.0000245445.36116.c6
8 Knight M, Kurinczuk JJ, Spark P, Brocklehurst PUnited Kingdom Obstetric Surveillance System Steering Committee. Cesarean delivery and peripartum hysterectomy. Obstet Gynecol. 2008; 111(01):97–105. Doi: 10.1097/01.AOG.0000296658.83240.6d
9 Kacmar J, Bhimani L, Boyd M, Shah-Hosseini R, Peipert J. Route of delivery as a risk factor for emergent peripartum hysterectomy: a case-control study. Obstet Gynecol. 2003;102(01):141–145. Doi: 10.1016/s0029-7844(03)00404-6
10 Bodelon C, Bernabe-Ortiz A, Schiff MA, Reed SD. Factors associated with peripartum hysterectomy. Obstet Gynecol. 2009;114(01): 115–123. Doi: 10.1097/AOG.0b013e3181a81cdd
11 Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol. 1997; 177(01):210–214. Doi: 10.1016/s0002-9378(97)70463-0
12 Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, Thom EA, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol. 2006;107 (06):1226–1232. Doi: 10.1097/01.AOG.0000219750.79480.84
13 Knight MUKOSS. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG. 2007; 114(11):1380–1387. Doi: 10.1111/j.1471-0528.2007.01507.x
14 Wright JD, Devine P, Shah M, Gaddipati S, Lewin SN, Simpson LL, et al. Morbidity and mortality of peripartum hysterectomy. Obstet Gynecol. 2010;115(06):1187–1193. Doi: 10.1097/AOG.0b013e3181df94fb
15 Shellhaas CS, Gilbert S, Landon MB, Varner MW, Leveno KJ, Hauth JC, et al; Eunice Kennedy Shriver National Institutes of Health and

Human Development Maternal-Fetal Medicine Units Network. The frequency and complication rates of hysterectomy accompanying cesarean delivery. Obstet Gynecol. 2009;114(2 Pt 1):224–229. Doi: 10.1097/AOG.0b013e3181ad9442

16 Cheng HC, Pelecanos A, Sekar R. Review of peripartum hysterectomy rates at a tertiary Australian hospital. Aust N Z J Obstet Gynaecol. 2016;56(06):614–618. Doi: 10.1111/ajo.12519

17 Imudia AN, Hobson DT, Awonuga AO, Diamond MP, Bahado-Singh RO. Determinants and complications of emergent cesarean hysterectomy: supracervical vs total hysterectomy. Am J Obstet Gynecol. 2010;203(03):221.e1–221.e5. Doi: 10.1016/j.ajog.2010.04.007

18 Eller AG, Bennett MA, Sharshiner M, Masheter C, Soisson AP, Dodson M, Silver RM. Maternal morbidity in cases of placenta accreta managed by a multidisciplinary care team compared with standard obstetric care. Obstet Gynecol. 2011;117(2 Pt 1):331–337. Doi: 10.1097/aog.0b013e3182051db2

19 Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. BJOG. 2014;121(01):62–70, discussion 70–71. Doi: 10.1111/1471-0528.12405

20 Eller AG, Porter TF, Soisson P, Silver RM. Optimal management strategies for placenta accreta. BJOG. 2009;116(05):648–654. Doi: 10.1111/j.1471-0528.2008.02037.x

Is it Possible to Predict Massive Bleeding in Nulliparous Women with Placenta Previa?

Gokcen Orgul[1] Sule Goncu Ayhan[1] Gulhan Cetinkaya Saracoglu[1] Aykan Yucel[1]

[1] Department of Perinatology, University of Health Sciences, Ankara, Turkey

Rev Bras Ginecol Obstet 2021;43(1):9–13.

Address for correspondence Gokcen Orgul, MD, Etlik Zubeyde Hanim Women's Health Care, Training and Research Hospital, University of Health Sciences, 06050 Yenimahalle, Ankara, Turkey (e-mail: gokcenorgul@gmail.com).

Abstract

Objective We evaluated risk factors to determine if there were specific risk factors that could predict massive bleeding in nulliparous women with placenta previa.

Methods The participants were classified into two groups. Women with a calculated blood loss $\geq$ 1,000 mL were included in the massive bleeding group. Women without any signs or symptoms related with hypovolemia or with a calculated bleeding volume $<$ 1,000 mL were categorized into the non-massive bleeding group.

Results There were 28 patients (40.6%) with massive bleeding and 41 cases (59.4%) with non-massive bleeding. The calculated blood loss and number of cases that required red cell transfusions were statistically different between the groups ($<$ 0.005 and 0.002, respectively). There were no statistically significant differences in terms of maternal or fetal factors, placental location, or delivery characteristics between the two groups.

Conclusion We could not determine the predictive features for massive hemorrhage based on clinical features, delivery features, or placental location.

Keywords

- cesarean section
- nulliparity
- placenta previa
- postpartum hemorrhage
- uterine bleeding

Introduction

Placenta previa refers to an abnormally placed placenta, which covers the internal ostium of the cervix. The underlying etiologic reason has not been fully understood yet. Impaired endometrial receptivity in the upper part of the uterus (previous placenta previa and caesarean section scar) and big placental volume (multiple pregnancies) are found to be the main risk factors.[1] On the other hand, some risk factors for placenta previa have also been described in the literature, such as advanced maternal age, multiparity, spontaneous or induced miscarriage, cigarette smoking, and assisted reproductive technology (ART) pregnancies.[2,3]

The prevalence of placenta previa is $\sim$ 3 to 5 per 1,000 deliveries.[4] This obstetric issue is related with serious maternal complications and adverse fetal/neonatal outcomes. Maternal morbidity and mortality is increased in women with placenta previa, most frequently due to massive bleeding and surgical complications.[5,6] Uterotonic medications, intrauterine balloon tamponade, serious surgical interventions (uterine compression sutures, uterine/hypogastric artery ligation, etc.) and hysterectomy may be required to control the massive hemorrhage.[7]

The abnormal implantation of the placenta in a nulliparous woman is interesting, and the etiology remains unclear. Moreover, these women are also at increased risk for massive bleeding during surgery. Therefore, we aimed to investigate the risk factors to predict massive bleeding in nulliparous women with placenta previa.

Methods

We have retrospectively evaluated the data of pregnant women who delivered between September 2010 and September 2016

received
April 16, 2020
accepted
September 30, 2020

DOI https://doi.org/10.1055/s-0040-1721355.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

at the Etlik Zubeyde Hanim Women's Health Care, Training and Research Hospital, University of Health Sciences, Ankara, Turkey. The study group consisted of 69 nulliparous women with prenatally diagnosed placenta previa. The exclusion criteria were: previous delivery history ($>$ 500 gr or $>20^{th}$ gestational week), previous uterine surgery, multiple pregnancy, and fetuses with any chromosomal abnormality or structural malformation.

Prenatal complete placenta previa diagnosis was based on the transvaginal ultrasonographic findings of the classical image of the placental tissue covering the internal cervical os totally. For cases with a placental distance to the cervical os <20 mm, the diagnosis was as low-lying placenta previa.

Data of the maternal characteristics (age, body mass index, previous miscarriage history, and coexisting diseases), obstetric outcome (preterm delivery, intrauterine growth restriction [IUGR], fetal demise, and premature rupture of membranes [PPROM]), and neonatal outcome (birthweight, APGAR scores at 1^{th} and 5^{th} minute, and gestational week at birth) were analyzed. All cases were delivered by caesarean section. Operative interventions such as uterine compression sutures, intrauterine balloon tamponade, and uterine/hypogastric artery ligation were recorded from the files of the patients. Need for red blood cell transfusion was also assessed.

The cases were classified into two groups in terms of bleeding complications. Postpartum massive hemorrhage diagnosis was based on the criteria defined by American College of Obstetricians and Gynecologists.[8] Estimated blood loss was calculated with the following formula: calculated pregnancy volume (0.75 [maternal height X 50]+ [maternal weight X 25]) x blood volume loss percentage (predelivery hematocrit – postdelivery hematocrit/predelivery hematocrit).Women with a calculated blood loss $\geq$ 1,000 mL were included in the massive bleeding group. Women without any signs or symptoms related with hypovolemia or calculated bleeding volume $<$ 1,000 mL were categorized into the non-massive bleeding group. Estimated blood loss was calculated by using the formulas previously described in the literature. Maternal height together with weight and hematocrit levels (both predelivery and postdelivery) were used for this purpose.[9] The transfusion of each unit of packed red blood cells was accepted to raise postoperative hemoglobin and hematocrit levels by 1% (g/dL) and 3%, respectively. Estimated blood loss was calculated carefully for women who were transfused with red blood cell packages. The groups were compared in terms of the maternal and fetal characteristics described above.

The study protocol was approved by the Local Committee of Ethics of our hospital with the number of 219 (21.12.2016). The authors have complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research. Statistical analyses were performed by using the IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY, USA). The mean and standard deviation values along with the median, minimum, and maximum values were calculated, and the percentages were calculated where necessary. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Parametric data were examined with independent two-sample or *t*-test, and non-parametric data were compared using Mann Whitney-U test. Percentages were compared with chi-squared test. A p-value <0.05 indicates statistically significant differences.

Results

The total number of deliveries were 93,045 during the study period. Placenta previa was diagnosed in 395 women, with a rate of 0.42%. Among all placenta previa cases, there were 69 nulliparous women (17.4%), who were included in the study group. There was no definitive diagnosis of placenta accreta spectrum disorders in these cases.

Among all cases, 73.9% ($n=51$) were primigravida, while the remaining patients had at least one miscarriage history. The number of previous miscarriages was once in 12 cases (17.4%), twice in 3 cases (4.3%), 3 times in 2 cases (2.9%), and 4 times in 1 case (1.4%).

The mean maternal age was 28.55 ± 5.88, and the mean body mass index (BMI) was found to be 27.38 ± 3.96. Spontaneous pregnancy was noted in 59 cases (85.5%), while the number of intrauterine insemination and in vitro fertilization pregnancies were 2 (2.9%) and 8 (%11.6), respectively. The cigarette smoking rate was 5.8% among all cases.

Total placenta previa was observed in 40 cases, with a rate of 58%, and the remaining 29 pregnancies were complicated by low-lying placenta. Placenta was located anteriorly in 36 cases (52.2%), while 33 cases (47.8%) had posterior placenta. Cesarean delivery was performed at 37 weeks of gestation for planned cases. Uterine compression sutures, intrauterine balloon tamponade, and uterine artery ligation were performed in 7.2% ($n=5$), 13% ($n=9$), and 1.4% ($n=1$) of the cases, respectively.

Gestational week at birth ranged between 20 and 40 (35.9 ± 2.48) weeks, and the mean birthweight was found to be $2{,}719 \pm 567$ g. The preterm delivery rate was 43.5%, and 9 out of 30 cases were before the 34^{th} week of gestation. Also, PPROM was noted in 3 cases, with a rate of 4.3%. There was 1 intrauterine fetal demise (1.4%) and 11 cases of IUGR (15.9%).

There were 28 patients (40.6%) in the massive bleeding group, whereas the remaining 41 cases (59.4%) had a calculated blood loss $<$ 1,000 mL. Red blood cell transfusion was required in 14 cases (20.3%). The majority of the cases ($n=10$) had been stabilized after the transfusion of 2 units. In the remaining 4 cases, more transfusion of red blood cell packages was necessary (3, 4, and 5 units of red blood cell packages in 2, 1 and 1 cases, respectively). There was no statistically significant difference in terms of maternal, fetal, and delivery characteristics between the two groups, as shown in ►**Table 1**. Calculated blood loss and number of cases with requirement of red blood cell transfusion were statistically different between the groups (<0.005 and 0.002, respectively).

Table 1 Comparison of the groups

	Non-massive bleeding ($n = 41$)	Massive bleeding ($n = 28$)	*p*-value
Calculated blood loss (mL)	411.52 (102–976)	1,393 (1,000–3,431)	< 0.005
Transfusion requirement	3 (7.3%)	11 (39.3%)	0.002
Age	28.02 ± 5.794	29.32 ± 6.019	0.637
BMI	27.34 ± 3.779	27.43 ± 4.290	0.438
Miscarriage history	10 (24.4%)	8 (28.5%)	0.783
Assisted reproductive technology	5 (12.2%)	5 (17.9%)	0.221
IUI	2 (4.9%)	0	
IVF	3 (7.3%)	5 (17.9%)	
Smoking	3 (7.3%)	1 (3.6%)	0.513
Placenta location			0.625
Anterior	20 (48.8%)	16 (57.1%)	
Posterior	21 (51.2%)	12 (42.9%)	
Type of previa			0.806
Placenta previa	18 (43.9%)	11 (39.3%)	
Low-lying placenta	23(56.1%)	17 (60.7%)	
Preterm delivery	17 (41.5%)	13 (46.4%)	0.806
IUGR	5 (12.2%)	6 (21.4%)	0.304
PPROM	3 (7.3%)	0	0.143
Gestational week at birth	37 (27–40)	37 (27–39)	0.904
Birthweight (grams)	2,890 (1,040–3,400)	2,765 (1,110–3,775)	0.673
Postpartum hospital stay (day)	2 (2–5)	3 (2–11)	0.369
Preoperative Hb (g/dL)	11.2 ± 1.326	11.3 ± 1.516	0.847
Preoperative Htc (%)	33.7 ± 3.851	34.4 ± 4.295	0.566

Abbreviations: BMI, body mass index; IUI, intrauterine insemination; IVF, in vitro fertilization; IUGR, intrauterine growth restriction; PPROM, premature rupture of membranes.

Discussion

Placenta previa may be responsible for peripartum massive bleeding, and the risk increases with adherent placenta. Additionally, hysterectomy, blood transfusion, septicemia and thrombophlebitis are also responsible for increased maternal morbidity and mortality in these women.[10] Thus, placenta previa should be managed in an experienced center with a team consisting of an obstetrician, a pediatrician, and an anesthesiologist.

A recent systematic review reported the incidence of massive hemorrhage in women with placenta previa. They have shown that the frequency of postpartum bleeding was 22.3% in placenta previa cases.[11] On the other hand, controversial results were also given by different authors, and rates differed from the lowest (3%) to the highest (56%) in these heterogeneous studies.[12,13] Nur Azurah et al.[14] reported that postpartum hemorrhage rate was 23.4% in primigravida women without a significant difference from multigravidas. Our study found higher incidence of massive bleeding in nulliparous women with placenta previa. Among 61 women, 40.6% of the deliveries were complicated with postpartum hemorrhage. This can be explained by two scenarios. First, our hospital is a referral hospital located in the capital city of Turkey. Referred patients may be admitted to our center at a later stage, when delivery has already started. Second, the operators are not the same in all surgeries, and experience levels differ among the surgeons. Most of the elective surgeries are performed in the morning shifts after preparing blood products. A team composed of residents of perinatology and gynecology and obstetrics perform the surgery under the supervision of a maternal fetal medicine specialist. In the night shifts, there is also a team consisting of residents on duty every day.

Identifying risk factors, even in the antenatal period, to predict excessive bleeding may be useful. Several studies were conducted for this purpose.[14,15] The most important factor related with bleeding is reported to be placental adherence, with an adjusted odds ratio [OR] of 123.1 (95% CI, 4.5–3,395.2).[15] Placenta previa in a patient with a prior caesarean section is the prominent factor for placenta accreta spectrum. Repeated cesarean sections are also known to increase the risk of placenta accreta $\sim$ 2.6 times.[16] Because of the worldwide increased rates of caesarean delivery, adherent placenta and related complications started to be a major health problem. However, placenta accreta spectrum is very rare in nulliparous pregnancies, and no placental attachment disorder was diagnosed in our series.

Some studies have shown that complete placenta previa is more likely related with peripartum bleeding because of the increased placental area on the cervix.[17,18] Additionally, anterior placenta is reported to be associated with increased hemorrhage compared with posterior placenta. The risk was especially important in the occurrence of a previous uterine scar.[18,19] However, a recent article has shown that the rate of postpartum massive bleeding in pregnancies with an incomplete and posterior placenta previa is 11%.[20] In the current study, we did not find a significant difference between the localization of the placenta and bleeding volume. These findings together with the previous results show that placenta previa may be complicated by excessive hemorrhage beside the type of placenta previa. Thus, all women with placenta previa should be managed carefully in the pre- and perinatal periods because of the potential excessive bleeding risk.

Maternal characteristic and ultrasonographic findings are used to create a scoring model to identify women at high risk for massive bleeding. Caesarean delivery, advanced maternal age and sponge-like appearance of the cervix were reported to be risk factors for postpartum hemorrhage in placenta previa cases.[15] Caucasian ethnicity and multiple pregnancy has also been found to be related with bleeding complications.[4] However, most of the previous studies were designed to diagnose placenta accreta spectrum disorders. On the other hand, advanced maternal age, antepartum bleeding history, anterior placenta, multiple lacunae in placenta, and increased vascularity have been shown to be related with massive bleeding in placenta previa cases, even without an adherent placenta.[21] Because of the retrospective design of our study, ultrasonographic findings could not be evaluated in the present study. It seems reasonable to use sonography carefully and use an internationally accepted standard protocol in all placenta previa cases.

Fetal and neonatal complications are another important point of placenta previa management. Previous studies revealed that the rate of preterm delivery, fetal growth restriction, and perinatal mortality has been higher in pregnancies complicated with placenta previa.[22] The histopathological evaluation of the placenta previa by Weiner et al.[23] has shown that placental vascular problems (both hemorrhage and thrombosis) are more common in placenta previa. Thus, abnormal placentation is related with impaired maternal fetal perfusion, which is most probably responsible from improper fetal growth.[23] Preterm delivery and its consequences are another issue related with placenta previa. A recent systematic meta-analysis has found that prematurity, perinatal mortality, and neonatal intensive care unit admission are increased in placenta previa cases. The preterm delivery rate is especially higher in the presence of adherent placenta and vasa previa.[24] According to our findings, preterm delivery rate is 43.5% and IUGR is 15.9% in nulliparous women with placenta previa, in accordance with the findings in the literature.

Conclusion

Maternal excessive bleeding may complicate placenta previa pregnancies in nulliparous women. We did not find any predictive features for massive hemorrhage based on clinical features, delivery features, or placental location in primigravida patients. Thus, all women with a placenta previa diagnosis carry a risk for bleeding, regardless of their placenta location or type and maternal characteristics. Moreover, these women should be monitored in terms of preterm delivery and IUGR during antenatal care. An experienced team and blood bank are the key points to minimize the maternal and fetal adverse outcomes.

Contributors
All of the authors contributed with the project and data interpretation, the writing of the article, 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.

References

1 Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. Obstet Gynecol. 2006;107(04):927–941. Doi: 10.1097/01.AOG.0000207559.15715.98
2 Severi FM, Bocchi C, Vannuccini S, Petraglia F. Placenta previa. In: Malvasi A, Tinelli A, Di Renzo GC, editors. Management and therapy of late pregnancy complications: third trimester and puerperium. Cham: Springer; 2017:179–9190
3 Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. J Matern Fetal Neonatal Med. 2003;13(03):175–190. Doi: 10.1080/jmf.13.3.175.190
4 Burgers M, Rengerink KO, Eschbach SJ, Muller MM, van Pampus MG, Mol BWJ, de Graaf IM. Predictors for massive haemorrhage during caesarean delivery due to placenta praevia. Int J Clin Med. 2015;6(02):96–104. Doi: 10.4236/ijcm.2015.62014
5 Young BC, Nadel A, Kaimal A. Does previa location matter? Surgical morbidity associated with location of a placenta previa. J Perinatol. 2014;34(04):264–267. Doi: 10.1038/jp.2013.185
6 Altinkaya SO, Nergiz S, Guldas M, Sezer SD, Yuksel H. Antepartum risk factors for peripartum hysterectomy in women with placenta previa. Gynecol Obstet Reprod Med.. 2016;20(01):24–28
7 Oya A, Nakai A, Miyake H, Kawabata I, Takeshita T. Risk factors for peripartum blood transfusion in women with placenta previa: a retrospective analysis. J Nippon Med Sch. 2008;75(03):146–151. Doi: 10.1272/jnms.75.146
8 Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: postpartum hemorrhage. Obstet Gynecol. 2017;130(04):e168–e186. Doi: 10.1097/AOG.0000000000002351
9 Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol. 2008;199(05):519.e1–519.e7. Doi: 10.1016/j.ajog.2008.04.049
10 Crane JM, Van den Hof MC, Dodds L, Armson BA, Liston R. Maternal complications with placenta previa. Am J Perinatol. 2000;17(02):101–105. Doi: 10.1055/s-2000-9269
11 Fan D, Xia Q, Liu L, Wu S, Tian G, Wang W, et al. The incidence of postpartum hemorrhage in pregnant women with placenta previa: a systematic review and meta-analysis. PLoS One. 2017;12(01):e0170194. Doi: 10.1371/journal.pone.0170194
12 Ogueh O, Morin L, Usher RH, Benjamin A. Obstetric implications of low-lying placentas diagnosed in the second trimester. Int J Gynaecol Obstet. 2003;83(01):11–17. Doi: 10.1016/s0020-7292(03)00211-x

13 Zlatnik MG, Cheng YW, Norton ME, Thiet MP, Caughey AB. Placenta previa and the risk of preterm delivery. J Matern Fetal Neonatal Med. 2007;20(10):719–723. Doi: 10.1080/14767050701530163
14 Nur Azurah AG, Wan Zainol Z, Lim PS, Shafiee MN, Kampan N, Mohsin WS, et al. Factors associated with placenta praevia in primigravidas and its pregnancy outcome. ScientificWorldJournal. 2014;2014:270120. Doi: 10.1155/2014/270120
15 Hasegawa J, Matsuoka R, Ichizuka K, Mimura T, Sekizawa A, Farina A, Okai T. Predisposing factors for massive hemorrhage during Cesarean section in patients with placenta previa. Ultrasound Obstet Gynecol. 2009;34(01):80–84. Doi: 10.1002/uog.6426
16 Creanga AA, Bateman BT, Butwick AJ, Raleigh L, Maeda A, Kuklina E, Callaghan WM. Morbidity associated with cesarean delivery in the United States: is placenta accreta an increasingly important contributor? Am J Obstet Gynecol. 2015;213(03):384.e1–384.e11. Doi: 10.1016/j.ajog.2015.05.002
17 Sekiguchi A, Nakai A, Kawabata I, Hayashi M, Takeshita T. Type and location of placenta previa affect preterm delivery risk related to antepartum hemorrhage. Int J Med Sci. 2013;10(12):1683–1688. Doi: 10.7150/ijms.6416
18 Pivano A, Alessandrini M, Desbriere R, Agostini A, Opinel P, d'Ercole C, Haumonte JB. A score to predict the risk of emergency caesarean delivery in women with antepartum bleeding and placenta praevia. Eur J Obstet Gynecol Reprod Biol. 2015; 195:173–176. Doi: 10.1016/j.ejogrb.2015.10.015
19 Usta IM, Hobeika EM, Musa AAA, Gabriel GE, Nassar AH. Placenta previa-accreta: risk factors and complications. Am J Obstet Gynecol. 2005;193(3 Pt 2):1045–1049. Doi: 10.1016/j.ajog.2005.06.037
20 Lee HJ, Lee YJ, Ahn EH, Kim HC, Jung SH, Chang SW, Lee JY. Risk factors for massive postpartum bleeding in pregnancies in which incomplete placenta previa are located on the posterior uterine wall. Obstet Gynecol Sci. 2017;60(06):520–526. Doi: 10.5468/ogs.2017.60.6.520
21 Lee JY, Ahn EH, Kang S, Moon MJ, Jung SH, Chang SW, Cho HY. Scoring model to predict massive post-partum bleeding in pregnancies with placenta previa: A retrospective cohort study. J Obstet Gynaecol Res. 2018;44(01):54–60. Doi: 10.1111/jog.13480
22 Ananth CV, Demissie K, Smulian JC, Vintzileos AM. Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. Obstet Gynecol. 2001;98 (02):299–306. Doi: 10.1016/s0029-7844(01)01413-2
23 Weiner E, Miremberg H, Grinstein E, Mizrachi Y, Schreiber L, Bar J, Kovo M. The effect of placenta previa on fetal growth and pregnancy outcome, in correlation with placental pathology. J Perinatol. 2016;36(12):1073–1078. Doi: 10.1038/jp.2016.140
24 Vahanian SA, Lavery JA, Ananth CV, Vintzileos A. Placental implantation abnormalities and risk of preterm delivery: a systematic review and metaanalysis. Am J Obstet Gynecol. 2015;213(4, Suppl)S78–S90. Doi: 10.1016/j.ajog.2015.05.058

Intercultural Childbirth: Impact on the Maternal Health of the Ecuadorian Kichwa and Mestizo People of the Otavalo Region

Parto intercultural: impacto na saúde materna dos equatorianos Kichwa e mestiços da região de Otavalo

Susana Eulalia Dueñas Matute[1,2] Edson Zangiacomi Martinez[1] Eduardo Antônio Donadi[3]

[1] Department of Social Medicine, Ribeirão Preto Medical School, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
[2] Facultad de Ciencias Médicas, Cátedra de Pediatría, Universidad Central del Ecuador, Quito, Ecuador
[3] Department of Internal Medicine, Ribeirão Preto Medical School, Universidade de São Paulo, Ribeirão Preto, Brazil

Address for correspondence Edson Zangiacomi Martinez, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes 3900, Monte Alegre, 14049-900, Ribeirão Preto, SP, Brazil (e-mail: edson@fmrp.usp.br).

Rev Bras Ginecol Obstet 2021;43(1):14–19.

Abstract

Objective Considering the increased frequency of maternal deaths reported from 2001 to 2005 for Indigenous and mestizo women from the Ecuadorian rural area of Otavalo, where the Kichwa people has lived for centuries, the objective of the present article is to describe how the efforts of the local health community and hospital workers together with a propitious political environment facilitated the implementation of intercultural childbirth, which is a strategy that respects the Andean childbirth worldview.

Methods We evaluated a 3-year follow-up (2014–16) of the maternal mortality and the childbirth features (4,213 deliveries).

Results Although the Western-style (lying down position) childbirth was adopted by 80.6% of the pregnant women, 19.4% of both mestizo and Indigenous women adopted the intercultural delivery (squatting and kneeling positions). Both intercultural (42.2%) and Western-style (57.8%) childbirths were similarly adopted by Kichwa women, whereas Western-style childbirth predominated among mestizo women (94.0%). After the implementation of the intercultural strategy in 2008, a dramatic decrease of maternal deaths has been observed until now in both rural and urban Otavalo regions.

Conclusion This scenario reveals that the intermingling of cultures and respect for childbirth traditions have decreased maternal mortality in this World Health Organization-awarded program.

Keywords
- maternal mortality
- intercultural childbirth
- Kichwa
- Otavalo
- Ecuador

Resumo

Objetivo Considerando a crescente frequência de mortes maternas notificadas de 2001 a 2005 entre mulheres indígenas e mestiças da área rural equatoriana de Otavalo, onde o povo Kichwa vive há séculos, o objetivo deste artigo é descrever como os esforços da comunidade local de saúde e dos trabalhadores hospitalares, juntamente com um

received
December 16, 2019
accepted
September 30, 2020

DOI https://doi.org/10.1055/s-0040-1721353.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

ambiente político propício, facilitaram a implementação do parto intercultural, que é uma estratégia que respeita a visão de mundo do parto andino.

Métodos Foram avaliadas as características da mortalidade materna e do parto (4.213 partos) por um período de 3 anos (2014–16)

Resultados Embora o parto no estilo ocidental (posição deitada) tenha sido adotado por 80,6% das gestantes, 19,4% das mestiças e indígenas adotaram o parto intercultural (posições de agachamento e ajoelhamento). Os partos interculturais (42,2%) e ocidentais (57,8%) foram adotados de maneira semelhante pelas mulheres Kichwa, enquanto o parto ocidental predominou entre as mestiças (94,0%). Após a implementação da estratégia intercultural em 2008, foi observada uma redução drástica de mortes maternas nas regiões rurais e urbanas de Otavalo.

Conclusão Esse cenário revela que a mistura de culturas e o respeito às tradições do parto diminuíram a mortalidade materna neste programa premiado pela Organização Mundial de Saúde.

Palavras-chave
- mortalidade materna
- parto intercultural
- Kichwa
- Otavalo
- Equador

Introduction

Maternal mortality has been considered a serious and persistent challenge worldwide. In 2015, most of the 303,000 maternal deaths occurred in low-income countries, primarily due to inequities in the access to health services, underlined by large disparities between countries in rural and urban populations, and cultural differences.[1,2] Approximately 16 women die every day from pregnancy or childbirth in Latin America and in the Caribbean countries, with hemorrhages, infections and pregnancy-induced hypertension being the most common causes of maternal mortality.[3,4] In the years 2000, 2005, 2010, 2015, and 2017, the maternal mortality ratios (MMRs) in Ecuador were, respectively, 122, 94, 78, 63, and 59 deaths per 100,000 live births.[5,6] Maternal mortality ratio is a central indicator in the Sustainable Development Goals proposed by the United Nations, and efforts should be made to decrease this elevated number of deaths.[7]

Indigenous peoples present poor health indicators throughout the world, characterized by inequality and inequity between Indigenous and non-Indigenous populations, which is the result of socioeconomic conditions due to the historical social exclusion of these peoples.[8] Ecuador has not been the exception, so only 30% of the Indigenous population has access to specialty care, contrasting with 80% of non-Indigenous women.[9] The Law for the Provision of Free Maternity and Child Care (in Spanish, *Ley de Maternidad Gratuita y Atención a la Infancia*, LMGAI) was an incremental health policy first introduced in 1994 and officially made into a mandate in 2002, as the result of the concerted effort of key stakeholders to improve health outcomes for the most vulnerable Ecuadorian women.[10] As a positive impact of the LMGAI, an increase of the number of institutional births by 39% was noted.[10] However, an ecological study using data for 2014 from the 24 Ecuadorian provinces showed that the MMR was higher in the provinces with the highest percentage of Indigenous population.[11]

Despite improving demographic and economic disparities, Indigenous women in rural areas do not have access to formal health services.[12] A report from the United Nations (UN) Economic Commission for Latin America and the Caribbean (ECLAC), including disaggregated health care utilization according to the Indigenous status of women, showed that, in 2004, the percentage of Ecuadorian Indigenous women who attended prenatal care, gave birth in a health facility, and received follow-up attention was systematically lower than among non-Indigenous women.[13,14] In addition, from 2001 to 2005, an increased number of maternal deaths, primarily Indigenous women from the rural areas, were observed in the Ecuadorian area of Otavalo.[15]

With the aim of improving maternal health conditions for Indigenous women and reducing maternal mortality, a pioneering project has been implemented at the San Luis de Otavalo Hospital, in Ecuador. This project aimed to encompass the knowledge, beliefs, and rituals of the pregnant Kichwa women in the health care. Considering that interculturality is the recognition of differences, paying respect to the values of each culture,[16–19] several strategies were included to reduce maternal death, primarily in the rural areas of Otavalo. In 2007, a sustained process of community and hospital health personnel training was initiated to introduce the intercultural childbirth. This strategy was able to reduce the Kichwa and mestizo maternal mortality in the following years, and this program was awarded by the World Health Organization (WHO) in the category "Good Practices and Safe Maternity."[20] In the present study, we further evaluated the impact of intercultural childbirth on maternal mortality and the compliance of Kichwa and mestizo women to the cultural appropriate delivery (squatting, kneeling, and standing positions) in comparison to the Western-style (lying down position) delivery.

Methods

Setting

The present retrospective study evaluated all pregnant Indigenous and non-Indigenous women from the Otavalo canton who gave birth at the San Luis de Otavalo Hospital (SLOH), from 2014

to 2016. A total of 4,213 women was studied, of whom 1,560 (aged 13–45 years, median 33.5, predominating women aged 20–35 years) were Indigenous and 2,653 (median 34.5) were mestizo. Data regarding the total number of deliveries, number of intercultural deliveries and maternal mortality were retrieved from the database and statistical register of the SLOH, according to the proceedings of the Pan American Health Organization (PAHO) and of the Ecuadorian Ministry of Public Health. Since SLOH does not have a computerized information system, all data were obtained from non-electronic medical records. Written informed consent was not feasible because the present study was based on retrospective data.

Intercultural Birth

The definition of intercultural childbirth adopted here includes, among other aspects, the birth of a baby respecting cultural traditions, in a comfortable position for the mother. According to the cultural values of the Kichwa woman, childbirth is performed adopting the vertical position (standing, sitting, squatting, kneeling, semi-sitting), while being attended by the midwife.[21] To perform intercultural childbirth, several actions were taken by the Otavalo hospital, including, i) the woman's right to choose the mode of delivery; ii) the implementation of a physical area according to the cultural Indigenous conception to delivery care, including a small kitchen to heat water to make herb infusions; iii) the identification, training, evaluation, and certification of the canton midwives to take care of the patients before and after childbirth, and permanent accompaniment of the patient during labor; iv) permission for the husband or another family member to stay in the room during labor and to cut the umbilical cord after delivery; v) the provision of adequate clothes to the mother, such as a sterilized flannel dress with a wide abdominal opening to keep the patient warm and to respect pregnant woman privacy; and vi) authorization and permission for traditional practices that are harmless to health.[21] According to the Kichwa traditions, these practices include the permission to use a coriander seeds herbal infusion to prevent pain during delivery and a fig leaf infusion to prevent bleeding after delivery; permission for the patient to have chicken broth before delivery and broth made of a young lamb's head after delivery; and the granting of the placenta to the family to bury it in their homes.[21]

Features of the Otavalo Canton

The 24 Ecuadorian provinces are divided into cantons, and these cantons are divided into parishes (the smallest administrative units). The Otavalo canton is located in the province of Imbabura, in the northern part of Ecuador, presenting an area of 579 km^2. The city of Otavalo is the capital of the canton of the same name, situated 110 km from the capital Quito at a height of 2,565 m above sea level at the following coordinates: 78° 15' 49' West longitude and 0° 13' 43"' North latitude. Of the 145,000 inhabitants (51.9% woman), 62.3% are of the Kichwa nationality (Cayambis and Otavalos) and 37.5% are mestizos (*Instituto Nacional de Estadística y Censos*, all information retrieved from www.ecuadorencifras.gob.ec). The Otavalo canton has two urban and nine rural parishes. The economically active population is 52.3%, and the main productive activities are trade (82.5%), manufacturing industries (3.4%) and other professions (3.4%). Poverty reaches 32.8% of the population and illiteracy predominates among women (22.5%) compared with men (12.7%). The city is well known for its handicrafts and music, but economic development is uneven, rich Indigenous people tend to live in urban areas, but the vast majority of the Indigenous populations live in rural areas, where access to health services at childbirth is more difficult. Otavalo has a major primary care hospital (SLOH) for urban and rural populations and an ambulatory care center only for urban outpatient care.

Results

Of the 4,213 births attended at the SLOH from 2014 to 2016, 19.4% were intercultural births and 80.6% were conventional childbirth. Considering childbirth among the Kichwa women, 42.2% adopted the intercultural childbirth, and 57.8% adopted the Western-style delivery. Among the non-Indigenous women, 6.0% preferred the intercultural childbirth and 94.0% preferred the conventional delivery. Maternal mortality has remained at 0/100,000 live births, maintaining the same scenario since 2008, the year in which the intercultural delivery strategy was implemented. Among all patients who preferred the intercultural childbirth, the squatting (49.7%) and kneeling (46.7%) positions were preferred when compared with the seating position (3.5%). ►**Table 1** summarizes these results.

Table 1 Childbirth features and maternal mortality among rural and urban Indigenous and mestizo women of the Otavalo canton attended

	Year			Total	
	2014	**2015**	**2016**	**n**	**%**
Total deliveries	1,417	1,337	1,459	4,213	100.0
Intercultural childbirth	300	219	299	818	19.4
Western style childbirth	1,117	1,118	1,160	3,395	80.6
Deliveries among Kichwa					
Intercultural childbirth	261	198	200	659	42.2
Western style childbirth	94	118	689	901	57.8
Deliveries among mestizo					
Intercultural childbirth	39	21	99	159	6.0
Western style childbirth	1 023	1 000	471	2 494	94.0
Maternal mortality	0	0	0	0	0

Discussion

Compared with other Latin American countries, the access to health services for the Indigenous population is greater in Ecuador than in Mexico and Peru. Beginning in 2008, after the successful experience in Otavalo, intercultural childbirth has been established as a public policy of the Ministry of Public Health, which helped to reduce the intercultural distance between the Indigenous and non-Indigenous populations.

A report published in 2017 by the Epidemiological Surveillance System of Ecuador register a striking decreased number of maternal deaths compared with the previous decades.[22] In 2001, the provinces that exhibited the highest number of general mortality were those in the Central and Northern areas (Chimborazo, Cotopaxi and Tungurahua), where rural Indigenous populations are predominant. In 2016, the provinces with the highest number of deaths were those in the coastal zone (Guayas, Manabí and Esmeraldas), while the Northern and Central provinces reported lower rates of maternal mortality. It is noteworthy that in the provinces of Chimborazo, Imbabura (Canton Otavalo), and Tungurahua, which are areas with a large Indigenous rural population and that historically exhibited the highest rate of maternal mortality, this rate has also dropped greatly.[22]

International health organizations, such as the WHO, the International Federation of Gynecology and Obstetrics (FIGO), and the International Confederation of Midwives, have been establishing strategies and policies for the promotion of pregnancy, childbirth, and newborn care. Given the challenges of improving health care, comprehensive strategies such as the cultural childbirth have been proposed, including the needs of the pregnant women and their rituals and beliefs related to the pregnancy and childbirth processes.[23] These strategies aim to impart knowledge, respect indigenous cultures, and understand their specific needs and motivations to ensure better access to health services, thus breaking the cultural barriers that may exist between two ethnic populations that share the same territory. In this sense, the introduction of intercultural strategies in the public health policy has contributed to reduce maternal mortality, primarily in the rural Indigenous sectors by providing access to health services. Taking into account that Ecuador still maintains a high number of maternal deaths (43/100,000),[24] the striking reduction of the Indigenous and non-Indigenous maternal mortality in Otavalo is noteworthy. Different social and political actors contributed to the successful strategy of intercultural childbirth, including: i) the new Ecuadorian Constitution (2008) that widened the rights to indigenous people, recognizing the presence of indigenous leaders in strategic positions, ii) by the first time, an Indigenous hospital manager was appointed to take care of the Indigenous health care at the Otavalo canton, iii) the empowerment of the internal (technical and administrative staff of the hospital) and external actors (local government, non-governmental organizations, midwives, and the indigenous health facilities).[25,26] In this context, it is important to emphasize the role of Indigenous midwifes who played a pivotal linkage between the rural Indigenous communities and the hospital staff, and provided maternal care during the pre and postchildbirth periods. A group of 36 midwives were certified by the Ministry of Health to participate in the intercultural strategy; however, just one midwife, who is paid by the government, accompanies the women in the intercultural hospital facility. Although other midwifes are not paid by their services, they are proud of their roles on helping Kichwa women before and after delivery. In addition to these actors, private physicians who worked in Quito and had experience in performing vertical childbirth contributed to the success of the humanized childbirth.

Overall, despite the introduction of the humanized childbirth, the conventional Western-style childbirth continues to be the most frequent position, and it was adopted by 80.6% of the women, contrasting with 19.4% of women who adopted the intercultural childbirth. Notwithstanding, intercultural childbirth was primarily adopted by the Kichwa women and, at a lesser extent, by the mestizo women. It is worth mentioning that the squatting and kneeling positions were the chosen ones by Indigenous and non-Indigenous women. The vertical childbirth does not represent only a delivery position, but an integral attention to the women, respecting their beliefs, rituals, and Andean cosmovision. Considering that public health institutions have historically adopted the Western-style childbirth, the implementation the humanized childbirth represents a new approach to the acceptance of public health institutions to this different concept of childbirth attention. Since the introduction of the intercultural childbirth in Ecuador in 2007, this strategy has also been adopted in other Ecuadorian regions.[26] The Ministry of Heath determined that all provinces and cantons with major Indigenous populations must have two facilities for childbirth, including an intercultural one. Despite this public policy, that had encompassed all indigenous communities, this WHO awarded strategy provided to the Otavalo canton one of the best maternal survival rates in Ecuador.

Considering that the MMRs observed in Ecuador were 63 and 59 deaths per 100,000 live births in 2015 and 2017, respectively, a maternal mortality equal to zero reported in this period in SLOH highlights the importance of studies about intercultural childbirth.[5] However, since it would not be expected for mortality to be higher for women attended inside health facilities, although submitted to traditional practices, it is difficult to conclude that a possible reduction of the mortality in SLOH is necessarily due to intercultural childbirth. In contrast, Otavalo is not the area of the country with the highest MMR, and the pioneer practice of intercultural childbirth of SLOH provides a basis for new studies for better understanding of their benefits and how the intercultural health policy could be implemented.[25]

Our study has important limitations. The SLOH does not have an electronic medical record system, and collection of data from medical charts had to be done manually. Consequently, information about maternal and neonatal outcomes, such as postpartum hemorrhage prevalence, Apgar scores, hospitalization time, and infections were not adequately available. Our results are based on mortality alone, and this limits our results. In addition, MMRs in the years preceding the adoption of the intercultural childbirth by the SLOH are also not available. As

another limitation of the present study, the database was not adjusted for missing data as the WHO estimates are. Since we used retrospective data, important perceptions of the women about aspects of the intercultural births were not possible to obtain. Therefore, future prospective studies should be conducted to investigate intercultural births and their possible impacts on maternal health, including more adequate information regarding maternal and neonatal outcomes.

Despite all these problems, the present article is an important first step in exploring the possible impacts of intercultural childbirth adopted in SLOH on maternal mortality and serves as motivation for improvements in the hospital information system to enable more complete studies. San Luis de Otavalo Hospital was a pioneer institution in the implementation of "vertical birth" in Ecuador, as an intercultural health policy practice that aims to increase the access of Indigenous women to maternity care.[25,27] We can understand that this intercultural strategy alone was not the sole factor that strongly influenced the reduction of maternal mortality.

Conclusion

However, communion between the rural Indigenous communities and the public institutions possessing an integral concept regarding childbirth attention has contributed to reduce maternal mortality among Indigenous populations. As a corollary to this strategy, an important hitchhiking effect was also observed for mestizo women, and further investigation is encouraged.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 WHO, UNICEF, UNFPA, World Bank Group, United Nations Population Division. Trends in maternal mortality: 1990 to 2015 [Internet]. Geneva: WHO; 2015 [cited 2020 Mar 9]. Available from: http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2015/en/

2 Roos N, von Xylander SR. Why do maternal and newborn deaths continue to occur? Best Pract Res Clin Obstet Gynaecol. 2016; 36:30–44. Doi: 10.1016/j.bpobgyn.2016.06.002

3 Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clin Obstet Gynecol. 2010;53(01): 147–156. Doi: 10.1097/GRF.0b013e3181cc406d

4 Acosta AA, Cabezas E, Chaparro JC. Present and future of maternal mortality in Latin America. Int J Gynaecol Obstet. 2000;70(01): 125–131. Doi: 10.1016/S0020-7292(00)00235-6

5 UNICEF. Maternal mortality data [Internet]. 2019 [cited 2020 Jul 6]. Available from: https://data.unicef.org/resources/dataset/maternal-mortality-data/

6 Pino A, Albán M, Rivas A, Rodríguez E. Maternal deaths databases analysis: Ecuador 2003–2013. J Public Health Res. 2016;5(02): 692. Doi: 10.4081/jphr.2016.692

7 Griggs D, Stafford-Smith M, Gaffney O, Rockström J, Ohman MC, Shyamsundar P, et al. Policy: Sustainable development goals for people and planet. Nature. 2013;495(7441):305–307. Doi: 10.1038/495305a

8 King M. An overall approach to health care for indigenous peoples. Pediatr Clin North Am. 2009;56(06):1239–1242. Doi: 10.1016/j.pcl.2009.09.005

9 Centro de Estudios de Población y Desarrollo Social. Encuesta Demográfica y de Salud Materna e Infantil - ENDEMAIN 2004 [Internet]. Quito: Cepar; 2005 [cited 2018 May 10]. Available from: https://cssr-ecuador.org/downloads/2016/11/32.-Encuesta-Demografica-y-de-salud-materna-e-infantil-ENDEMAIN.pdf

10 Chiriboga SR. Incremental health system reform policy: Ecuador's law for the provision of free maternity and child care. J Ambul Care Manage. 2009;32(02):80–90. Doi: 10.1097/JAC.0b013e3181994306

11 Sanhueza A, Roldán JC, Ríos-Quituizaca P, Acuña MC, Espinosa I. Social inequalities in maternal mortality among the provinces of Ecuador. Rev Panam Salud Publica. 2017;41:e97. Doi: 10.26633/RPSP.2017.97

12 Camacho AV, Castro MD, Kaufman R. Cultural aspects related to the health of Andean women in Latin America: a key issue for progress toward the attainment of the Millennium Development Goals. Int J Gynaecol Obstet. 2006;94(03):357–363. Doi: 10.1016/j.ijgo.2006.04.028

13 Organización Panamericana de la Salud, Organización Mundial de la Salud. Situación de salud: Ecuador 2006 [Internet]. 2006 [cited 2018 May 10]. Available from: https://www.paho.org/ecu/index.php?option=com_docman&view=download&category_slug=technical-documentation&alias=29-situacion-de-salud-2006&Itemid=599

14 Oyarce AM, Ribotta B, Pedrero M. Salud materno-infantil de pueblos indígenas y afrodescendientes de América Latina: aportes para una relectura desde el derecho a la integridad cultural. Santiago de Chile: CEPAL; 2010

15 Castro A, Savage V, Kaufman H. Assessing equitable care for Indigenous and Afrodescendant women in Latin America. Rev Panam Salud Publica. 2015;38(02):96–109

16 Gallegos CA, Waters WF, Kuhlmann AS. Discourse versus practice: are traditional practices and beliefs in pregnancy and childbirth included or excluded in the Ecuadorian health care system? Int Health. 2017;9(02):105–111. Doi: 10.1093/inthealth/ihw053

17 Herrera D, Hutchins F, Gaus D, Troya C. Intercultural health in Ecuador: an asymmetrical and incomplete project. Anthropol Med. 2019;26(03):328–344. Doi: 10.1080/13648470.2018.1507102

18 Finerman RD. Part 5: pregnancy and childbirth in Saraguro: implications for health care delivery in Southern Ecuador. Med Anthropol. 1982;6(04):269–278. Doi: 10.1080/01459740.1982.9987023

19 Matute SED, Donadi EA, Nunes AA, Martinez EZ. Clinical response to antibiotics in indigenous versus non-indigenous children under 5 years old with community-acquired pneumonia in Otavalo, Ecuador. Rev Soc Bras Med Trop. 2020;53:e20200038. Doi: 10.1590/0037-8682-0038-2020

20 Vivar SC. Ecuador addresses cultural issues for pregnant women. Lancet. 2007;370(9595):1302. Doi: 10.1016/S0140-6736(07)61561-X

21 Rosero CMC, Quinaluisa SEC. Impacto y acogida del parto culturalmente adecuado por el equipo de profesionales de salud del Hospital San Luis de Otavalo en el año 2011–2012 [tesis]. Ibarra: Universidad Tecnica del Norte; 2012 [cited 2018 May 10]. Available from: http://repositorio.utn.edu.ec/handle/123456789/2076

22 Instituto Nacional de Estadística y Censos. Estimación de la razón de mortalidad materna en el Ecuador [Internet]. Quito: INEC; 2017 [cited 2018 May 10]. Available from: http://www.ecuadorencifras.gob.ec/documentos/web-inec/Poblacion_y_Demografia/Nacimientos_Defunciones/2016/RMM_Nota_metodologica_INEC _2016.pdf

23 Coast E, Jones E, Lattof SR, Portela A. Effectiveness of interventions to provide culturally appropriate maternity care in increasing uptake of skilled maternity care: a systematic review. Health Policy Plan. 2016;31(10):1479–1491. Doi: 10.1093/heapol/czw065

24 Gaceta Epidemiológica Ecuador [Internet]. Quito: Ministerio de Salud Pública. Subsecretaria de Vigilancia de la Salud Pública. Dirección Nacional de Vigilancia EpidemiológicaNo. 52;2016 [cited 2018 May 10]. Available from: https://www.salud.gob.ec/wp-content/uploads/2013/02/GACETA-GENERAL-SE52.pdf

25 Llamas A, Mayhew S. The emergence of the vertical birth in Ecuador: an analysis of agenda setting and policy windows for intercultural health. Health Policy Plan. 2016;31(06):683–690. Doi: 10.1093/heapol/czv118

26 Waters WF, Ehlers J, Ortega F, Kuhlmann AS. Physically demanding labor and health among Indigenous women in the Ecuadorian Highlands. J Community Health. 2018;43(02):220–226. Doi: 10.1007/s10900-017-0407-7

27 Llamas A, Mayhew S. "Five hundred years of medicine gone to waste"? Negotiating the implementation of an intercultural health policy in the Ecuadorian Andes. BMC Public Health. 2018;18(01):686. Doi: 10.1186/s12889-018-5601-8

Agreement Analysis between Sonographic Estimates and Birth Weight, by the WHO and Intergrowth-21st Tables, in Newborns of Diabetic Mothers

Análise de concordância entre estimativas ultrassonográficas e peso ao nascer, pelas tabelas da OMS e Intergrowth-21st, em recém-nascidos de mães diabéticas

Marcus Vinícius Rodrigues de Souza[1] Lívia Pinto e Fróes[1] Pedro Afonso Cortez[2] Márcio Weissheimer Lauria[1] Regina Amélia Lopes de Aguiar[1] Kamilla Maria Araújo Brandão Rajão[1]

[1] Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
[2] Universidade Metodista de São Paulo, São Bernardo do Campo, São Paulo, SP, Brazil

Address for correspondence Kamilla Maria Araújo Brandão Rajão, MSc, Professor Alfredo Balena Avenue, 110, Belo Horizonte, MG, 30130-100, Brazil (e-mail: kamillarajao@gmail.com).

Rev Bras Ginecol Obstet 2021;43(1):20–27.

Abstract

Objective To analyze the agreement, in relation to the 90th percentile, of ultrasound measurements of abdominal circumference (AC) and estimated fetal weight (EFW), between the World Health Organization (WHO) and the International Fetal and Newborn Growth Consortium for the 21st Century (intergrowth-21st) tables, as well as regarding birth weight in fetuses/newborns of diabetic mothers.

Methods Retrospective study with data from medical records of 171 diabetic pregnant women, single pregnancies, followed between January 2017 and June 2018. Abdominal circumference and EFW data at admission (from 22 weeks) and predelivery (up to 3 weeks) were analyzed. These measures were classified in relation to the 90th percentile. The Kappa coefficient was used to analyze the agreement of these ultrasound variables between the WHO and intergrowth-21st tables, as well as, by reference table, these measurements and birth weight.

Results The WHO study reported 21.6% large-for-gestational-age (LGA) newborns while the intergrowth-21st reported 32.2%. Both tables had strong concordances in the assessment of initial AC, final AC, and initial EFW (Kappa = 0.66, 0.72 and 0.63, respectively) and almost perfect concordance in relation to final EFW (Kappa = 0.91). Regarding birth weight, the best concordances were found for initial AC (WHO: Kappa = 0.35; intergrowth-21st: Kappa = 0.42) and with the final EFW (WHO: Kappa = 0.33; intergrowth- 21st: Kappa = 0.35).

Conclusion The initial AC and final EFW were the parameters of best agreement regarding birth weight classification. The WHO and intergrowth-21st tables showed high agreement in the classification of ultrasound measurements in relation to the 90th

Keywords
- abdominal circumference
- estimated fetal weight
- birth weight
- gestational diabetes
- growth charts

received
November 25, 2019
accepted
September 17, 2020

DOI https://doi.org/10.1055/s-0040-1719146.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

percentile. Studies are needed to confirm whether any of these tables are superior in predicting short- and long-term negative outcomes in the LGA group.

Resumo

Objetivo Analisar a concordância, em relação ao percentil 90, das medidas ultrassonográficas da circunferência abdominal (CA) e peso fetal estimado (PFE), entre as tabelas da Organização Mundial de Saúde (OMS) e do *International Fetal and Newborn Growth Consortium for the 21st Century* integrowth-21st, bem como em relação ao peso ao nascer em fetos/recém-nascidos de mães diabéticas.

Métodos Estudo retrospectivo com dados de prontuários de 171 gestantes diabéticas, com gestações únicas, seguidas entre Janeiro de 2017 e Junho de 2018. Foram analisados dados da CA e do PFE na admissão (a partir de 22 semanas) e no pré-parto (até 3 semanas). Essas medidas foram classificadas em relação ao percentil 90. O coeficiente Kappa foi utilizado para analisar a concordância entre as tabelas da OMS e Intergrowth-21st, assim como, por tabela de referência, entre as medidas e o peso ao nascer.

Resultados O estudo da OMS relatou 21,6% dos recém nascidos grandes para a idade gestacional (GIG) enquanto que o estudo do intergrowth-21st relatou 32,2%. Ambas as tabelas tiveram fortes concordâncias na avaliação da CA inicial e final e PFE inicial (Kappa = 0,66, 0,72 e 0,63, respectivamente) e concordância quase perfeita em relação ao PFE final (Kappa = 0,91). Em relação ao peso ao nascer, as melhores concordâncias foram encontradas para a CA inicial (OMS: Kappa = 0,35; intergrowth-21st: Kappa = 0,42) e com o PFE final (OMS: Kappa = 0,33; intergrowth-21st: Kappa = 0,35).

Conclusão A CA inicial e o PFE final foram os parâmetros de melhor concordância em relação à classificação do peso ao nascer. As tabelas da OMS e intergrowth-21st mostraram alta concordância na classificação das medidas ultrassonográficas em relação ao percentil 90. Estudos são necessários para confirmar se alguma dessas tabelas é superior na previsão de resultados negativos a curto e longo prazo no grupo GIG.

Palavras-chave
- circunferência abdominal
- peso fetal estimado
- peso ao nascer
- diabetes gestacional
- gráficos de crescimento

Introduction

Diabetes mellitus (DM) is a major public health problem, and its prevalence has increased over the years, including in women of childbearing age, because of the epidemic of overweight and obesity in the world.[1] In Brazil, this prevalence varies from 1.3%, in the age group between 18 and 24 years, to 4.6%, in the 35 to 44 years age group; thus, Brazil is ranked 5th in the DM prevalence among adults in the world.[2–4]

Regarding diabetes in pregnancy, one in six women giving birth in the world has hyperglycemia, of which 84% are due to gestational diabetes mellitus (GDM).[5] The Brazilian Gestational Diabetes Study has documented a prevalence of 7.6% of GDM using the 1999 World Health Organization (WHO) criteria.[6] However, according to the criteria of the International Association of Diabetes in Pregnancy Study Group (IADPSG), the GDM prevalence in the Brazilian public health care system has reached 18%.[7,8]

The use of ultrasound scanning is fundamental to monitor fetal growth, especially when there is an increased risk of large for gestational age (LGA), as it occurs with diabetic mothers' fetuses.[9] Some of the parameters used for this estimate are the abdominal circumference (AC) and the estimated fetal weight (EFW).[9] Abdominal circumference is considered the earliest and, therefore, the most sensitive parameter in the evaluation of fetal macrosomia, reflecting liver growth abnormalities.[10] Estimated fetal weight is an indirect measurement calculated with formulas that use multiple biometric parameters, and it is subject to a higher percentage of errors.[11] Detecting fetal growth abnormalities is very important for therapeutic decisions, both to correct predisposing factors and to predict the type and moment of delivery.[12]

Nevertheless, the occurrence of LGA is also associated with obstetric and neonatal adverse outcomes, such as increased cesarean delivery rates, neonatal hypoglycemia, jaundice, 5-minute Apgar score < 7, higher stillbirth rate, and respiratory distress.[13,14] Some studies have also pointed out that the consequences of being born LGA may go beyond the neonatal period, increasing the risk of precocious puberty, childhood obesity, and metabolic syndrome in childhood and adulthood.[15,16]

Until recently, references of ultrasound assessment of fetal growth have been based on single-center studies, with a few measurements from North American populations with low ethnic variability.[17] To create more representative references of the world population, two studies were conducted with representativeness of the Brazilian population: one by WHO and the other by the International Fetal and Newborn Growth Consortium for the 21st Century (intergrowth-21st).[18,19]

Given the divergences observed in the clinical practice between the LGA classifications by the WHO's and intergrowth-21st's studies—which resulted in an increase in LGA cases after the adoption of these reference tables—and the apparent divergence between the EFG and the real birth

weight, we proposed the development of the present study. Our aim was (i) to analyze the level of agreement of these two LGA classifications in a population of diabetic pregnant women and (ii) to compare the birth weight results in relation to the ultrasound variables during the third trimester of pregnancy, to determine whether there was any disagreement between these results.

Methods

Participants

This is a retrospective cohort study based on a survey of medical records of 171 diabetic pregnant women followed up by the Obstetrics and Endocrinology Services of one tertiary Hospital from Belo Horizonte, in the state of MG, Brazil. The participants received care between January 2017 and June 2018. Data were collected between August and November 2018. This study was approved by the Research Ethics Committee (CAAE: 50724015.3.0000.5149), and all participants signed the informed consent form.

First, we obtained the record from all the patients representing 310 diabetic and non diabetic pregnant patients. Then, we applied the exclusion criteria: a) non diabetics; b) patients lost to follow-up; c) missing data on patient medical records to include in the study. We excluded 139 patients. All the other 171 participants were included in the present study and attended the following inclusion criteria: pregnant women diagnosed with pregestational or gestational diabetes, with single pregnancies, aged $\geq$18 years, regularly monitored during the previously mentioned period, with available ultrasound measurements (the availability of EFW at the first ultrasound scan and the data on birth weight and gestational age at birth were mandatory), and those women who consented to participate in the research. Twin pregnancies were excluded because they were not represented in the WHO's and intergrowth-21st's studies. The inclusion and exclusion criteria are shown in ►**Fig. 1**.

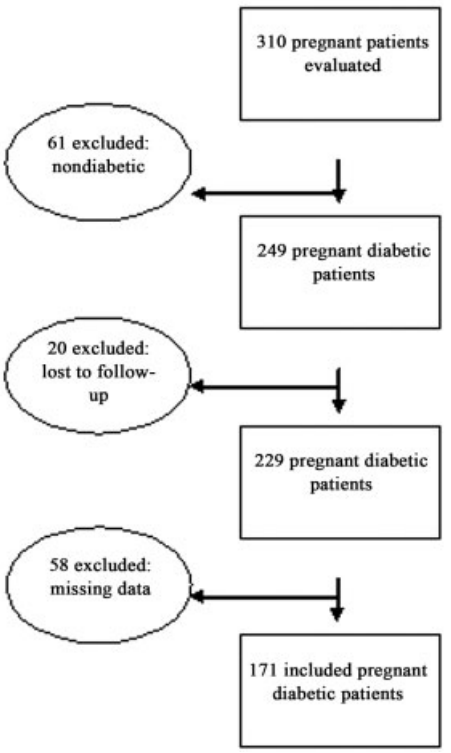

Fig. 1 Participants exclusion and inclusion criteria.

The clinical variables reported were maternal age (years), type of diabetes (gestational or pregestational), classification of pregestational diabetes cases (type 1 DM [T1D], type 2 DM [T2D], overt diabetes, or diabetes due to other causes), gestational age at birth (weeks), and birth weight (g). Gestational age was calculated by the Obstetrics Service based on the date of women's last period or the first ultrasound scan available, as recommended by the American College of Obstetricians and Gynecologists.[20]

All pregnant women who had no previous diagnosis of diabetes were screened with a fasting glucose test up to 20 weeks of gestation. When the initial fasting blood glucose was $<$ 92 mg per deciliter [5.11 nmol per liter], the diagnosis of GDM was based on the IADPSG recommendations, endorsed by the American Diabetes Association (ADA), using the 75G-OGTT (oral glucose tolerance test) at 24 to 28 weeks of gestational age (fasting $\geq$ 92 mg per deciliter [5.1 nmol per liter] or 1 hour post dextrosol $\geq$180 mg per deciliter [10 nmol per liter] or 2 hours post dextrosol $\geq$ 153 mg per deciliter [8.5 nmol per liter]).[7,21] When the fasting glucose test result before 20 weeks was between 92 to 125 mg per deciliter [5.1 to 6.9 nmol per liter], with a second confirmatory sample, early GDM was diagnosed, following the protocol recommended by the Pan American Health Organization (PAHO).[2] The diagnosis of pre-gestational DM was defined according to the patient's report of previous diagnosis and treatment, or defined according to ADA recommendations, based on the following criteria: presence of classic symptoms of hyperglycemia and random glucose $\geq$ 200 mg per deciliter [11.1 nmol per liter] or asymptomatic patient with two altered tests: fasting glucose (8 hours) $\geq$ 126 mg per deciliter [7 nmol per liter] and/or glycohemoglobin (HbA1c) $\geq$ 6.5% (using a method approved by the National Glycohemoglobin Standardization Program) and/or 75 g-OGTT $\geq$ 200 mg per deciliter [11.1 nmol per liter].[21]

During prenatal care, EFW $\geq$ 90th percentile (p90) was considered LGA. During the newborn assessment, LGA was applied to birth weight, according to gestational age, as $\geq$ p90.[22] This classification was performed according to the WHO's (for gender and gestational age) and intergrowth-21st's (for gestational age) studies.[18,19] The sonographic measurements used in the present study were obtained by trained professionals from the obstetrics service. The AC and EFW values obtained in the first ultrasound performed after 22 weeks of gestation were reported as "initial" values, and the same variables measured in the last ultrasound performed up to three weeks before delivery were reported as "final" values and considered for analysis, according to data availability in the medical records. The EFW was calculated in the obstetrics service according to the recommendations

previously published by Hadlock et al. (1984).[23] These measurements were categorized as < p90 or ≥ p90 for comparison with the same birth weight percentiles.

Statistical Analysis

A statistical analysis was performed using MedCalc version 19.1 (MedCalc Software Ltd, Ostend, Belgium). The Shapiro-Wilk normality test was applied to quantitative variables to verify normality distribution (for maternal age: $W = 0.98$; $p = 0.0099$; for gestational age at birth: $W = 0.79$, $p < 0.0001$; and for birth weight: $W = 0.96$; $p = 0.0001$). Since none of them had a normal distribution, these variables were reported as median and interquartile range (p25–75).

Estimated fetal weight, AC, and birth weight were categorized as < p90 or ≥ p90 and reported as proportions. The Kappa coefficient was used to analyze clinimetric evidence considering the agreement of results in relation to ultrasound measurements between the WHO's and intergrowth-21st's classifications. Then, the Kappa coefficient was also used to analyze the agreement, within the same classification table, between the sonographic variables (AC and EFW, at initial and final ultrasonography) in relation to birth weight. The Kappa coefficient between 0 and 0.2 is considered weak; between 0.21 and 0.4, reasonable; between 0.41 and 0.6, moderate; between 0.61 and 0.8, strong; and between 0.81 and 1, almost perfect.[24]

Results

We analyzed data from the medical records of 171 pregnant women who met the inclusion criteria. Of this total, 65 (38.0%) participants had pregestational DM and 106 (62.0%) GDM, with a median age of 33 years (29–37 years). Regarding the pregestational DM group, 21.5% ($n = 14$) were T1D, 46.2% ($n = 30$) T2D, 30.8% ($n = 20$) overt diabetes, and 1.5% ($n = 1$) had other cause of DM (pancreatic). The median gestational age at birth was 38 weeks (37–38 weeks). The median birth weight was 3,185 g (2,757–3,519 g). Considering the LGA outcome according to the WHO classification, 37 cases (21.6%) were detected; according to the intergrowth-21st classification, 55 cases were detected (32.2%).

The first ultrasound scans were performed at a median of 30 weeks (21–36 weeks), and the final ultrasound scans at a median of 35 weeks (26–39 weeks). Descriptive analysis comparing the two reference tables used in this study regarding AC, EFW and birth weight is shown in ►**Table 1**. The agreement of classifications was considered strong for initial AC, final AC, initial EFW and birth weight, and almost perfect for the final EFW. ►**Table 2** shows the results.

Considering birth weight as a reference measurement, we analyzed the agreement of this measure with the ultrasound parameters, AC and EFW. ►**Table 3** presents the analysis made according to the WHO classification, and ►**Table 4** displays the results based on the intergrowth-21st classification. The best

Table 1 Classification of sonographic variables and birth weight, based on the WHO's and intergrowth-21st's studies

	WHO		Intergrowth-21st		Total
	≥ p90	< p90	≥ p90	< p90	
	N (%)	N (%)	N (%)	N (%)	
Initial AC	40 (27.4)	106 (72.6)	61 (41.8)	85 (58.2)	146 (100.0)
Initial EFW	66 (38.6)	105 (61.4)	79 (46.2)	92 (53.8)	171 (100.0)
Final AC	30 (25.6)	87 (74.4)	42 (35.9)	75 (64.1)	117 (100.0)
Final EFW	37 (28.2)	94 (71.8)	40 (30.5)	91 (69.5)	131 (100.0)
Birth weight	37 (21.6)	134 (78.4)	55 (32.2)	116 (67.8)	171 (100.0)

Abbreviations: AC, abdominal circumference; EFW, estimated fetal weight; WHO, World Health Organization.

Table 2 Agreement analysis between sonographic variables based on the WHO's and intergrowth-21st's studies

	Agreement with ≥ p90 N (%)	Agreement with < p90 N (%)	Disagreement N (%)	Kappa	CI95%
Initial AC	39 (26.7)	84 (57.5)	23 (15.8)	0.66	[0.54;0.78]
Initial EFW	57 (33.3)	83 (48.6)	31 (18.1)	0.63	[0.52;0.75]
Final AC	29 (24.8)	74 (63.2)	14 (12.0)	0.72	[0.59;0.85]
Final EFW	36 (27.5)	90 (68.7)	5 (3.8)	0.91	[0.83;0.99]
Birth weight	37 (21.6)	116 (67.8)	18 (10.5)	0.74	[0.62;0.85]

Abbreviations: AC, abdominal circumference; CI, confidence interval; EFW, estimated fetal weight; WHO, World Health Organization.

Table 3 Agreement analysis between sonographic variables and birth weight based on the WHO classification

	Agreement with ≥ p90 N (%)	Agreement with < p90 N (%)	Disagreement N (%)	Kappa	CI95%
Initial AC	19 (13.0)	91 (62.3)	36 (24.7)	0.35	[0.18;0.52]
Initial EFW	21 (12.3)	89 (52.0)	61 (35.7)	0.18	[0.04;0.32]
Final AC	11 (9.4)	71 (60.7)	35 (29.9)	0.19	[0.00;0.38]
Final EFW	17 (13.0)	80 (61.1)	34 (25.9)	0.33	[0.15;0.51]

Abbreviations: AC, abdominal circumference; CI, confidence interval; EFW, estimated fetal weight; WHO, World Health Organization.

Table 4 Agreement analysis between sonographic variables and birth weight based on the intergrowth-21st classification

	Agreement with ≥ p90 N (%)	Agreement with < p90 N (%)	Disagreement N (%)	Kappa	CI95%
Initial AC	35 (24.0)	71 (48.6)	40 (27.4)	0.42	[0.27;0.57]
Initial EFW	36 (21.1)	73 (42.7)	62 (36.2)	0.18	[0.04;0.32]
Final AC	22 (18.8)	58 (49.6)	37 (31.6)	0.30	[0.12;0.48]
Final EFW	23 (17.6)	71 (54.2)	37 (28.2)	0.35	[0.18;0.52]

Abbreviations: AC, abdominal circumference; CI, confidence interval; EFW, estimated fetal weight.

agreement results were obtained for the initial AC and final EFW parameters, both in the WHO and intergrowth-21st classifications, and they are considered reasonable. However, the Kappa value was higher in relation to the reference measurements obtained by the intergrowth-21st classification.

Discussion

This unprecedented study analyzed—in a sample of 171 diabetic pregnant women treated in a Brazilian public tertiary care service—the agreement between ultrasound parameters (AC and EFW) and birth weight, comparing of WHO's and intergrowth-21st's LGA classifications, which have representativeness of Brazilian pregnant women. We found a high agreement between the two studies regarding the measurements of initial AC, final AC, and initial EFW, and an almost perfect agreement with the final EFW. This study was justified because it approaches a population at risk of excessive fetal growth, and it is based on the observation of the alarming number of referrals of LGA cases based on the first fetal ultrasound scan, even though glycemic control and other lifestyle changes can positively affect the reduction of negative gestational and neonatal clinical outcomes.

The EFW measurement is extremely important in clinical practice, especially for the management of high-risk pregnancies, such as diabetic pregnant women.[18] The final EFW was one of the measurements with the highest agreement in relation to birth weight (Kappa = 0.33; CI95% [0.18;0.52] for WHO; Kappa = 0.35; CI95% [0.15;0.51] for intergrowth-21st). Barel et al.[25] found that the accuracy of these measurements has decreased in weight extremes (< 2,000 g or > 4,000 g)—which may have resulted in such poor agreement with the initial EFW—, and more LGA cases were detected in the first ultrasound scan. In a retrospective cohort study with macrosomic fetuses (from 4,000 g to ≥ 4,750 g), Zafman et al.[26] found overestimated weight values by ultrasound scans in more than 50% of cases, especially in the groups with higher fetal weight, as high as reported in this paper. In another cohort study, in which 32-week-old ultrasound scans of 521 diabetic pregnant women were analyzed, the authors found that EFW had a reasonable sensibility (80.3%) and a high negative predictive value (96%), but a low positive predictive value (38%) in LGA detection.[27]

In addition to weight extremes, late gestational ages and obesity itself can reduce the accuracy of ultrasound results in diabetic pregnant women compared with low-risk pregnant women.[27] However, as it is a calculated indirect measurement, the EFW has an estimated margin of error of 10 to 15%.[28] Thus, all these factors point us to look differently to the measurements of this population.

Another measurement that showed one of the best agreement regarding birth weight percentiles was the initial AC (Kappa = 0.35; CI95% [0.18;0.52] for WHO; Kappa = 0.42; CI95% [0.15;0.51] for intergrowth-21st). In a Chinese prospective multicenter study of 8,272 DM cases and 729 pre-gestational DM cases, Yan et al. showed that the growth rates assessed by means of AC were higher in the GDM and pre-gestational DM groups with macrosomic babies than in non-macrosomic groups, with statistically significant differences between groups older than 22 weeks of gestation ($p = 0.001$).[9] In another cohort in South Africa, Macauley et al.[29] followed up 741 women with serial ultrasound measurements and showed that AC among pregnant women with GDM (24–28 weeks) was significantly higher in all measurements, from 14 weeks to 38 weeks of gestational age, especially between 27 and 32 weeks ($p < 0.001$), regardless of BMI (body mass index).[29] In addition, Brand et al.[30] showed that, in a population of South Asian and English descendants, fetal growth accelerates after 24 weeks of age until birth in pregnant

women with GDM, even before they are diagnosed with GDM.[30] These findings reinforce the importance of this measurement as an early warning of excessive fetal growth.

Differences between the WHO's and intergrowth-21st's studies are evident. For example, in the LGA classification at birth, 21.6% of cases ($n = 37/170$) were detected by the WHO and 32.2% ($n = 55/170$) by intergrowth-21st. With a population similar to the one investigated in the present study, the WHO used Hadlock's formula to calculate EFW, while intergrowth-21st created its own formula to calculate the EFW using only AC and head circumference. Further, starting at 25 weeks, EFW's p90 cutoff in intergrowth-21st's is lower than in WHO's (for example: for 38 weeks, cutoffs would be 3,540 g in intergrowth-21st's and 3,616 g in WHO's). Concerning AC, this difference can be observed as early as 14 weeks (in the same example, at 38 weeks, AC's p90 cutoff is 356.4 mm in the intergrowth-21st's study and 364 mm in the WHO's study).[31]

In addition, the populations included in the studies were different. The WHO's study included 1,387 healthy pregnant women with good socioeconomic, environmental and nutritional status, aged 18 to 40 years, in single pregnancies, and from 10 countries (Brazil, Germany, Argentina, Congo, Norway, Thailand, India, France, and Egypt). In Brazil, the University of Campinas (Campinas, SP) was the center that participated in the study, with a total of 148 women. The pregnancies had an average duration of 39 weeks. Significant differences were observed in EFW among countries, both in the lowest (3.5%) and the highest percentiles (4.5%). Maternal age, weight and parity contributed to these differences. These variations between countries and the number of countries represented in it were limiting conditions for the widespread use of this scale, according to the authors.[18]

The intergrowth-21st's study included, for the purpose of generating growth tables, 1,556 healthy, well-nourished pregnant women with low risk of maternal and perinatal adverse events, between 14 weeks of gestation and with babies up to 2 years of age, from 8 countries (Brazil, China, United Kingdom, Oman, Italy, Kenya, India, and United States of America). Brazil was represented by the Federal University of Pelotas (Pelotas, RS). This study, like WHO's, worked as the prescriptive concept of growth, in which healthy populations have similar growth patterns, but did not perform statistical analysis between the populations of the different countries included.[19]

Some studies have compared LGA and AC detection rates above p90 between the intergrowth-21st and reference tables generated by population studies in different countries. In an Australian retrospective hospital-based cohort study with 2,966 unselected pregnant women, 16.5% of newborns were classified as LGA after 33 weeks of gestation using intergrowth-21st's p90.[32] This represented 66% more cases detected when compared with the reference growth tables for the country's population. Multivariate analysis identified two independent predictors: the presence of pregestational diabetes and high pregestational BMI.[32] A French cohort study conducted by Heude et al.[33] analyzed 14,607 single pregnancies, of which 34% were at low risk according to the inclusion criteria of intergrowth-21st, with 5 to 10% of gestational diabetes cases. The authors reported 16.7% of AC cases $\geq$ p90 according to intergrowth-21st, compared with 7.1% of cases according to French population's specific growth curves. These findings, however, were similar between unselected population and low-risk cases, both in the second and third trimester.[33] Brazil has not had any comprehensive study to develop a representative table of its population. A recent meta-analysis with studies of the Brazilian population has found between 4.1 and 30.1% cases of excessive fetal growth. The criteria adopted varied among the different studies, which accepted as excessive fetal growth birth weight $\geq$ 90 and macrosomia while birth weight $\geq$ 4,000 g.[12] Thus, it is necessary, in our country, with its wide territorial extension and ethnic variety, to carry out a study to establish national clinimetric evidence for Brazilian reference curves.[34]

There are several limitations to our work. This is a retrospective study based on medical record data, with a limited number of participants, some data loss, and a poor description of the procedures and results that could contribute to a more complete analysis. In addition, patient admission was not homogeneous and, sometimes, even late, limiting the early appropriate execution of interventions and even ultrasound measurements, especially in pregnant women with pregestational DM. As a research agenda, future studies may investigate, prospectively and in a multicenter way, the Brazilian population to determine whether the differences between these two studies, regarding LGA detection, affects neonatal outcomes, such as complications and mortality, so they can be safely inserted into clinical practice.

Conclusion

In a Brazilian population of diabetic pregnant women, we found strong agreement for ultrasound measurements of AC and EFW between the WHO's and intergrowth-21st's studies, with a tendency to overestimate weight based on the first ultrasound scans. The initial AC and EFW at the last ultrasound scan were the best agreement parameters for birth weight, as corroborated by other studies in the international literature, with a better agreement obtained by the intergrowth-21st classification. Higher LGA detection rates were observed in intergrowth-21st's tables. Further studies are needed to define the study that better applies to our population, objectively analyzing outcomes such as short and long-term neonatal and postnatal complications in relation to LGA fetuses.

Contributions

Souza M. V. R. contributed by collecting data and writing the first draft; Cortez P. A. contributed by performing the statistical analysis and writing the first draft; Fróes L. P. and Rajão K. M. A. B. had the original idea for the present study, supervised the data collecton and reviewed the first draft; Aguiar R. A. L. and Lauria M. W. reviewed the first draft and the final version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Mañé L, Flores-Le Roux JA, Benaiges D, Chillarón JJ, Prados M, Pedro-Botet P. Impact of overt diabetes diagnosed in pregnancy in a multi-ethnic cohort in Spain. Gynecol Endocrinol. 2019;35(04): 332–336. Doi: 10.1080/09513590.2018.1521387

2 Organização Pan-Americana da Saúde, Ministério da Saúde, Federação Brasileira das Associações de Ginecologia e Obstetrícia, Sociedade Brasileira de Diabetes. Rastreamento e diagnóstico de diabetes mellitus gestacional no Brasil [Internet]. Brasília (DF): OPAS; 2017 [cited 2019 Sep 1]. Available from: https://www.diabetes.org.br/profissionais/images/pdf/diabetes-gestacional-relatorio.pdf

3 Ministério da Saúde Secretaria de Vigilância em Saúde Departamento de Análise em Saúde e Vigilândia de Doenças não Transmissíveis. Vigitel Brasil 2018: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2018 [Internet]. Brasília (DF)Editora do Ministério da Saúde2019 [cited 2019 Sep 1]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2019/julho/25/vigitel-brasil-2018.pdf

4 International Diabetes Federation. IDF Diabetes Atlas. 9 th ed. Brussels: IDF; 2019

5 Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet. 2015; 131(Suppl 3):S173–S211. Doi: 10.1016/S0020-7292(15)30033-3

6 Branchtein L, Schmidt MI, Matos MC, Yamashita T, Pousada JM, Duncan BB. Brazilian Gestational Diabetes Study Group. Short stature and gestational diabetes in Brazil. Diabetologia. 2000;43 (07):848–851. Doi: 10.1007/s001250051460

7 Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(03):676–682. Doi: 10.2337/DC09-1848

8 Trujillo J, Vigo A, Reichelt A, Duncan BB, Schmidt MI. Fasting plasma glucose to avoid a full OGTT in the diagnosis of gestational diabetes. Diabetes Res Clin Pract. 2014;105(03):322–326. Doi: 10.1016/j.diabres.2014.06.001

9 Yan J, Yang H, Meng W, Wang Y, Shang L, Cai Z, et al. Abdominal circumference profiles of macrosomic infants born to mothers with or without hyperglycemia in China. J Matern Fetal Neonatal Med. 2020;33(01):149–156. Doi: 10.1080/14767058.2018.1487941

10 Trindade TC. Influência do controle glicêmico no potencial de crescimento fetal em pacientes com diabetes mellitus gestacional [dissertação]. São Paulo: Universidade de São Paulo; 2012

11 Rosati P, Arduini M, Giri C, Guariglia L. Ultrasonographic weight estimation in large for gestational age fetuses: a comparison of 17 sonographic formulas and four models algorithms. J Matern Fetal Neonatal Med. 2010;23(07):675–680. Doi: 10.3109/14767050903410631

12 Czarnobay SA, Kroll C, Schultz LF, Malinovski J, Mastroeni SSBS, Mastroeni MF. Predictors of excess birth weight in Brazil: a systematic review. J Pediatr (Rio J). 2019;95(02):128–154. Doi: 10.1016/j.jped.2018.04.006

13 Gyurkovits Z, Kálló K, Bakki J, Katona M, Bitó T, Pál A, Orvos H. Neonatal outcome of macrosomic infants: an analysis of a two-year period. Eur J Obstet Gynecol Reprod Biol. 2011;159(02): 289–292. Doi: 10.1016/j.ejogrb.2011.08.003

14 Yu L, Zeng XL, Cheng ML, Yang GY, Wang BI, Xiao ZW, et al. Quantitative assessment of the effect of pre-gestational diabetes and risk of adverse maternal, perinatal and neonatal outcomes. Oncotarget. 2017;8(37):61048–61056. Doi: 10.18632/oncotarget.17824

15 Di Giovanni I, Marcovecchio ML, Chiavaroli V, de Giorgis T, Chiarelli F, Mohn A. Being born large for gestational age is associated with earlier pubertal take-off and longer growth duration: a longitudinal study. Acta Paediatr. 2017;106(01): 61–66. Doi: 10.1111/apa.13633

16 Kapral N, Miller SE, Scharf RJ, Gurka MJ, DeBoer MD. Associations between birthweight and overweight and obesity in school-age children. Pediatr Obes. 2018;13(06):333–341. Doi: 10.1111/ijpo.12227

17 Zhang J, Merialdi M, Platt LD, Kramer MS. Defining normal and abnormal fetal growth: promises and challenges. Am J Obstet Gynecol. 2010;202(06):522–528. Doi: 10.1016/j.ajog.2009.10.889

18 Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Jensen LN, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med. 2017;14(01): e1002220. Doi: 10.1371/journal.pmed.1002220

19 Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, et al; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Scientific Advisory Committee Steering Committees INTERGROWTH-21st INTERBIO-21st Executive Committee In addition for INTERBIO 21st Project Coordinating Unit Data Analysis Group Data Management Group In addition for INTERBIO 21st Ultrasound Group In addition for INTERBIO-21st Anthropometry Group In addition for INTERBIO-21st Laboratory Processing Group Neonatal Group Environmental Health Group Neurodevelopment Group Participating countries and local investigators In addition for INTERBIO-21st In addition for INTERBIO-21st. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2017;49(04):478–486. Doi: 10.1002/uog.17347

20 Committee on Obstetric Practice, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine. Committee Opinion No 700: Methods for Estimating the Due Date. Obstet Gynecol. 2017;129(05):e150–e154. Doi: 10.1097/AOG.0000000000002046

21 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2019*. Diabetes Care. 2019;42(Suppl 1):S13–S28. Doi: 10.2337/dc19-S002

22 Ministério da Saúde Secretaria de Atenção à Saúde Departamento de Ações Programáticas Estratégicas. Gestação de alto risco: manual técnico. 5a ed. Brasília (DF): Ministério da Saúde; 2012

23 Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. Radiology. 1984; 150(02):535–540. Doi: 10.1148/radiology.150.2.6691115

24 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(01):159–174. Doi: 10.2307/2529310

25 Barel O, Vaknin Z, Tovbin J, Herman A, Maymon R. Assessment of the accuracy of multiple sonographic fetal weight estimation formulas: a 10-year experience from a single center. J Ultrasound Med. 2013; 32(05):815–823. Doi: 10.7863/ultra.32.5.815

26 Zafman KB, Bergh E, Fox NS. Accuracy of sonographic estimated fetal weight in suspected macrosomia: the likelihood of overestimating and underestimating the true birthweight. J Matern Fetal Neonatal Med. 2020;33(06):967–972. Doi: 10.1080/14767058.2018.1511697

27 Dude AM, Yee LM. Identifying fetal growth disorders using ultrasonography in women with diabetes. J Ultrasound Med. 2018;37(05):1103–1108. Doi: 10.1002/jum.14446

28 Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol. 2005;25(01):80–89. Doi: 10.1002/uog.1751

29 Macaulay S, Munthali RJ, Dunger DB, Norris SA. The effects of gestational diabetes mellitus on fetal growth and neonatal birth measures in an African cohort. Diabet Med. 2018;35(10):1425–1433. Doi: 10.1111/dme.13668

30 Brand JS, West J, Tuffnell D, Bird PK, Wright J, Tilling K, Lawlor DA. Gestational diabetes and ultrasound-assessed fetal growth in South Asian and White European women: findings from a prospective pregnancy cohort. BMC Med. 2018;16(01):203. Doi: 10.1186/s12916-018-1191-7
31 Grantz KL, Hediger ML, Liu D, Buck Louis GM. Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study. Am J Obstet Gynecol. 2018;218(2S, Suppl)S641–55.e28, 655.e28. Doi: 10.1016/j.ajog.2017.11.593
32 Park FJ, de Vries B, Hyett JA, Gordon A. Epidemic of large babies highlighted by use of INTERGROWTH21st international standard. Aust N Z J Obstet Gynaecol. 2018;58(05):506–513. Doi: 10.1111/ajo.12748
33 Heude B, Le Guern M, Forhan A, Scherdel P, Kadawathagedara M, Dufourg MN, et al. Are selection criteria for healthy pregnancies responsible for the gap between fetal growth in the French national Elfe birth cohort and the Intergrowth-21st fetal growth standards? Paediatr Perinat Epidemiol. 2019;33(01):47–56. Doi: 10.1111/ppe.12526
34 Fava GA, Tomba E, Sonino N. Clinimetrics: the science of clinical measurements. Int J Clin Pract. 2012;66(01):11–15. Doi: 10.1111/j.1742-1241.2011.02825.x

The Graduated Embryo Score of Embryos from Infertile Women with and without Peritoneal Endometriosis

Escore embrionário graduado em embriões de mulheres inférteis com e sem endometriose peritoneal

Juliana Caran[1] Vanessa Krebs Genro[1,2] Carlos Augusto Bastos de Souza[1] João Sabino Cunha-Filho[1,2]

[1] Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[2] Department of Obstetrics and Gynecology, Centro de Reprodução Humana Insemine, Porto Alegre, RS, Brazil

Address for correspondence João Sabino Cunha-Filho, MD, PhD, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Av. Protásio Alves, 211, Santa Cecilia, Porto Alegre, RS, 90035-903, Brazil (e-mail: jfilho@hcpa.edu.br).

Rev Bras Ginecol Obstet 2021;43(1):28–34.

Abstract

Objective To determine embryo quality (mean graduated embryo score [GES]) in infertile patients with endometriosis undergoing in vitro fertilization with embryo transfer (IVF-ET) compared with infertile patients without endometriosis.

Methods A case-control study was performed comparing 706 embryos (162 patients) divided into 2 groups: 472 embryos derived from patients without endometriosis ($n = 109$, infertile patients with tubal infertility) and 234 embryos from patients in the study group ($n = 53$, infertile patients with peritoneal endometriosis). All patients were subjected to IVF using an oestradiol-antagonist-recombinant follicle-stimulating hormone (FSH) protocol for ovarian stimulation. The mean GES was performed to evaluate all embryos at 3 points in time: 16 to 18 hours, 25 to 27 hours, and 64 to 67 hours. Embryo evaluation was performed according to the following parameters: fragmentation, nucleolar alignment, polar body apposition, blastomere number/morphology, and symmetry. The primary outcome measure was the mean GES score. We also compared fertilization, implantation, and pregnancy rates.

Results Although the number of embryos transferred was greater in patients with endometriosis than in the control group (2.38 ± 0.66 versus 2.15 ± 0.54; $p = 0.001$), the mean GES was similar in both groups (71 ± 19.8 versus 71.9 ± 23.5; $p = 0.881$). Likewise, the fertilization rate was similar in all groups, being 61% in patients with endometriosis and 59% in the control group ($p = 0.511$). No significant differences were observed in the implantation (21% versus 22%; [$p = 0.989$]) and pregnancy rates (26.4% versus 28.4%; $p = 0.989$).

Conclusion Embryo quality measured by the mean GES was not influenced by peritoneal endometriosis. Likewise, the evaluated reproductive outcomes were similar between infertile patients with and without endometriosis.

Keywords
- endometriosis
- in vitro fertilization
- graduated embryo score
- infertility

received
April 15, 2020
accepted
October 23, 2020

DOI https://doi.org/10.1055/s-0040-1721855.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Resumo

Objetivo Determinar a qualidade do embrião (média de escore embrionário graduado [EEG]) em pacientes inférteis com endometriose submetidas à fertilização in vitro com transferência de embrião (FIV-TE) em comparação com pacientes inférteis sem endometriose.

Métodos Realizamos um estudo de caso-controle comparando 706 embriões (162 pacientes) divididos em dois grupos: 472 embriões derivados de pacientes sem endometriose ($n = 109$, pacientes inférteis com infertilidade tubária) e 234 embriões de pacientes do grupo de estudo ($n = 53$, inférteis pacientes com endometriose peritoneal). Todos os pacientes foram submetidos à fertilização in vitro usando um protocolo *follicle-stimulating hormone* (FSH) recombinante de estradiol-antagonista para estimulação ovariana. A média do EEG foi realizada para avaliar todos os embriões em três momentos: de 16 a 18 horas, 25 a 27 horas e 64 a 67 horas. A avaliação embrionária foi realizada de acordo com os seguintes parâmetros: fragmentação, alinhamento nucleolar, aposição do corpo polar, número de blastômeros/morfologia e simetria. A medida de desfecho primário foi o escore médios embrionário (EEG). Também avaliamos como desfechos secundários as taxas de fertilização, implantação e gravidez.

Resultados Embora o número de embriões transferidos tenha sido maior em pacientes com endometriose do que no grupo controle ($2{,}38 \pm 0{,}66$ versus $2{,}15 \pm 0{,}54$; $p = 0{,}001$), o EEG médio foi semelhante nos dois grupos ($71 \pm 19{,}8$ versus $71{,}9 \pm 23{,}5$; $p = 0{,}881$). Da mesma forma, a taxa de fertilização foi semelhante em todos os grupos, sendo 61% nos pacientes com endometriose e 59% no grupo controle ($p = 0{,}511$). Não foram observadas diferenças significativas nas taxas de implantação (21% versus 22%; [$p = 0{,}989$]) e nas taxas de gravidez (26,4% versus 28,4%; $p = 0{,}989$).

Conclusão A qualidade embrionária medida pelo EEG médio não foi influenciada pela endometriose peritoneal. Da mesma forma, os resultados reprodutivos avaliados foram semelhantes entre pacientes inférteis com e sem endometriose.

Palavras-chave

- endometriose
- fertilização in vitro
- escore do embrião
- infertilidade

Introduction

In vitro fertilization with embryo transfer (IVF-ET) has been prescribed in many cases of endometriosis-associated infertility. This process has enabled us to study how this disease affects a patient's fertility and IVF outcomes.[1–3]

Although previous studies on IVF outcomes have produced controversial results, it has been shown that patients with endometriosis have altered hormonal status, luteal phase deficiency, and folliculogenesis, as well as oocyte dysfunction, which may affect their embryo quality.[4–8] Recently, several new studies have failed to identify a clear link between endometriosis and decreased IVF results.[3,9,10]

Embryo quality evaluation for the selection and transfer into the uterus is a critical step in IVF treatment to maximize the probability of pregnancy, especially when we choose to transfer only one embryo.[11,12] Previous retrospective studies have evaluated embryo quality in patients with endometriosis and observed a decrease in their morphological parameters, as well as a higher percentage of abnormal embryos in these patients.[13,14] Furthermore, several recent studies have shown a decreased oocyte quality and number in endometriotic patients. Nevertheless, when analyzing embryo development, the effect of endometriosis has not been thoroughly elucidated to date.[15,16]

The graduated embryo score (GES) is a system of classification that relies on a combination of pronuclear morphology, early cleavage and day 3 morphology used to identify which embryos have a high potential for blastocyst conversion, as well as a higher probability of implantation and pregnancy. The present system is based on three evaluations for embryo assessment after insemination and awards a total possible score of 100 points.[12]

The primary objective of this study was to verify if the embryo quality based on the mean GES scoring is different between infertile patients with peritoneal endometriosis and patients in the control group (tubal infertility). In addition, as secondary objectives, we compared several reproductive outcomes, such as implantation, fertilization, and pregnancy rates, between the groups.

Methods

Design

We performed a prospective case-control study.

Setting

Infertile patients undergoing in vitro fertilization treatment at the Insemine Center for Human Reproduction, in Brazil, were

recruited from 2010 to 2015. The patients were followed-up during the controlled ovarian stimulation until 12 days after the embryo transfer (first pregnancy test), and data collection was performed in the initial assessment (first ultrasound scan) and the laboratory results (embryo score as described below).

Patients/Methods

A total of 162 women who underwent IVF-ET for the treatment of infertility in our unit were included. The patients were divided into two groups according to the presence (study group) or absence (control group, tubal occlusion) of endometriosis, after signing the free informed consent form. The eligibility criteria were: infertile women with endometriosis or tubal factor submitted to IVF for the first time, ages between 20 and 40 years old, no active use of tobacco, BMI < 30 Kg/m^2, no active inflammatory pelvic disease in the year prior to IVF, and no presence of hydrosalpinx. The study group was comprised of infertile women with proven (laparoscopy and biopsy, at least 6 months prior to in vitro fertilization) endometriosis according to the American Society for Reproductive Medicine classification (ASRM) (1997).[17] The included patients presented only peritoneal endometriosis. The control group was comprised of infertile patients with tubal factor confirmed by laparoscopy. The exclusion criteria were: no evidence of autoimmune disease, patients negative for anti-thyroid antibodies, normal serum prolactin, thyroid-stimulating hormone, diagnosis of endometrioma or ovarian cyst, a poor response to ovulation induction, the presence of moderate/severe male factor, intracytoplasmic sperm injection during IVF treatment, and polycystic ovary syndrome. All patients were submitted to laparoscopy during their infertility investigation as previously mentioned.

Ovarian Stimulation

An oestradiol-antagonist-recombinant follicle-stimulating hormone (FSH) protocol was used for ovulation induction in all patients. Briefly, 4 mg/day oestradiol was initiated on the 20th day of the preceding cycle. Gonadotropin was initiated at a standard dose of 225 UI of recombinant FSH (Puregon, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) applied subcutaneously (SC) on the second day of the current cycle. From the 6th day of recombinant FSH therapy onwards, the daily FSH doses were adjusted according to oestradiol levels and/or the number of growing follicles. Hormone serum levels of oestradiol, progesterone, and luteinizing hormone (LH) were evaluated, as was the follicular response, which was estimated by transvaginal ultrasound scans. The use of antagonist (Orgalutran, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) started on day 6 of the treatment cycle. When three or more follicles reached a size ≥ 17 mm, the final oocyte maturation was induced with a subcutaneous injection of human chorionic gonadotropin (hCG). Oocyte pick up under general anesthesia followed 36 hours later. Embryo transfer was performed on day 3 after insemination.

Risk of Bias

We controlled the risk of bias using a strict eligibility and exclusion criteria as described before. Moreover, we performed a baseline group comparison and a multivariable analysis to detect any differences between both groups.

Embryo Quality (Embryo Score)

The GES was performed based on three evaluations occurring at 16 to 18 hours, 25 to 27 hours and 64 to- 67 hours post-insemination by the same embryologist. The score was composed of the following criteria: nucleolar alignment along pronuclear axis, regular cleavage and degree of fragmentation at the first cell division, and cell number and morphology on day 3 after insemination. The mean score was calculated by the sum of the embryo scores divided by the number of obtained embryos, and the mean transferred embryo score was calculated by the sum of GES divided by the number of transferred embryos (►**Fig. 1**).

Statistical Analysis

Absolute data were analyzed with the chi-square test or Fisher exact test. Continuous variables were compared using the Student *t*-test or analysis of variance (ANOVA). Multivariable analysis was done using linear or binary regression, controlling embryo score for endometriosis, body mass index (BMI), age, infertility length and number of retrieved oocytes. Data were analyzed using the SPSS Version 18.0 software package (SPSS Inc., Chicago, IL, USA). Significance was set at $p < 0.05$. Sample size was calculated from a pilot study conducted in 2009, and 70 patients were needed to have a 90% chance of detecting, at a 5% significance level, a decrease in the primary outcome measure from 92 in the control group to 85 in the experimental group.[18] In this pilot study, developed by Genro et al. (2009),[11] a GES value of 92 ± 12 was recorded in the control group without endometriosis, compared with 85 ± 9 in those infertile patients with endometriosis.

Fig. 1 Embryos with 100, 80, 60, and 40 points according to the graduated embryo score.

Ethics

This study was approved by the Ethical Committee of Hospital de Clínicas de Porto Alegre (IRB equivalent, #2002–0329). We utilized the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for observational studies.[19]

Results

We assessed 170 eligible patients and excluded 8 (3 with endometrioma and 5 with polycystic ovary syndrome). Thus, we compared and analyzed 53 patients in the endometriosis group and 109 patients in the control group (►**Figure 2**). During the study period, 706 fertilized embryos were produced from 162 patients undergoing the IVF-ET procedure for infertility treatment. Of these embryos, 234 corresponded to patients with a diagnosis of endometriosis, and 472 corresponded to those from the control group. Of these embryos, 360 were transferred to the uterus on day 3 after insemination.

In the endometriosis group ($n = 53$), 26 patients were classified as having grade I severity (minimal endometriosis), 13 as having grade II severity (mild endometriosis), 5 as having grade III severity (moderate endometriosis), and 9 as having grade IV severity (severe endometriosis). The clinical characteristics of both groups are shown in ►**Table 1**. One thousand and nine oocytes were retrieved during the study period, of which 42% (424) were collected in the study group, and 58% (858) were collected in the control group.

Table 1 Subjects characteristics and laboratory/clinical outcomes of control and endometriosis groups (mean ± standard deviation) ($n = 162$)

	Control group n = 109	Endometriosis group n = 53	*p*-value*
Age (years)	33.6 ± 5.61	33.0 ± 3.84	0.43
BMI (kg/m^2)	23.6 ± 3.96	23.8 ± 2.93	0.80
Menarche (years)	12.5 ± 1.5	12.5 ± 1.2	0.90
Parity (n)	0.43 ± 0.82	0.17 ± 0.43	0.29
Abortion (n)	0.16 ± 0.46	0.15 ± 0.41	0.76
Time of infertility (months)	47.5 ± 45.3	48.5 ± 31.2	0.89
Mean GES	71.9 ± 23.5	71 ± 19.8	0.801
AFC (n)	11.6 ± 6.9	11.5 ± 4.8	0.93
FSH (mUI/mL)	7.4 ± 4.6	6.4 ± 2.0	0.62
TSH (mUI/mL)	2.51 ± 1.77	2.28 ± 1.18	0.38
Prolactin (ng/mL)	17.9 ± 12.9	14.4 ± 7.3	0.50
Estradiol (pg/mL)	61.3 ± 43.2	46.5 ± 25.1	0.25
Total gonadotropin dose (UI)	2,634 ± 785.8	2,777 ± 711.8	0.27
Number of oocytes retrieved (n)	8.48 ± 4.2	8.38 ± 3.1	0.86

Abbreviations: AFC, antral follicle count; BMI, body mass index; FSH, follicle-stimulating hormone; Mean GES, mean graduated embryo score; TSH, thyroid-stimulating hormone.
*Student t-test.

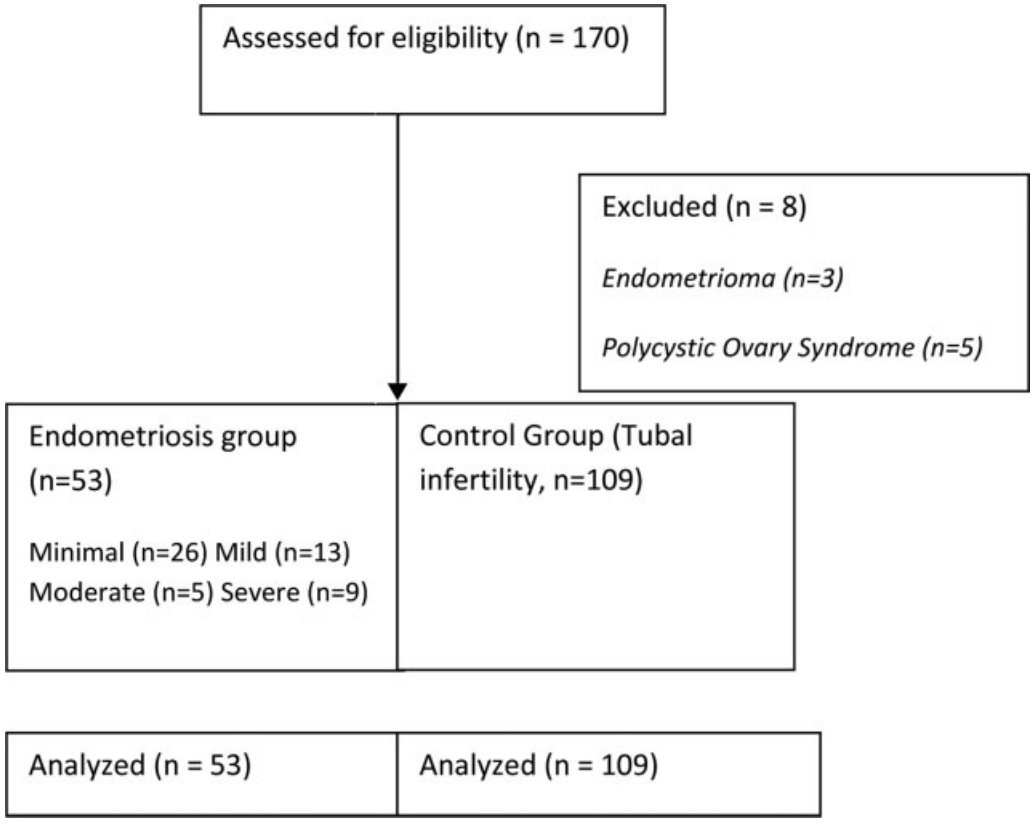

Fig. 2 Study flowchart.

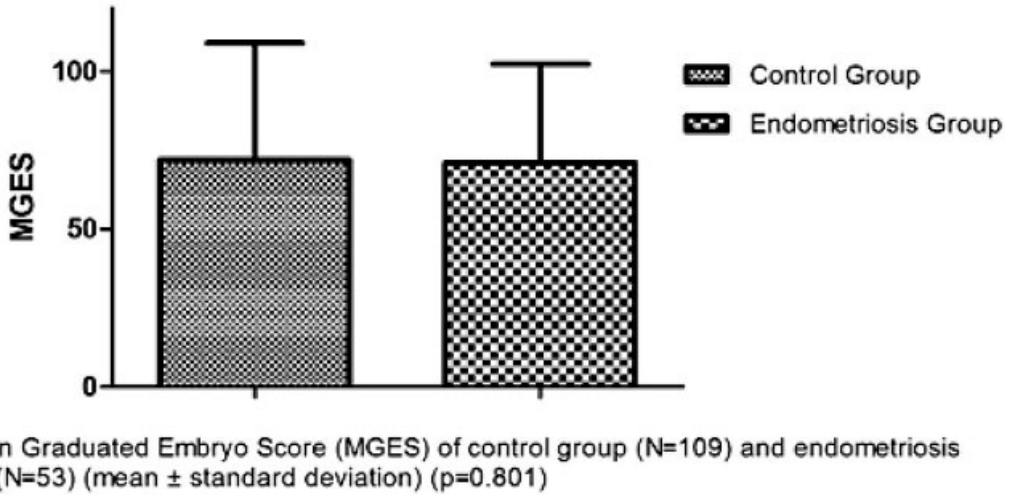

Fig. 3 Mean graduated embryo score of control group and endometriosis group.

Groups were compared according to their infertility characteristics (primary or secondary), with no significant difference being observed between groups ($p = 0.295$). The abortion rate was similar in patients in the control group (12.8%, $n = 14$) and in those with endometriosis (13.2%, $n = 7$). There was no statistically significant difference for this endpoint ($p = 0.767$).

The number of embryos obtained was similar in both groups (4.42/patient in study group and 4.33/patient in control group, $P > 0.05$). However, the number of transferred embryos in patients with endometriosis (2.38 ± 0.66) was significantly higher compared with the control group (2.15 ± 0.54; $p = 0.001$).

The mean GES of transferred embryos was 71 ± 19.8 in infertile patients with endometriosis and 71.9 ± 23.5 in patients from the control group (Graph 1), and there was no significant difference ($p = 0.801$). When the different degrees of endometriosis were compared (ANOVA test), this study found the following scores: grade I (66 ± 18; $n = 26/53$); grade II (76.4 ± 24.7; $n = 13/53$); grade III (70 ± 9.2; $n = 5/53$); and grade IV (80 ± 19.6; $n = 9/53$), $P > 0.05$ (►**Figure 3**).

With regard to the GES of all embryos obtained, there was no difference when comparing the control and study groups. There was also no difference observed when comparing patients with endometriosis according to the degree of severity of the disease. The observed values according to different grades were as follows: grade I (62.3 ± 21); grade II (63.7 ± 19); grade III (63.8 ± 20); and grade IV (66.8 ± 16), with $p = 0.945$, ANOVA test.

To check for differences between the groups, we performed a secondary analysis considering that embryos with scores higher than 70 points have a higher implantation rate (11). Among the 109 control patients, 42 (38.5%) had mean GES scores greater than 70 compared with 20 patients from the 53 patients with endometriosis (37.7%). There was no significant difference between groups ($p = 0.888$).

The fertilization rate was similar between both groups, corresponding to 61% of patients with endometriosis and 59% of the control group ($p = 0.511$). Similarly, there was no difference between the study and control groups in terms of the cleavage rates, which were 89% and 90%, respectively ($p = 0.713$). Among the patients with different degrees of endometriosis, the fertilization ($p = 0.976$) and cleavage rates were also similar ($p = 0.432$).

There was no statistically significant difference between patients with and without endometriosis with regard to their implantation rates, which corresponded to 21% and 22%, respectively ($p = 0.989$). The pregnancy rates were (26% *vs* 28%) similar between the groups ($p = 0.853$).

Discussion

Several studies have suggested that endometriosis may impair fertility through different pathways, such as hormonal unbalance, oocyte dysfunction and endometrial receptivity.[6,7,20] We investigated if patients with this disease exhibit altered embryo quality when assessed based on the mean GES score system. We observed that the presence of endometriosis in infertile patients undergoing in vitro fertilization does not affect the mean GES. There were no previous reports in the literature comparing the use of GES between infertile patients with and without endometriosis (with tubal infertility). Moreover, we utilized the mean score because this is not affected by the embryo number. Therefore, the most important variable is the embryo quality, as measured by the mean score and not the number of embryos.

Altered embryo quality diagnosed by an abnormal embryo development and embryo blockage in patients with endometriosis has been described in the literature by several authors.[21,22] Moreover, these data have been supported by other studies on oocyte donation programmes.[13] However, several papers have reported that endometriosis does not affect embryo development or pregnancy rates. The most important and relevant aspect of endometriosis related infertility in patients submitted to in vitro fertilization is a drop in the ovarian reserve, causing a decreased number of oocytes after controlled ovarian stimulation for in vitro fertilization cycle.[3,8,9]

Embryo selection for transfer is a critical step in in vitro fertilization treatment to optimize implantation rates and, finally, patient's pregnancy chance. Correctly evaluating the embryo quality before transfer is, therefore, of critical importance.[23–25] Thus, understanding if and how endometriosis affects the embryo quality may help clinicians in making everyday decisions.

In our population, although the number of embryos obtained was similar between the groups, we transferred a higher number of embryos in patients with endometriosis, as shown by others investigators.[16] Although we have found no difference in the implantation and pregnancy rates, the initial choice for this management was based on previous data, suggesting lower implantation and pregnancy rates in this group of patients.[5]

The number of retrieved oocytes, fertilization rates, and total number of transferred embryos were similar in infertile patients with and without endometriosis. These findings were disputed by others with conflicting results.[3,9,26] The heterogeneity of patients, the difficulty in standardizing laboratory routines, and the presence of outcomes assessed in different ways between studies are limiting factors, and any results must, therefore, be critically evaluated.

Endometriosis has a wide spectrum of symptoms, and there is no consensus regarding how the different stages of the disease may affect women's fertility. Our population is composed predominantly of patients with minimal and mild disease, and we have not included patients with endometriomas. We have chosen to exclude patients with endometrioma to obtain an homogeneous and representative sample of patients with peritoneal endometriosis; however, it may have lowered our results and explain, at least partly, the lack of difference found in our sample. Moreover, patients with a poor response toward ovarian stimulation had their cycles cancelled before oocyte pickup and were excluded from our sample, as embryo quality analysis was not possible. This finding may mean that the most severe cases are not represented in our paper.

Furthermore, the embryo scores we have chosen to use to evaluate embryo competence involves considerable subjectivity. We have attempted to control for this factor by having a single observer perform all analysis in our study. The development of a scoring method for embryo evaluation on the third day after insemination or on blastocyst stage with higher reproducibility may be necessary to detect more subtle differences. The usefulness of comparing the mean embryo score instead of the total number of embryos per patient is to control for the effect of the individual number of embryos.[12]

Our study has some flaws that we should discuss: a) we included only peritoneal endometriosis, which represents 70% of endometriosis phenotypes and, consequently, excluded the more severe forms of endometriosis; b) nowadays, embryo quality could be better evaluated using a time-lapse/artificial intelligence; however, this is a new and expensive technique for the majority of in vitro fertilization centers; c) our sample size was calculated using embryo score as the primary endpoint, but for comparisons of pregnancy or implantation rates our study was underpowered; d) the fact of including only peritoneal endometriosis could represent an early endometriosis presentation if compared with endometrioma. Therefore, we should analyze with caution our findings before extrapolating to all endometriosis phenotypes.

Conclusion

In conclusion, the presence of peritoneal endometriosis in infertile patients submitted for IVF-ET did not affect embryo quality when measured by the mean GES. Further studies involving different scoring methods and mechanisms involved in the subfertility of patients with endometriosis are warranted.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Falconer H, Sundqvist J, Gemzell-Danielsson K, von Schoultz B, D'Hooghe TM, Fried G. IVF outcome in women with endometriosis in relation to tumour necrosis factor and anti-Müllerian hormone. Reprod Biomed Online. 2009;18(04):582–588. Doi: 10.1016/s1472-6483(10)60138-1

2 Mekaru K, Yagi C, Asato K, Masamoto H, Sakumoto K, Aoki Y. Effects of early endometriosis on IVF-ET outcomes. Front Biosci (Elite Ed). 2013;5:720–724. Doi: 10.2741/e652

3 González-Comadran M, Schwarze JE, Zegers-Hochschild F, Souza MD, Carreras R, Checa MA. The impact of endometriosis on the outcome of Assisted Reproductive Technology. Reprod Biol Endocrinol. 2017;15(01):8. Doi: 10.1186/s12958-016-0217-2

4 Hu Y, Maxson WS, Hoffman DI, Ory SJ, Eager S, Dupre J, Lu C. Maximizing pregnancy rates and limiting higher-order multiple conceptions by determining the optimal number of embryos to transfer based on quality. Fertil Steril. 1998;69(04):650–657. Doi: 10.1016/s0015-0282(98)00024-7

5 Coccia ME, Rizzello F, Mariani G, Bulletti C, Palagiano A, Scarselli G. Impact of endometriosis on in vitro fertilization and embryo transfer cycles in young women: a stage-dependent interference. Acta Obstet Gynecol Scand. 2011;90(11):1232–1238. Doi: 10.1111/j.1600-0412.2011.01247.x

6 De Conto E, Matte U, Cunha-Filho JS. BMP-6 and SMAD4 gene expression is altered in cumulus cells from women with endometriosis-associated infertility. Acta Obstet Gynecol Scand. 2020; •••;. Doi: 10.1111/aogs.13931 [ahead of print]

7 De Conto E, Matte Ú, Bilibio JP, Genro VK, Souza CA, Leão DP, Cunha-Filho JS. Endometriosis-associated infertility: GDF-9, AMH, and AMHR2 genes polymorphisms. J Assist Reprod Genet. 2017;34(12):1667–1672. Doi: 10.1007/s10815-017-1026-z

8 Lemos NA, Arbo E, Scalco R, Weiler E, Rosa V, Cunha-Filho JS. Decreased anti-Müllerian hormone and altered ovarian follicular cohort in infertile patients with mild/minimal endometriosis. Fertil Steril. 2008;89(05):1064–1068. Doi: 10.1016/j.fertnstert.2007.04.048

9 Barbosa MAP, Teixeira DM, Navarro PA, Ferriani RA, Nastri CO, Martins WP. Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014;44(03):261–278. Doi: 10.1002/uog.13366

10 Yang X, Huang R, Cai M, Liang X. Endometriosis has no negative impact on outcomes of in vitro fertilisation in women with poor ovarian response. BJOG. 2016;123(Suppl 3):76–81. Doi: 10.1111/1471-0528.14018

11 Genro V, Souza C, Guedes da Luz L, Silva D, Andreoli C, Cunha-Filho J. The graduated embryo score (GES) and total graduated embryo score (TGES) were not associated to endometriosis. Fertil Steril. 2009;92(03):S112–S113. Doi: 10.1016/j.fertnstert.2009.07.1103

12 Fisch JD, Rodriguez H, Ross R, Overby G, Sher G. The Graduated Embryo Score (GES) predicts blastocyst formation and pregnancy rate from cleavage-stage embryos. Hum Reprod. 2001;16(09):1970–1975. Doi: 10.1093/humrep/16.9.1970

13 Garrido N, Navarro J, García-Velasco J, Remoh J, Pellice A, Simón C. The endometrium versus embryonic quality in endometriosis-related infertility. Hum Reprod Update. 2002;8(01):95–103. Doi: 10.1093/humupd/8.1.95

14 Simón C, Gutiérrez A, Vidal A, de los Santos MJ, Tarín JJ, Remohí J, Pellicer A. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum Reprod. 1994;9(04):725–729. Doi: 10.1093/oxfordjournals.humrep.a138578

15 Cohen J, Ziyyat A, Naoura I, Chabbert-Buffet N, Aractingi S, Darai E, Lefevre B. Effect of induced peritoneal endometriosis on oocyte and embryo quality in a mouse model. J Assist Reprod Genet. 2015;32(02):263–270. Doi: 10.1007/s10815-014-0390-1

16 Shebl O, Sifferlinger I, Habelsberger A, Oppelt P, Mayer RB, Petek E, Ebner T. Oocyte competence in in vitro fertilization and intracytoplasmic sperm injection patients suffering from endometriosis and its possible association with subsequent treatment outcome: a matched case-control study. Acta Obstet Gynecol Scand. 2017;96(06):736–744. Doi: 10.1111/aogs.12941

17 Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67(05):817–821. Doi: 10.1016/s0015-0282(97)81391-x

18 Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004;23(12):1921–1986. Doi: 10.1002/sim.1783

19 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JPSTROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(04):344–349. Doi: 10.1016/j.jclinepi.2007.11.008

20 Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A. Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril. 2008;90(02):247–257. Doi: 10.1016/j.fertnstert.2008.02.093

21 Brizek CL, Schlaff S, Pellegrini VA, Frank JB, Worrilow KC. Increased incidence of aberrant morphological phenotypes in human embryogenesis–an association with endometriosis. J Assist Reprod Genet. 1995;12(02):106–112. Doi: 10.1007/BF02211378

22 Pellicer A, Valbuena D, Bauset C, Albert C, Bonilla-Musoles F, Remohí J, Simón C. The follicular endocrine environment in stimulated cycles of women with endometriosis: steroid levels and embryo quality. Fertil Steril. 1998;69(06):1135–1141. Doi: 10.1016/S0015-0282(98)00085-5

23 Sjöblom P, Menezes J, Cummins L, Mathiyalagan B, Costello MF. Prediction of embryo developmental potential and pregnancy based on early stage morphological characteristics. Fertil Steril. 2006;86(04):848–861. Doi: 10.1016/j.fertnstert.2006.03.040

24 Terriou P, Sapin C, Giorgetti C, Hans E, Spach JL, Roulier R. Embryo score is a better predictor of pregnancy than the number of transferred embryos or female age. Fertil Steril. 2001;75(03):525–531. Doi: 10.1016/s0015-0282(00)01741-6

25 Luna M, Copperman AB, Duke M, Ezcurra D, Sandler B, Barritt J. Human blastocyst morphological quality is significantly improved in embryos classified as fast on day 3 (>or=10 cells), bringing into question current embryological dogma. Fertil Steril. 2008;89(02):358–363. Doi: 10.1016/j.fertnstert.2007.03.030

26 Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril. 2002;77(06):1148–1155. Doi: 10.1016/s0015-0282(02)03112-6

Residual Disease after Operative Hysteroscopy in Patients with Endometrioid Endometrial Cancer Associated with Polyps

Doença residual após histeroscopia cirúrgica em pacientes com câncer de endométrio endometrioide associado a pólipo endometrial

Marcelo Simonsen[1] Henrique Mantoan[2] Carlos Chaves Faloppa[2] Lillian Yuri Kumagai[2] Levon Badiglian Filho[2] Andrea Guerreiro Machado[1] Najla Mohamed Tayfour[1] Glauco Baiocchi[2]

[1] Department of Gynecologic Oncology, Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo, São Paulo, SP, Brazil
[2] Department of Gynecologic Oncology, Hospital AC Camargo, São Paulo, SP, Brazil

Address for correspondence Marcelo Simonsen, Rua Pedro de Toledo, 1800, Vila Clementino, São Paulo, SP, 04039-000, Brazil (e-mail: drmarcelosimonsen@gmail.com).

Rev Bras Ginecol Obstet 2021;43(1):35–40.

Abstract

Objective To evaluate the presence of residual disease in the uterine specimen after hysteroscopic polypectomy or polyp biopsy in patients with endometrioid endometrial cancer (EC).

Methods We analyzed a series of 104 patients (92 cases from the Hospital AC Camargo and 12 from the Hospital do Servidor Público Estadual de São Paulo) with polyps that were diagnosed by hysteroscopy, showing endometrioid EC associated with the polyp or in the final pathological specimen. Patients underwent a surgical approach for endometrial cancer from January 2002 to January 2017. Their clinical and pathological data were retrospectively retrieved from the medical records.

Results In 78 cases (75%), the polyp had EC, and in 40 (38.5%), it was restricted to the polyp, without endometrial involvement. The pathologic stage was IA in 96 cases (92.3%) and 90 (86.5%) had histologic grade 1 or 2. In 18 cases (17.3%), there was no residual disease in the final uterine specimen, but only in 9 of them the hysteroscopy suggested that the tumor was restricted to the polyp. In 5 cases (4.8%) from the group without outside of the polyp during hysteroscopy, myometrial invasion was noted in the final uterine specimen. This finding suggests the possibility of disease extrapolation through the base of the polyp.

Conclusion Patients with endometrioid EC associated with polyps may have the tumor completely removed during hysteroscopy, but the variables shown in the present study could not safely predict which patient would have no residual disease.

Keywords
- endometrial neoplasm
- hysteroscopy
- endometrial polyp

received
February 26, 2020
accepted
September 14, 2020

DOI https://doi.org/10.1055/s-0040-1719145.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Resumo

Objetivo Avaliar a presença de doença residual no exame anatomopatológico definitivo de pacientes com câncer de endométrio endometrioide após polipectomia ou biópsia de pólipo histeroscópica.

Métodos Analisamos 104 pacientes (92 casos do Hospital AC Camargo e 12 casos do Hospital do Servidor Público Estadual de São Paulo) com pólipos diagnosticados durante histeroscopia e cuja biópsia histeroscópica ou exame patológico final do útero acusaram câncer de endométrio endometrioide. As pacientes foram submetidas a cirurgia para câncer de endométrio de janeiro de 2002 a janeiro de 2017. Os dados clínicos e anatomopatológicos de cada paciente foram retirados dos prontuários médicos

Resultados Em 78 casos (75%), o pólipo continha a neoplasia, e em 40 (38.5%), ela estava restrita ao tecido do pólipo, sem envolvimento endometrial adjacente. O estadio final foi IA em 96 casos (92.3%) e em 90 (86.5%) tratava-se de grau 1 ou 2. Em 18 casos (17.3%), não havia doença residual no espécime uterino, mas em apenas 9 deles a histeroscopia sugeriu doença restrita ao pólipo. Em 5 casos (4.8%), não havia doença aparente extrapólipo na histeroscopia, mas havia invasão miometrial, sugerindo extravasamento do tumor pela base do pólipo.

Conclusão Pacientes com câncer de endométrio associado a pólipos podem ter o tumor completamente removido durante a histeroscopia, mas, com as variáveis avaliadas, é difícil predizer com segurança qual paciente ficará sem tumor residual.

Palavras-chave

- câncer de endométrio
- histeroscopia
- pólipo endometrial

Introduction

Patients with endometrial cancer (EC) present with polyps at the time of diagnosis between 10 and 30% of the cases.[1,2] If the tumor originates from a typical polyp, it is described as a neoplastic polyp, but if the cancer acquires a polypoid configuration, it is classified as a polypoid cancer.[2] Patients with concomitant endometrial polyps and cancer usually present in earlier stages than those with tumors that are not associated with a polyp.[1]

Molecularly, the epithelium of the polyp differs from that of the endometrium,[3,4] but can be as prone to carcinogenesis as the normal endometrium.[1] Although the risk factors for endometrial neoplasms are the same for polyps and normal endometrium,[1,5] the histological findings of the polyp might not reflect the condition of the adjacent endometrium.[5]

Few studies have described the aggressiveness of a tumor that is associated with polyps.[1,6] In the case of EC in a polyp, the thickness of the parenchyma of the polyp can be a protective factor against myometrial invasion, based on reports of the absence of residual disease after polypectomy in patients with EC.[1,2]

Atypical hyperplasia in a polyp usually requires a more conservative treatment.[7,8] Even histologically high-grade cancer that originates in a polyp can present as confined uterine disease[9] and thus receive less adjuvant treatment.[10] Moreover, endometrioid tumors appear to be less aggressive when they are restricted to a polyp,[11] but studies that have characterized such tumors are lacking.

Our aim was to correlate the location of endometrioid EC (within the polyp and/or the adjacent endometrium) with clinical and pathological factors, trying to find a subgroup of patients prone to the absence of residual neoplasia in the final uterine specimen.

Methods

We analyzed a sequential series of 104 patients (92 cases from the Hospital AC Camargo and 12 from the Hospital do Servidor Público Estadual de São Paulo) who had presented endometrial polyps in the hysteroscopy and undergone surgery for EC from January 2002 to January 2017. Clinical and pathological data were retrospectively retrieved from their medical records. The respective institutional ethical review boards approved the present study (approval CAAE numbers 70580117.9.1001.5463/ 70580117.9.2001.5432).

We included patients with polyps and a diagnosis of EC. The diagnosis was achieved by hysteroscopic biopsy/polypectomy or defined after hysterectomy, based on the definitive pathologic uterine specimen. Patients with nonendometrioid tumors were excluded. Staging and grade were defined according to the International Federation of Gynecology and Obstetrics (FIGO) classification.[12]

A database was constructed using SPSS for Mac, version 20.0 (SPSS, Inc., Chicago, IL, USA). The chi-squared and Fisher exact tests were used to analyze the correlations between categories and clinicopathological variables. For all tests, an α error of up to 5% ($p < 0.05$) was considered significant.

Table 1 Clinical and pathological variables of the 104 patients with a diagnosis of endometrial polyps and cancer

Clinical variables	n = 104	%
Age - years old (mean)	58	
Menopause	87	83.7
Bleeding	61	58.1
Lymph node dissection	75	72.1
Absence of residual tumor	18	17.3

Results

The clinical and pathological characteristics are summarized in ►**Table 1**. Menopause was described in 87 patients (83.7%), and the main symptom was vaginal bleeding. A high percentage of patients had lymph node dissection (72%), but no cases of lymph node involvement were observed.

►**Table 2** lists the pathological variables according to the location of the tumor. In 78 cases (75%), the EC involved the polyp and the adjacent endometrium and in 40 (38.5%), it was restricted to the polyp, with no endometrial involvement. Moreover, in 16 cases (15.3%), the EC involved only the adjacent endometrium. In 10 (9.6%) cases, the polyp biopsy showed atypical hyperplasia and EC was detected only in the final pathological specimen. There was no correlation between the presence of postmenopausal bleeding and the exact location of the EC ($p = 0.42$).

Most cases ($n = 96$; 92.3%) were classified as stage IA and 90 (86.5%) were classified as grade 1 or 2. In 18 cases (17.3%), there was no residual tumor in the definitive hysterectomy specimen (►**Table 3**); however, of the 40 cases in which the tumor was apparently restricted to the polyp, 5 (12.5%) showed deep myometrial invasion in the definitive uterine specimen.

Cancer that was localized in the polyp by hysteroscopy was unrelated to a higher percentage of final specimens without disease (►**Table 3**). Even when cases with tumor involvement outside of the polyp were grouped, there was no significant impact on the presence of residual disease ($p = 0.20$). Moreover, there was no significant association between polyp-restricted tumors and early-stage disease ($p = 0.13$). Grade 3 tumors occurred irrespective of the precise location of the neoplasm. Of the 14 high-grade tumors (13.4%), 3 were IB tumors (►**Table 3**). Complete removal (with no residual disease) of the 14 grade 3 tumors by hysteroscopy was achieved in 5 patients (35.6%) and in 13 of the 90 grade 1 or 2 tumors (14.4%) ($p = 0.064$).

Table 2 Symptoms and hysteroscopic findings of the 104 patients with a diagnosis of endometrial polyps and cancer

Data	Status	Polyp involvement ($n = 40$)	Polyp and endometrial involvement ($n = 38$)	Endometrial involvement ($n = 16$)	Neoplasm only in final specimen (10)	*p-value*
Bleeding	Yes	24	25	8	4	0.42
	No	16	13	8	6	
Number of polyps	1	17	16	8	3	0.25
	2	6	2	0	3	
	3+	4	6	0	0	
	Not described	13	14	8	4	
Polyp procedure	Excision	18	28	7	4	0.59
	Biopsy	3	4	1	2	
	not described	19	6	8	4	

Table 3 Final pathological report variables of the 104 patients with a diagnosis of endometrial polyps and cancer

Data	Status	Polyp involvement ($n = 40$)	Polyp and endometrial involvement ($n = 38$)	Endometrial involvement ($n = 16$)	Neoplasm only in final specimen ($n = 10$)	Total	*p-value*
Residual tumor	Absent	9	6	3	0	18	0.45
	Present	31	32	13	10	86	
Stage	IA	35	35	16	10	96	0.48
	IB	5	3	0	0	8	
Grade	1	18	22	10	9	59	0.32
	2	14	12	4	1	31	
	3	8	4	2	0	14	

Discussion

Several studies have evaluated concomitant EC and endometrial polyps,[1,4,13] but this group of patients must be better characterized, aiming to tailor surgery and adjuvant treatment. The present study was performed at 2 cancer centers, where besides oncologic treatment, hysteroscopies are also usually performed to diagnose endometrial diseases.

The mean age and menopausal status of our patients were similar to those in previous studies.[14–16] We recorded a higher rate of asymptomatic patients, compared with previous studies,[17,18] concluding that hysteroscopic investigation of polyps can identify cases of initial EC, even in patients who still have no symptoms, such as vaginal bleeding.[1,19,20] Indeed, cancer that is associated with polyps appears to present at earlier stages, compared with those that do not,[1] but this probably does not cause an impact on survival rates.[21]

The diagnosis of cancer as an unexpected finding occurred in 9.6% of the patients. They had undergone a pathological examination of polyps, which suggested a benign alteration (atypical hyperplasia), but the definitive pathological report described adenocarcinoma. This finding has been corroborated by other studies.[7,8,22] This situation was less frequent than that reported in the GOG 167, in which the prevalence of endometrial cancer after hysterectomy with atypical hyperplasia was 42.6%.[23] Notably, a systematic review confirmed that when the atypical hyperplasia is restricted to polyps, $< 10\%$ of the final specimen would be expected to have cancer.[7]

At least 10 studies have evaluated definitive pathological reports of patients with an endometrial tumor that involved polyps (►**Table 4**). The criteria for patient selection varied significantly among studies, with some having a hysteroscopic focus[1,24,25] and others evaluating oncological outcomes and detailing the staging and follow-up.[2,5,6,26–29]

In our series, when the polyp was associated with cancer, the tumor in most cases involved the polyp, (78 cases, 75%), but in 38.5%, it was restricted to the polyp and in 36.5%, there was also endometrial involvement. With our findings, it was not possible to establish whether the malignancy is more likely to affect the polyp tissue or the adjacent endometrium. Conversely, our data suggest that the tumor randomly affects the adjacent polyp or the endometrium. Similarly, Farrell et al.[2] reported the involvement of the adjacent endometrium in 61.5% (16/26) of cases and 6 cases had no residual disease in the final pathologic uterine specimen (23%).

Complete removal of the polyp when the tumor was restricted to the polyp was achieved in 18/40 cases (45%), but only in 9 (50%) of them it resulted in a uterine specimen without cancer. This finding suggests that hysteroscopy is not very accurate for distinguishing neoplastic tissue and that the complete resection of the polyp does not always match the definitive pathological result.[27]

It is possible that an early neoplasm, opportunistically diagnosed in asymptomatic patients, allows for the tumor to be resected entirely by hysteroscopy. If the disease develops, it is expected that tumors that are initiated in pre-existing polyps will affect the base of the polyp and the endometrium. In this context, it would no longer be possible to distinguish the neoplastic polyp from a polypoid neoplasm.[2]

It is more difficult for extra-polyp disease to be removed by hysteroscopy, but 6 (15.7%) of 38 patients in this group had a definitive uterine specimen without cancer. Removal of all EC tissue by hysteroscopy was reported previously in some exceptional situations.[28,30]

Almost all the series described tumors with stages $>$ IA (►**Table 4**), with the prevalence ranging between 0 and 30%, and some of them have also described stages II-IIIA.[1,6,26] Although in the present study and in most of the previous

Table 4 Previous studies with endometrioid uterine neoplasms associated with polyps

	n	n (%) Restricted to polyps in hysteroscopy	Grade 1 or 2	Stage IA (n/%)	Absence of residual tumor in hysterectomy
Salm (1972)*	4	ND	4	ND	1 (25%)
Farrell et al. (2005)*	26	ND	25 (96.1%)	26 (100%) (selected just IA)	6 (23%)
Fernández-Parra et al. (2006)[2,25,29]	10	10	ND	8 (80%)	3 (30%)
Giordano et al. (2007)*	5	5 (100%)	5 (100%)	3 (60%)	0 (0%)
Vilos et al. (2007)[26,28]	10	10 (100%)	10	10 (100%)	2 (20%)
Mittal et al. (2008)*	18	11 (61%)	ND	16 (88.9%)	1 (5.6%)
Perri et al. (2010)**	125	ND	96 (76.8%)	96 (76.8%)	13 (10.4%)
Wethington et al. (2011)**	13	3 (23.1%)	ND	ND	ND
Gambadauro et al. (2014)*	12	ND	11 (91.6%)	8 (66.7%)	0 (0%)
Elyashiv et al. (2017)[1,5,6,24,27]	18	ND	ND	13 (72.2%)	4 (22.2%)
Present study	104	40 (38.5%)	86.5	96 (92.3%)	18 (17.3%)

Abbreviation: ND, not described.
*Other histological types were excluded from this table.
**Other histological types included in the analysis.

series there was no lymph node involvement, one previous study documented stages III and IV,[1] suggesting that lymph node evaluation could not be omitted. We excluded non-endometrioid types from our analysis, due to the particularly aggressive behavior of the disease in this group.[2]

The inherent nature of a retrospective study hindered a more precise hysteroscopic characterization of the biopsy site, especially the location of the tumor in the polyp. Conversely, several years would be necessary to recruit this sample in a prospective study.

Because blind biopsies usually have a lower diagnostic accuracy,[31,32] a potential bias of our study is that, in certain cases, the biopsy was performed after a diagnostic hysteroscopy with curettage, rather than with a working instrument. Nevertheless, blind avulsion of the polyp using the appropriate materials and standardized technique leads to an adequate pathological analysis.[33] In the case of curettage, the sample fragmentation makes it impossible to differentiate whether the biopsy came from the polyp or the endometrium.[34]

Another concern is that certain patients with polypoid cancer were inadvertently included, due to poor hysteroscopic descriptions when the exam was performed outside of the referred services. In some hysteroscopies, only the appearance of the polyp, and not that of the adjacent endometrium, was described.

The absence of pathological indicators of the low aggressiveness of tumors that are restricted to polyps is our most important finding. The strength of our study is its large sample size in comparison with other studies on polyps and cancer, and our data confirm that even patients with endometrioid EC that is apparently restricted to the polyp in hysteroscopy, regardless of histological grade, can experience deep myometrial invasion.

Conclusion

In conclusion, there was no association between polyp location of the EC during hysteroscopy and less residual disease or absence of deep myometrial invasion in the final uterine specimen.

Contributions

Study concepts: Simonsen M. and Baiocchi Neto G. Study design: Simonsen M. and Baiocchi Neto G. Data acquisition: Simonsen M., Mantoan H., Faloppa C. C., Kumagai L. Y., Badiglian-Filho L., Machado A. G., Tayfour N. M., Baiocchi Neto G. Quality control of data and algorithms: Mantoan H., Faloppa C. C., Kumagai L. Y., Badiglian-Filho L., Machado A. G., Tayfour N. M. Data analysis and interpretation: Simonsen M. and Baiocchi Neto G. Statistical analysis: Simonsen M. and Baiocchi Neto G. Manuscript preparation: Simonsen M. and Baiocchi Neto G. Manuscript editing: Simonsen M. and Baiocchi Neto G. Manuscript review: Simonsen M., Mantoan H., Faloppa C. C., Kumagai L. Y., Badiglian-Filho L., Machado A. G., Tayfour N. M., Baiocchi Neto G.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors acknowledge Mrs. Bruna Tirapelli Gonçalves from the Hospital AC Camargo for supporting the research data enabling appropriate statistical analysis.

References

1 Perri T, Rahimi K, Ramanakumar AV, Wou K, Pilavdzic D, Franco EL, et al. Are endometrial polyps true cancer precursors? Am J Obstet Gynecol. 2010;203(03):232.e1–232.e6. Doi: 10.1016/j.ajog.2010.03.036
2 Farrell R, Scurry J, Otton G, Hacker NF. Clinicopathologic review of malignant polyps in stage 1A carcinoma of the endometrium. Gynecol Oncol. 2005;98(02):254–262. Doi: 10.1016/j.ygyno.2005.03.044
3 Dias DS, Bueloni-Dias FN, Dias R, Nahás-Neto J, Nahás EAP, Leite NJ, et al. Usefulness of clinical, ultrasonographic, hysteroscopic, and immunohistochemical parameters in differentiating endometrial polyps from endometrial cancer. J Minim Invasive Gynecol. 2014;21 (02):296–302. Doi: 10.1016/j.jmig.2013.09.015
4 Antunes A Jr, Costa-Paiva L, Arthuso M, Costa JV, Pinto-Neto AM. Endometrial polyps in pre- and postmenopausal women: factors associated with malignancy. Maturitas. 2007;57(04):415–421. Doi: 10.1016/j.maturitas.2007.04.010
5 Mittal K, Da Costa D. Endometrial hyperplasia and carcinoma in endometrial polyps: clinicopathologic and follow-up findings. Int J Gynecol Pathol. 2008;27(01):45–48. Doi: 10.1097/pgp.0b013e3 18074fd60
6 Gambadauro P, Martínez-Maestre MA, Schneider J, Torrejón R. Malignant and premalignant changes in the endometrium of women with an ultrasound diagnosis of endometrial polyp. J Obstet Gynaecol. 2014;34(07):611–615. Doi: 10.3109/01443615.2014.916255
7 de Rijk SR, Steenbergen ME, Nieboer TE, Coppus SF. Atypical endometrial polyps and concurrent endometrial cancer: a systematic review. Obstet Gynecol. 2016;128(03):519–525. Doi: 10.1097/AOG.0000000000001566
8 Pivano A, Crochet P, Carcopino X, Cravello L, Boubli L, Agostini A. Risk of coexisting endometrial carcinoma in case of atypical endometrial hyperplasia diagnosed on total hysteroscopic resection. Eur J Obstet Gynecol Reprod Biol. 2016;203:210–213. Doi: 10.1016/j.ejogrb.2016.05.049
9 Ouyang C, Frimer M, Hou LY, Wang Y, Goldberg GL, Hou JY. Malignant endometrial polyps in uterine serous carcinoma: the prognostic value of polyp size and lymphovascular invasion. Int J Gynecol Cancer. 2018;28(03):524–528. Doi: 10.1097/IGC.0000000000001213
10 Chang-Halpenny CN, Natarajan S, Hwang-Graziano J. Early stage papillary serous or clear cell carcinoma confined to or involving an endometrial polyp: outcomes with and without adjuvant therapy. Gynecol Oncol. 2013;131(03):598–603. Doi: 10.1016/j.ygyno.2013.10.010
11 Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, et al. The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol. 2004;115(02):206–210. Doi: 10.1016/j.ejogrb.2004.02.002
12 National Comprehensive Cancer Network. NCCN guidelines for treatment of cancer by site: Uterine neoplasms: NCCN guidelines [Internet]. 2020 [cited 2020 Jan 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
13 Bakour SH, Khan KS, Gupta JK. The risk of premalignant and malignant pathology in endometrial polyps. Acta Obstet Gynecol Scand. 2000; 79(04):317–320. Doi: 10.1034/j.1600-0412.2000.079004317.x
14 Tarney CM, Tian C, Wang G, Dubil EA, Bateman NW, Chan JK, et al. Impact of age at diagnosis on racial disparities in endometrial cancer patients. Gynecol Oncol. 2018;149(01):12–21. Doi: 10.1016/j.ygyno.2017.07.145
15 Sivridis E, Giatromanolaki A. The pathogenesis of endometrial carcinomas at menopause: facts and figures. J Clin Pathol. 2011; 64(07):553–560. Doi: 10.1136/jcp.2010.085951
16 Gawron I, Łoboda M, Babczyk D, Ludwin I, Basta P, Pityński K, Ludwin A. Endometrial cancer and hyperplasia rate in women before menopause with abnormal uterine bleeding undergoing endometrial sampling. Przegl Lek. 2017;74(04):139–143

17 Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol. 2018;38(08):1146–1149. Doi: 10.1080/01443615.2018.1458081
18 Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(02): 170–199. Doi: 10.6004/jnccn.2018.0006
19 Baiocchi G, Manci N, Pazzaglia M, Giannone L, Burnelli L, Giannone E, et al. Malignancy in endometrial polyps: a 12-year experience. Am J Obstet Gynecol. 2009;201(05):462.e1–462.e4. Doi: 10.1016/j.ajog.2009.05.055
20 Cohen I. Endometrial polyps in pre-and postmenopausal women: factors associated with malignancy. Maturitas. 2008;59(01): 99–100. Doi: 10.1016/j.maturitas.2007.08.005
21 Gemer O, Segev Y, Helpman L, Hag-Yahia N, Eitan R, Raban O, et al. Is there a survival advantage in diagnosing endometrial cancer in asymptomatic postmenopausal patients? An Israeli Gynecology Oncology Group study. Am J Obstet Gynecol. 2018;219(02):181.e1–181.e6. Doi: 10.1016/j.ajog.2018.05.013
22 Naaman Y, Diment J, Perlman S, Oustinov N, Vaisbuch E, Ben-Arie A. Can malignant potential of endometrial polyps be determined by incorporating the endometrial intraepithelial neoplasia (EIN) classification? Gynecol Oncol. 2015;136(02):254–257. Doi: 10.1016/j.ygyno.2014.12.014
23 Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJB II, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(04):812–819. Doi: 10.1002/cncr.21650
24 Wethington SL, Herzog TJ, Burke WM, Sun X, Lerner JP, Lewin SN, Wright JD. Risk and predictors of malignancy in women with endometrial polyps. Ann Surg Oncol. 2011;18(13):3819–3823. Doi: 10.1245/s10434-011-1815-z
25 Fernández-Parra J, Rodríguez Oliver A, López Criado S, Parrilla Fernández F, Montoya Ventoso F. Hysteroscopic evaluation of endometrial polyps. Int J Gynaecol Obstet. 2006;95(02):144–148. Doi: 10.1016/j.ijgo.2006.07.007
26 Giordano G, Gnetti L, Merisio C, Melpignano M. Postmenopausal status, hypertension and obesity as risk factors for malignant transformation in endometrial polyps. Maturitas. 2007;56(02): 190–197. Doi: 10.1016/j.maturitas.2006.08.002
27 Elyashiv O, Sagiv R, Kerner R, Keidar R, Menczer J, Levy T. Hysterscopic resection of premalignant and malignant endometrial polyps: is it a safe alternative to hysterectomy? J Minim Invasive Gynecol. 2017;24(07):1200–1203. Doi: 10.1016/j.jmig.2017.08.002
28 Vilos GA, Edris F, Al-Mubarak A, Ettler HC, Hollett-Caines J, Abu-Rafea B. Hysteroscopic surgery does not adversely affect the long-term prognosis of women with endometrial adenocarcinoma. J Minim Invasive Gynecol. 2007;14(02):205–210. Doi: 10.1016/j.jmig.2006.10.010
29 Salm R. The incidence and significance of early carcinomas in endometrial polyps. J Pathol. 1972;108(01):47–53. Doi: 10.1002/path.1711080106
30 Wang F, Yu A, Xu H, Zhang X, Li L, Lou H, et al. Fertility preserved hysteroscopic approach for the treatment of stage Ia endometrioid carcinoma. Int J Gynecol Cancer. 2017;27(09):1919–1925. Doi: 10.1097/IGC.0000000000001109
31 Spadoto-Dias D, Bueloni-Dias FN, Elias LV, Leite NJ, Modotti WP, Lasmar RB, Dias R. The value of hysteroscopic biopsy in the diagnosis of endometrial polyps. Womens Health (Lond). 2016; 12(04):412–419. Doi: 10.1177/1745505716653695
32 Svirsky R, Smorgick N, Rozowski U, Sagiv R, Feingold M, Halperin R, Pansky M. Can we rely on blind endometrial biopsy for detection of focal intrauterine pathology? Am J Obstet Gynecol. 2008;199(02):115.e1–115.e3. Doi: 10.1016/j.ajog.2008.02.015
33 Kanthi JM, Remadevi C, Sumathy S, Sharma D, Sreedhar S, Jose A. Clinical study of endometrial polyp and role of diagnostic hysteroscopy and blind avulsion of polyp. J Clin Diagn Res. 2016;10(06): QC01–QC04. Doi: 10.7860/JCDR/2016/18173.7983
34 Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, Bovicelli L. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. Am J Obstet Gynecol. 2003; 188(04):927–931. Doi: 10.1067/mob.2003.247

Efficacy of Endometrial Cancer Follow-up Protocols: Time to Change?

Amina Lubrano[1] Virginia Benito[1] Beatriz Pinar[2] Fernando Molano[3] Laureano Leon[4]

[1] Department of Gynecology and Obstetrics, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain
[2] Depatment of Radiotherapy, Hospital Dr. Negrin, Las Palmas de Gran Canaria, Spain
[3] Department of Medical Oncology, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain
[4] Department of Pathology, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain

Address for correspondence Amina Lubrano, Avenida Marítima del Sur, s/n, 35016, Las Palmas de Gran Canaria, Las Palmas, Spain (e-mail: alubranorosales@gmail.com).

Rev Bras Ginecol Obstet 2021;43(1):41–45.

Abstract

Objective The aim of the present study was to analyze relapse rates and patterns in patients with endometrial cancer with the aim of evaluating the effectiveness of current follow-up procedures in terms of patient survival, as well as the convenience of modifying the surveillance strategy.

Methods Retrospective descriptive study including all patients diagnosed with endometrial cancer relapse at the Department of Gynecology and Obstetrics of the Complejo Hospitalario Insular-Materno Infantil de Canarias, between 2005 and 2014.

Results Recurrence was observed in 81 patients (10.04% of the sample); 66.7% of them suffered relapse within 2 years and 80.2% within 3 years after the termination of the primary treatment; 41.9% showed distant metastases while the rest corresponded to local-regional (40.7%) or ganglionar (17.4%) relapse; 42% of these were symptomatic; 14 patients showed more than 1 site of relapse. Relapse was detected mainly through symptoms and physical examination findings (54.3%), followed by elevated serum marker levels (29.6%), computed tomography (CT) images (9.9%) and abnormal vaginal cytology findings (6.2%). No differences in global survival were found between patients with symptomatic or asymptomatic relapse.

Conclusion Taking into account that the recurrence rate of endometrial cancer is low, that relapse occurs mainly within the first 3 years post-treatment and that symptom evaluation and physical examination are the most effective follow-up methods, we postulate that a modification of the current model of hospital follow-up should be considered.

Keywords
- endometrial cancer relapse
- follow-up
- survival

Introduction

The incidence of cancer in Spain is rising. According to recent data from the Spanish Society of Medical Oncology, 277,394 new cases were diagnosed in 2019, and this figure is expected to increase to ~ 315,413 new cases in 2035.[1] Such an increase in the number of cases along with lower mortality rates due to scientific advances in cancer

received
June 29, 2020
accepted
September 28, 2020

DOI https://doi.org/10.1055/s-0040-1721352.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

screening, diagnosis and treatment, lead to higher prevalence rates and, consequently, to more survivors. From tumors affecting women, breast, colorectal and endometrial are most frequently associated with long-term survival. Endometrial cancer is the most frequent malignancy of the female genital tract in Western countries. About 382,069 new cases were diagnosed in 2018 worldwide.[2] In Spain, 6,784 new cases were detected in 2018. Survival is known to be closely related to disease stage, with local disease associated with $>$ 95% survival at 5 years.[3] Given that endometrial cancer is the most common gynecological neoplasm and that most patients present with early-stage disease, the amount of patients to be followed-up after treatment is rather high. Traditionally, the objective of post-treatment follow-up protocols has been to diagnose possible treatment-associated complications and detect relapse as soon as possible. Currently, other goals related to long-term follow-up are emerging, for example, control of delayed toxicity, management of physical consequences, rehabilitation and promotion of health and healthy habits. Overall, the goal is to improve the quality of life of survivors, as well as to help them retake their social, familial and working life.[4]

However, the follow-up model currently used for such patients, mainly focused on diagnosing relapse, is based on a multidisciplinary hospital-based approach, which may be redundant and requires several visits and interventions that lead to overuse of hospital resources. Thus, the aim of the present study was to analyze relapse rates and patterns in endometrial cancer patients managed at our hospital, to assess the effectiveness of current follow-up procedures in terms of patient survival, as well as the convenience of modifying the surveillance strategy.

Methods

The present retrospective descriptive study included all patients diagnosed with endometrial cancer relapse at the Department of Gynecology and Obstetrics of the Complejo Hospital Universitario Insular Materno Infantil de Canarias, between 2005 and 2014.

In our center, surgery is the primary treatment for endometrial cancer. Based on the national and international guidelines in use during the considered period, we conducted complete hysterectomy with bilateral salpingo-oophorectomy plus cytology of peritoneal washing fluids. In patients with endometrioid adenocarcinoma of histological grades 1 or 2, an intraoperatory finding of myometrial involvement (invasion $>$ 50%) leads to pelvic and paraaortic lymphadenectomy. In case of endometrioid adenocarcinoma grade 3 or histological type 2 (serous, clear cells, undifferentiated or carcinosarcoma), pelvic and paraaortic lymphadenectomy was performed regardless of myometrial involvement.

Traditionally, we have conducted surgery for endometrial cancer through laparotomy. However, since 2006, we adopted a minimally invasive approach, changing from 8% of laparoscopic surgeries in 2006 to $>$ 95% in 2009.

The patients were staged by using the system of the International Federation of Gynecology and Obstetrics (FIGO) from 2009. A multidisciplinary committee for tumors (meeting weekly) evaluated and classified the patients into three risk-groups on the basis of their anatomic pathology outcomes: 1) low-risk: including tumors of endometrioid histology stage I, grade 1–2, $<$ 50% myometrial invasion and negative lymphovascular space invasion (LVSI); 2) medium-risk: including tumors of endometrioid histology stage I, grade 1–2, $\geq$ 50% myometrial invasion and negative LVSI; and 3) high-risk: including endometrioid tumors grade 3, $\geq$ 50% myometrial invasion, stage II-III and type-2 endometrial cancer. Patients in the medium- or high-risk groups received adjuvant radiotherapy and/or chemotherapy treatment.

The follow-up protocol in the studied period included physical examination, cytology of the vaginal vault, measurement of tumor markers (CA 125) and imaging tests depending on the symptoms and findings. In-hospital oncologic follow-up visits took place every 4 months during the first 2 years post-treatment, every 6 months between the 2nd and 5th years post-treatment and once a year afterwards.

Relapse was defined as detection of disease after a 6-month disease-free period, following the termination of the primary treatment. Cases of relapse were evaluated taking into account: primary treatment, ganglionar involvement, disease stage, histological grade, symptoms, site of relapse, and the way of detection of relapse. Depending on the first relapse site, patients were grouped into local-regional relapse (vaginal vault, isolated pelvic relapse or peritoneal carcinomatosis), ganglionar relapse (pelvic and/or aortic) or systemic relapse (metastases of the bone, liver, lung, brain or supradiaphragmatic ganglia).

The cutoff point for the survival analysis was December 31st, 2017. The present study was approved by the local Ethics Committee (protocol number 2020–034–1). The statistical analysis was conducted with the SPSS for Windows, version 12 (SPSS Inc., Chicago, IL, USA). Quantitative variables were compared by using the Student *t*-test or the Mann-Whitney test. Categorical variables were analyzed with the chi-squared test or the Fisher exact test. Survival rates were analyzed with the Kaplan-Meier technique. The Cox proportional hazard model was used to identify risk factors for relapse or survival. Statistical significance was considered for p-values $<$ 0.05.

Results

During the studied period, 806 patients were diagnosed with endometrial cancer (mean: 80.6 cases/year). The mean follow-up time was 42.94 months (standard deviation [SD] 30.3). Relapse was detected in 81 patients (10.04% of the sample). At the moment of diagnosis, these patients were 67.72 years old (range 41–96 years old) on average; and the FIGO classification of the initial tumor was: stage I in 41 patients (50.6%), stage II in 12 patients (14.8%), stage III in 22 patients (27.2%) and stage IV in 6 patients (7.4%); 70.3% (57 patients) had type-1 endometrial adenocarcinoma (endometrioid) and 29.7% (24 patients) had type-2 endometrial adenocarcinoma (nonendometrioid); 28.4% (23 patients) had been initially treated with surgery only, while the rest of them had received adjuvant treatment depending on their risk group. The average time to relapse was

Table 1 Characteristics of patients with relapse

Characteristics	$n = 81$	Percentage (%)
FIGO 2009 stage		
I	41	50.6
II	12	14.8
III	22	27.2
IV	6	7.4
Histology		
Type 1	57	70.3
Type 2	24	29.7
Differentiation grade		
G1	24	29.6
G2	23	28.4
G3	34	42
Myometrial involvement		
< 0–50%	39	48.1
50%	38	46.9
No entry	4	5
Lymphadenectomy		
No	46	56.8
Yes	35	43.2
Tumor size		
< 4 cm	40	49.4
> 4 cm	33	40.7
Unknown	8	9.9
Lymphovascular involvement		
No	43	53
Yes	29	35.8
Unknown	9	11.2
Adjuvant treatment		
No	23	28.4
Radiotherapy (RT)	47	58
Chemotherapy/Hormone therapy	4	5
Radiotherapy + Chemotherapy	7	8.6
Relapse		
Local-regional	33	40.7%
Ganglionar	14	17.3%
Distant	34	41.9%
Multisite	14	17.3%

23.86 months (SD 19.4). ►**Table 1** shows the characteristics of the patients.

Within patients with relapse, 41.9% showed distant metastases, 40.7% showed local-regional, and 17.4% ganglionar relapse; 14 patients showed > 1 site of relapse (17.3%); 8.9% of recurrence cases (8 patients) belonged to the low-risk group, 14.8% (12 patients) to the medium-risk group, and 73.3% (61 patients) to high-risk groups; 66.7% of the relapses (54 cases) occurred within the 1st 2 years post-treatment, and 80.2% (65 cases) within the 1st 3 years post-treatment; 42% (34 cases) were symptomatic, the most frequent symptoms including: pain, vaginal hemorrhage and constitutional syndrome.

Table 2 Multivariate survival analysis of patients with endometrial cancer relapse

Variables	HR	95%CI		*p-value*
Stage III-IV vs Stage I-II	1.02	0.499	2.129	0.9
Grade 1 vs Grade 2	5.002	1.539	16.255	0.007
Grade 1 vs Grade 3	4.310	1.458	12.741	0.008
Histologic type Type 1 Type 2	0.62	3.41	0.3	0.38
Lymphovascular space involvement	2.714	1.429	6.328	0.002
Type of relapse Local-regional Distant	1.180	0.709	1.984	0.28
Single relapse episode vs Multiple relapse episodes	1.85	0.87	3.94	0.18
Symptomatic vs Asymptomatic relapse	0.94	0.33	2.65	0.7

Abbreviations: CI, confidence interval; HR, Hazard ratio.

Relapse was detected mainly through symptoms and physical findings (54.3%), followed by increased marker levels (29.6%), computed tomography (CT) (9.9%), and abnormal vaginal cytology findings (6.2%). A total of 45 patients died due to the disease. Postrelapse global survival rates were 74% at 2 years, 40.5% at 5 years and 32.8% at 10 years. In the multivariate analysis, only histological grade G3 and LVSI in the initial biopsy were associated with lower global survival ($p < 0.007$ and $p < 0.002$, respectively). No significant survival differences were found for single versus multiple relapse episodes ($p = 0.18$) or for different relapse sites (local-regional, ganglionar or distant) ($p = 0.28$). No differences were found in global survival between patients with symptomatic or asymptomatic relapse ($p = 0.7$) (►**Table 2**).

Discussion

Currently, no controlled studies support patient follow-up after the termination of treatment or indicate that such follow-up can improve survival.[5,6] Several studies have demonstrated that the global rate of endometrial cancer relapse after a completed primary treatment is relatively low, ~ 13% (95% confidence interval [CI]: 11–14%), with age, histological grade, mitotic activity, myometrial invasion, lymphovascular invasion and ganglionar involvement as main prognostic

factors.[7,8] In our series, which included > 800 cases, we found a 10.4% relapse rate, in line with other published data.

In 2016, the European Society of Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO) and the European Society of Therapeutic Radiology Oncology (ESTRO) published a consensus document on the classification of the risk of relapse, creating new subgroups to help design better adjusted and tailored treatments.[9]

In our study, 73.3% of recurrences belonged to the high-risk groups, and most relapse cases occurred within the 1st 3 years of follow-up (80.2%), in agreement with data published by other authors.[5,10]

Regarding the site of relapse, Morice at al.[11] showed in their series that distant metastases were more frequent than local relapse. Carraca et al.,[12] in a retrospective study including 282 patients, found local disease in 40.6%, distant disease in 32.5%, and concomitant local plus distant relapse in 26.9%. In our study, we found 41.9% cases of distant relapse, which was in agreement with the available evidence.

The role of follow-up is based on the concept that detecting relapse while still asymptomatic allows for better therapeutic options and outcomes. However, even with intensive surveillance, relapse is frequently detected through symptoms, which occur in 41 to 83% of patients.[7,13]

Sartori et al.[5] reported poorer outcomes in women with symptomatic relapse than in asymptomatic ones, diagnosed through clinical examination or imaging tests. Carrara et al.[12] reported higher median survival in asymptomatic than in symptomatic relapse (35 months versus 13 months) and concluded that early diagnosis, achieved through a planned follow-up procedure, enhanced clinical outcomes in these patients. However, other authors failed to detect differences in the survival of patients with asymptomatic versus symptomatic relapse.[6,14] Otsuka et al.[15] studied 51 patients with endometrial cancer relapse and found that the site of relapse and the time to relapse were independent prognostic factors influencing survival, although they also failed to find significant differences between patients with or without symptoms. They concluded that detecting asymptomatic relapse through imaging tests or tumor marker levels did not influence the prognosis.

In our series, 42% of relapse cases were symptomatic; and no significant differences were found in the survival of patients with versus without symptoms ($p = 0.7$). Hence the importance of providing good information about symptom detection and advising patients to seek medical advice as soon as they appear.

In the present study, > 50% of the cases of relapse were detected through symptoms and physical examination; followed by elevated levels of tumor marker Ca 125 (29.6% of the cases) and imaging techniques (9.9% of the cases). In other studies, cytology of the vaginal vault detected between 0 and 6.8% relapse in asymptomatic patients, most of them in early-stage low-grade disease.[9,16] In our study, cytology detected 6.2% of the relapses in the absence of symptoms or of physical examination findings. Thus, medical surveillance through vaginal cytology was not particularly efficient in detecting endometrial cancer relapse. We propose that the systematic use of cytology as a part of follow-up should be discouraged. Hunn et al.,[6] in a series of 92 cases of high-grade endometrial cancer relapse, showed that elevated Ca 125 levels detected 20% of asymptomatic relapses. Although routine measurement of CA-125 levels is not advised in patients at the initial stages of endometrial cancer, it may be suitable in selected patients with advanced disease, serous histology or elevated CA-125 levels before treatment.[10]

The usefulness of imaging tests in endometrial cancer follow-up is not clear. Similarly to our findings, other studies reported that CT detected 5 to 20.8% of asymptomatic endometrial cancer relapses.[6,13] The usefulness of pelvic ultrasound in local relapse detection is under study; although its detection rate is between 4% and 31%,[10] namely lower than detection through physical examination. These findings indicate that imaging techniques should also not be recommended in routine follow-up of asymptomatic patients, but should only when they were clinically indicated.

There is little evidence that the current approach to monitoring endometrial cancer in a hospital setting has an impact on survival. Given the rising number of gynecologic cancer survivors, intensive oncology specialist follow-up might turn unsustainable; additionally, it may be unnecessary for many patients.[17,18] In this regard, two clinical trials aimed at evaluating the efficacy of different endometrial cancer follow-up schedules are in course: the TOTEM trial (NCT00916708)[19] and the ENSURE trial (NCT02413606).[20]

There is growing evidence that cancer survivors have long-term physical, psychological and social needs that are not addressed in the traditional hospital follow-up. Thus, we postulate that the strategy of care should start to shift from a purely disease-focused to a more comprehensive health-focused approach.[21,22]

The main limitation of the present study was its retrospective nature. However, it has several strong points, such as including a significant number of patients (despite being a single center study) and the fact that all patients were managed by the same multidisciplinary team using identical follow-up protocols.

Conclusion

In summary, the recurrence rate of endometrial cancer in our environment is low (10.04%). Taking into account that 80% of the cases occur in the 1st 3 years post-treatment and that symptom evaluation and clinical examination are the most effective follow-up methods, a change should be considered in the current model of hospital-based monitoring. However, since most available studies are retrospective, prospective clinical trials (like the above-mentioned ones) are important to determine the actual role of follow-up procedures in endometrial cancer.

Contributors
All authors contributed with the project and data interpretation, the writing of the article, the critical review of

the intellectual content, and with the final approval of the version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Sociedad Española de Oncología Médica. Las cifras del cáncer en España: Depósito Legal: M-3266–2020 [Internet]. 2020 [cited 2020 Jan 15]. Available from: https://seom.org/seomcms/images/stories/recursos/Cifras_del_cancer_2020.pdf

2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(06):394–424. Doi: 10.3322/caac.21492

3 Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991;40(01):55–65. Doi: 10.1016/0090-8258(91)90086-k

4 Rubinstein EB, Miller WL, Hudson SV, Howard J, O'Malley D, Tsui J, et al. Cancer Survivorship Care in Advanced Primary Care Practices: A Qualitative Study of Challenges and Opportunities. JAMA Intern Med. 2017;177(12):1726–1732. Doi: 10.1001/jamainternmed.2017.4747

5 Sartori E, Pasinetti B, Chiudinelli F, Gadducci A, Landoni F, Maggino T, et al. Surveillance procedures for patients treated for endometrial cancer: a review of the literature. Int J Gynecol Cancer. 2010;20(06):985–992. Doi: 10.1111/IGC.0b013e3181e2abcc

6 Hunn J, Tenney ME, Tergas AI, Bishop EA, Moore K, Watkin W, et al. Patterns and utility of routine surveillance in high grade endometrial cancer. Gynecol Oncol. 2015;137(03):485–489. Doi: 10.1016/j.ygyno.2015.03.047

7 Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver TCancer Care Ontario Program in Evidence-based Care Gynecology Cancer Disease Site Group. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(03):520–529. Doi: 10.1016/j.ygyno.2006.02.011

8 Iavazzo C, Gkegkes ID, Vrachnis N. Early recurrence of early stage endometrioid endometrial carcinoma: possible etiologic pathways and management options. Maturitas. 2014;78(03):155–159. Doi: 10.1016/j.maturitas.2014.04.009

9 Colombo N, Creutzberg C, Amant F, Bosse T, González-Martin A, Ledermann J, et al; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27(01):16–41. Doi: 10.1093/annonc/mdv484

10 Salani R, Khanna N, Frimer M, Bristow RE, Chen LM. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol. 2017;146(01):3–10. Doi: 10.1016/j.ygyno.2017.03.022

11 Morice P, Levy-Piedbois C, Ajaj S, Pautier P, Haie-Meder C, Lhomme C, et al. Value and cost evaluation of routine follow-up for patients with clinical stage I/II endometrial cancer. Eur J Cancer. 2001;37(08):985–990. Doi: 10.1016/s0959-8049(01)00066-1

12 Carrara L, Gadducci A, Landoni F, Maggino T, Scambia G, Galletto L, et al. Could different follow-up modalities play a role in the diagnosis of asymptomatic endometrial cancer relapses?: an Italian multicentric retrospective analysis Int J Gynecol Cancer. 2012;22(06):1013–1019. Doi: 10.1097/IGC.0b013e31825ad3ee

13 Gadducci A, Cosio S, Fanucchi A, Cristofani R, Genazzani AR. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res. 2000;20(3B):1977–1984

14 Sartori E, Laface B, Gadducci A, Maggino T, Zola P, Landoni F, Zanagnolo V. Factors influencing survival in endometrial cancer relapsing patients: a Cooperation Task Force (CTF) study. Int J Gynecol Cancer. 2003;13(04):458–465. Doi: 10.1046/j.1525-1438.2003.13328.x

15 Otsuka I, Uno M, Wakabayashi A, Kameda S, Udagawa H, Kubota T. Predictive factors for prolonged survival in recurrent endometrial carcinoma: Implications for follow-up protocol. Gynecol Oncol. 2010;119(03):506–510. Doi: 10.1016/j.ygyno.2010.08.013

16 Novetsky AP, Kuroki LM, Massad LS, Hagemann AR, Thaker PH, Powell MA, et al. The utility and management of vaginal cytology after treatment for endometrial cancer. Obstet Gynecol. 2013;121(01):129–135. Doi: 10.1097/aog.0b013e31827499a9

17 Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists : challenges to assuring access to oncology services. J Oncol Pract. 2007;3(02):79–86. Doi: 10.1200/JOP.0723601

18 Rutledge TL, Kano M, Guest D, Sussman A, Kinney AY. Optimizing endometrial cancer follow-up and survivorship care for rural and other underserved women: Patient and provider perspectives. Gynecol Oncol. 2017;145(02):334–339. Doi: 10.1016/j.ygyno.2017.03.009

19 Beaver K, Williamson S, Sutton C, Hollingworth W, Gardner A, Allton B, et al. Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): a randomised, multicentre, non-inferiority trial. BJOG. 2017;124(01):150–160. Doi: 10.1111/1471-0528.14000

20 Trial between two follow up regimens with different test intensity in endometrial cancer treated patients (TOTEM) [Internet]. 2018 [cited 2019 Dec 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT00916708

21 16pt?>Ezendam NPM, de Rooij BH, Kruitwagen RFPM, Creutzberg CL, van Loon I, Boll D, et al. ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more? Evaluating patient satisfaction and cost-effectiveness of a reduced follow-up schedule: study protocol of a randomized controlled trial. Trials. 2018;19(01):227. Doi: 10.1186/s13063-018-2611-x

22 Jones JM, Ferguson S, Edwards E, Walton T, McCurdy N, Howell D. Experiences of care delivery: endometrial cancer survivors at end of treatment. Gynecol Oncol. 2012;124(03):458–464. Doi: 10.1016/j.ygyno.2011.10.037

Mid- to Long-Term Magnetic Resonance Imaging Results of Two Prolapse Surgeries for Apical Defect: A Secondary Analysis of a Randomized Controlled Trial

Resultados de ressonância magnética de médio a longo prazos de duas cirurgias de prolapso por defeito apical: Uma análise secundária de um ensaio clínico randomizado

Luiz Carlos Santos Junior[1] Luiz Gustavo Oliveira Brito[1] Edilson Benedito de Castro[1] Sergio Dertkigil[1] Cassia Raquel Teatin Juliato[1]

[1] Department of Obstetrics and Gynecology, Pelvic Floor Dysfunction Division, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, SP, Brazil

Address for correspondence Cássia Raquel Teatin Juliato, MD, PhD, Universidade Estadual de Campinas, Rua Alexander Fleming 101, Cidade Universitária Zeferino Vaz, Campinas, SP, 13083-881, Brazil (e-mail: cjuliato@unicamp.br).

Rev Bras Ginecol Obstet 2021;43(1):46–53.

Abstract

Objective Magnetic resonance imaging (MRI) has been considered another tool for use during the pre- and postoperative periods of the management of pelvic-organ prolapse (POP). However, there is little consensus regarding its practical use for POP and the association between MRI lines of reference and physical examination. We aimed to evaluate the mid- to long-term results of two surgical techniques for apical prolapse.

Methods In total, 40 women with apical POP randomized from 2014 to 2016 underwent abdominal sacrocolpopexy (ASC group; n = 20) or bilateral vaginal sacrospinous fixation with an anterior mesh (VSF-AM group; n = 20). A physical examination using the POP Quantification System (POP-Q) for staging (objective cure) and the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS: subjective cure), were applied and analyzed before and one year after surgery respectively. All MRI variables (pubococcigeous line [PCL], bladder base [BB], anorectal junction [ARJ], and the estimated levator ani subtended volume [eLASV]) were investigated one year after surgery. Significance was established at $p < 0.05$.

Results After a mean 27-month follow-up, according to the MRI criteria, 60% of the women were cured in the VSF-AM group versus 45% in ASC group ($p = 0.52$). The POP-Q and objective cure rates by MRI were correlated in the anterior vaginal wall ($p = 0.007$), but no correlation was found with the subjective cure. The eLASV was larger among the patients with surgical failure, and a cutoff of $\geq 33.5\ mm^3$ was associated with postoperative failure (area under the receiver operating characteristic curve [ROC]: 0.813; $p = 0.002$).

Conclusion Both surgeries for prolapse were similar regarding the objective variables (POP-Q measurements and MRI cure rates). Larger eLASV areas were associated with surgical failure.

Keywords

- pelvic organ prolapse
- magnetic resonance imaging
- cross-sectional studies

received
April 14, 2020
accepted
August 10, 2020

DOI https://doi.org/10.1055/s-0040-1718441.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Resumo

Objetivo A ressonância magnética (RM) tem sido considerada uma outra ferramenta para uso pré e pós-operatório em casos de prolapso de órgãos pélvicos. Contudo, pouco consenso existe sobre a sua prática para prolapso e a associação entre as linhas de referência da RM e o exame físico. Nós objetivamos avaliar resultados de médio a longo prazo de duas técnicas cirúrgicas para prolapso apical.

Métodos Um total de 40 mulheres com prolapso apical foram submetidas entre 2014 a 2016 a sacrocolpopexia abdominal (grupo SCA; n = 20) ou fixação bilateral vaginal no ligamento sacroespinhoso com tela anterior (grupo FVLS-TA; n = 20). Os exames físicos com estadiamento usando o Pelvic Organ Prolapse Quantification System (POP-Q: cura objetiva), e o International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS: cura subjetiva) foram analisados antes e depois de um ano da cirurgia, respectivamente. O exame de RM (linha pubococcígea [LPC], base vesical [BV], junção anorretal [JAR] e o volume subtendido estimado do levantador do ânus [VSELA]) foi realizado um ano antes da cirurgia. Estabeleceu-se o nível de significância em 5%.

Resultados Depois de uma média de 27 meses de seguimento, de acordo com a RM, 60% das mulheres foram curadas no grupo FVLS-TA versus 45% no grupo SCA ($p = 0.52$). As curas objetivas associadas ao POP-Q e à RM foram correlacionadas na parede vaginal anterior ($p = 0.007$), mas nenhuma correlação foi encontrada com a cura subjetiva. O VSELA foi maior entre as pacientes com fracasso da cirurgia, e um ponto de corte de $\geq 33.5\,mm^3$ esteve associado ao fracasso da cirurgia (area sob a curva característica de operação do receptor [COR]: 0.813; $p = 0.002$).

Conclusão Ambas as cirurgias para o prolapso foram similares nas curas objetivas tanto pelo POP-Q quanto pela RM. Áreas maiores de VSELA estiveram associadas com o fracasso das cirurgias.

Palavras-chave

- prolapso dos órgãos pélvicos
- ressonância magnética
- estudos transversais

Introduction

Pelvic organ prolapse (POP) is a major health issue worldwide, and treatment is often surgical. However, reoperation rates may vary from 5% to 40%; up to 30% of the patients undergo more than 1 surgery throughout their lives.[1] The symptoms of POP are not always associated with physical examination findings, and the role of magnetic resonance imaging (MRI) in cases of POP has been investigated in recent years.[2–4]

Many lines of reference and different protocols are used for the evaluation, and the most frequently used is the pubococcygeal line (PCL).[5] This line appears to have the best interobserver correlation and accordance with POP quantification systems (such as the Pelvic Organ Prolapse Quantification System, POP-Q), especially in the vaginal anterior wall.[4] In 2017, the European Society of Urogenital Radiology (ESUR) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) released a joint recommendation guideline for MRI in POP, also recommending the PCL as the line of reference.[6]

The role of the levator ani muscle (LAM) complex in pelvic support has been thoroughly described in the literature, as LAM alterations occur in women with POP, and are described on both ultrasound and MRI.[7] Rodrigues Junior et al.[8] have recently described the estimated levator ani subtended volume (eLASV) through MRI, and have showed significant posterior enlargement in patients with surgical failure following reconstructive prolapse surgery.[8,9]

Apical defects (uterine prolapse, vault prolapse) are usually corrected by abdominal sacrocolpopexy (ASC) or vaginal sacrospinous fixation (VSF). In a previous study (Juliato et al.[10]), our group showed that using an anterior mesh (VSF-AM) in the anterior compartment, the vaginal axis is deviated in both surgeries, however with no difference between them.[10] Nonetheless, we still have little data about the behavior of the MRI lines of reference for patients operated for POP and their association with physical examination findings and subjective cure using standardized questionnaires. Thus, we aimed to study these postoperative findings. Moreover, a receiver operating characteristic (ROC) curve was built for eLASV to look for a cutoff point as a failure of the surgical treatment.

Methods

Study Design

A secondary analysis of a prospective, randomized, single-blinded, two-arm, parallel study was performed from 2016 to 2017 in the Pelvic Floor Dysfunction Division, Department of Obstetrics and Gynecology, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (FCM/UNICAMP). The present study was approved by the institutional Review Board (CAAE 64652217.0.0000.5404), and this trial was

registered at the Clinical Trials Registry (http://www.ensaiosclinicos.gov.br, code RBR-7t6rg2). The present study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Inclusion Criteria

The randomized controlled trial (RCT) included postmenopausal women aged 55 to 75 years with advanced POP (stage 3 or 4 according to the POP-Q) with no current hormone replacement therapy, and no previous gynecological surgery or malignancy.[11] These women were randomized by a computer-generated sequence. The attending physicians in the postoperative period were blinded to the surgery performed. All surgeries were performed from 2014 to 2016 in the Women's Hospital at UNICAMP, and all women were revaluated at least one year postoperatively.

Exclusion Criteria

The exclusion criteria were the use of metallic implants (intrauterine devices, cardiac valves or stents, aneurism clips, orthopedic implants, or piercings), use of electronic implants (cardiac pacemakers, cochlear implants), claustrophobia, or recent tattoos.

Interventions

The women were randomized into two groups (►**Fig. 1**). The first group underwent surgery with hysterectomy and bilateral vaginal sacrospinous fixation with an anterior mesh (VSF-AM group). To correct the anterior vaginal wall, a polyvinylidene fluoride mesh (DynaMesh, FEG Textiltechnik, Aachen, North Rhine-Westphalia, Germany) was used in this group. The second group underwent abdominal supracervical hysterectomy with abdominal sacralcolpopexy (ASC group). Details of both intervention arms were published elsewhere.[11] If the patients presented concomitant stress urinary incontinence, they did not receive treatment for incontinence.

After at least one year of follow-up, the women underwent a physical examination performed by only one trained urogynecologist with at least five years of experience with the POP-Q who was blinded to the surgery performed.[12] During this visit, all women were instructed to answer a questionnaire regarding vaginal symptoms (International Consultation on Incontinence Questionnaire-Vaginal Symptoms, ICIQ-VS).[13] The MRI was scheduled no more than two weeks after the physical examination.

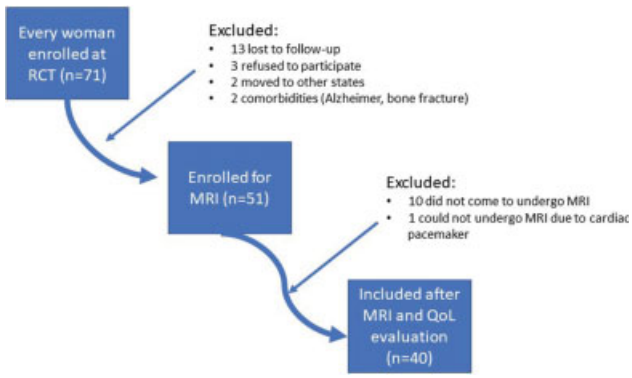

Fig. 1 Flowchart depicting the recruitment process of the patients.

MRI Protocol

Thei MRI was performed postoperatively. The women were instructed to empty their bladder within 2 hours before the MRI, and were taught the Valsalva maneuver for at least 20 seconds by a senior urogynecologist. Images were acquired in the supine position at rest and at maximum Valsalva using a 1.5-Tesla Philips Achieva Scanner v3.2 (Philips Medical Systems, Best, The Netherlands) with a 4-channel phased-array coil. At rest, T1-weighted sequences were obtained in the sagittal, coronal, and axial planes for the estimation of the pelvic anatomical structure and image planning. After vaginal introduction of 30 mL of ultrasound gel for better evaluation of the contours, T2-weighted single-shot fast spin-echo dynamic rest and Valsalva images were obtained through the midsagittal and parasagittal pelvic planes using the following parameters: repetition time, 1,300 milliseconds; echo time, 60 milliseconds; slice thickness, 6 mm; field of view, 36 cm; matrix size, 256 × 160. The description of this technique did not include one step of the ESUR/ESGAR guidelines with regard to the use of ultrasound gel in the rectal canal; we have had limitations regarding the use of this material in the steps to analyze rectal function (rest, straining, squeezing and evacuation). The images were interpreted with the aid of the MicroDicom software (Medical Imaging & Technology Alliance, Arlington, VA, US), using the PCL as references.[6] All images were analyzed independently by two professionals: a radiologist (SSD) with 18 years of experience in pelvic floor imaging, and a urogynecologist (LCSJ) with 5 years of experience in pelvic imaging. Both physicians were blinded to the surgery performed in each patient.

Outcomes

The primary endpoint was the postoperative mid- and long-term MRI findings for both surgical techniques. The anatomical MRI references followed the ESUR/ESGAR recommendations (►**Fig. 2**).[6]

The staging of the POP followed the ESUR/ESGAR recommendations. Regarding the PCL, the "rule of three" was used for the anterior and apical walls, and the POP was considered pathological starting at grade 2.[14] The anorectal junction (ARJ) has a different staging system; an ARJ descent > 5 cm is defined as grade II.[15] Measurement of the rectocele followed the "rule of two," with grade II (> 4 cm) considered pathological.[7,16]

Failure of the MRI was defined as bladder base stage ≥ 2, vaginal vault stage ≥ 2, or rectocele pouch stage ≥ 2.[6] Objective failure was defined as any point of prolapse beyond the hymen in the POP-Q (Points Ba [point B in the anterior vaginal wall, in centimeters]; Bp [point B in the posterior wall, in centimeters]; or C [point C in the apical wall] > 0).[17] Subjective cure was considered when ICIQ-VS questions 5a and 6a were equal to zero.

The H line (anteroposterior width of the levator hiatus), M-line (represent distance of its descent) and the width of the

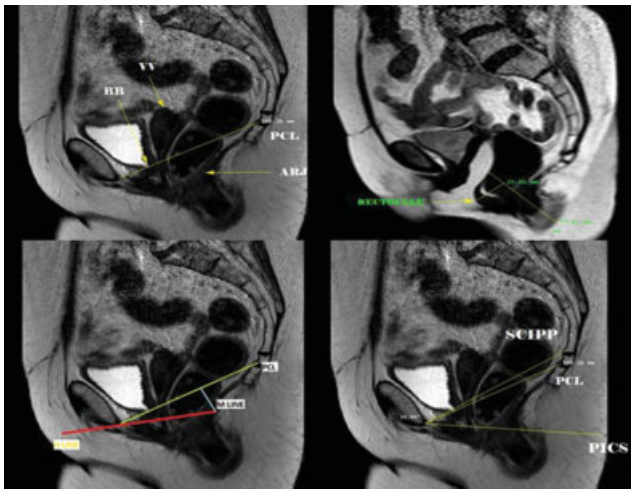

Fig. 2 MRI in sagittal view depicting anatomical points and lines of reference (static and dynamic). Upper left (static); abbreviations: ARJ, anorectal junction; BB, bladder base; PCL, pubococcygeal line; VV, vaginal vault. Upper right (dynamic): rectocele pouch measure. Bottom left (static); red: H-line; light blue: M-line; yellow: pubococcygeal line. Bottom right (static); abbreviations: PCL, pubococcygeal line; PICS, pelvic inclination correction system line; SCIPP, sacrococcygeal inferior pubic point line.

levator hiatus were also measured in millimeters in static MRI to calculate the eLASV: eLASV in $mm^3 = -72.838 + 0.598$ (H-line) + 1.217 (M-line) + 1.136 (width of levator hiatus).[9]

The variables of the physical examination were basically defined by POP-Q measurements.[12] Sociodemographic characteristics were also recorded.

Statistical Analysis

Objective measures, subjective measures, and cure rates are expressed as means or percentages, and the groups were compared using the Chi-squared test and the Fisher exact test. The Fisher exact test was used to compare the objective cure rate by physical examination, subjective cure rate, and MRI-based cure. The MRI and POP-Q were compared using the PCL as a line of reference. We also calculated the eLASV for each patient and compared it with surgical failure. A ROC curve was calculated to look for a cut-off point so that the eLASV could predict worse surgical outcomes. Correlations between the different methods (MRI versus POP-Q) were calculated using the Spearman correlation index. Values of $p < 0.05$ were considered statistically significant. The data were analyzed using the Statistical Analysis System (SAS, SAS Institute, Cary, NC, US) software for Windows, version 9.2.

Results

MRI and Physical Examination Results

►**Fig. 1** shows the flowchart of the studied patients, and ►**Table 1** displays their sociodemographic characteristics. Out of 71 women from the original RCT who were screened for the present study, 12 could not be reached (lost to follow-up), and another 19 patients dropped out because of: refusal to participate ($n = 3$), moved to other states ($n = 3$), health restrictions ($n = 2$), MRI restrictions (cardiac pacemaker; $n = 1$), and absence from 2 scheduled MRI examinations ($n = 10$) (►**Fig. 1**). The final sample comprised 40 women. The mean follow-up was of 27 months. ►**Table 1** shows the baseline characteristics and both groups are similar, except for a higher mean age of menopause for the ASC group ($p = 0.009$).

Table 1 Sample demographics and preoperative status

Variables	ASC ($n = 20$)	VSF-AM ($n = 20$)	*p*-value
Age (years) – mean (±SD)	67.9 (4.9)	67.1 (4.82)	0.75
< 60 years	1	2	
60–69 years	12	10	
> 70 years	7	8	
Pregnancies – mean (±SD)	4.85 (3.7)	5.4 (3)	0.28
Vaginal delivery – mean (±SD)	4.15 (3.39)	4.35 (3.08)	0.74
Body mass index (kg/m^2) – mean (±SD)	27.06 (3.72)	25.79 (4.84)	0.26
Tobacco use (current or previous)	3	4	0.66
Menopause (years of age) – mean (±SD)	51.85 (3.67)	48.4 (4.25)	0.009
Preoperative POP-Q			
Anterior			1.0
stages → 2	1	0	
3	10	10	
4	9	10	
Apical			0.75
stages → 3	11	10	
4	9	10	
Posterior			0.79
stages → 0	1	2	
1	31	2	
2	6	3	
3	3	3	
4	9	10	
GH – mean, in centimeters (±SD)	3.5 (1.08)	3.37 (1.72)	0.06
PB – mean, in centimeters (±SD)	2.15 (0.72)	2.05 (0.77)	0.77

Abbreviations: ASC, abdominal sacrocolpopexy; GH, genital hiatus; PB, perineal body; POP, Pelvic Organ Prolapse; POP-Q, Pelvic Organ Prolapse Quantification System; SD, standard deviation; VSF-AM, vaginal sacrospinous fixation with an anterior mesh.

Regarding the MRI results, the mean kappa coefficient between the two professionals presented good reliability (0.7). The measurements of the vaginal vault were larger for the VSF-AM group than for the ASC group (-0.08 ± 1.84 cm versus -1.43 ± 1.07 cm respectively; $p = 0.007$). The mean rectocele pouch was significantly larger in the ASC than in the VSF-AM group (3.91 ± 0.98 cm versus 3.38 ± 0.66 cm

respectively; $p = 0.033$). The MRI staging showed no significant difference between the groups with regard to the anterior wall ($p = 0.73$), the apical segment ($p = 1.0$), or the posterior wall (ARJ) ($p = 1.0$); however, the rectocele staging revealed significantly more stage-2 diagnoses in the ASC group ($p = 0.013$) (►**Table 2**).

When the physical examination using the POP-Q was performed, more patients in the ASC group had stage 2 and 3 posterior prolapses than those in the VSF-AM group (5 versus 1 respectively; $p = 0.013$). The rate of objective cure was of 65% ($n = 13$) and 75% ($n = 15$) in the VSF-AM and ASC groups respectively ($p = 0.49$) (►**Table 2**). The rate of subjective cure did not present any difference between the groups; in total 85% of the women were cured according the ICIQ-VS ($p = 1.0$) (►**Table 2**).

Table 2 MRI and POP-Q measurements of the operated patients

Variables	VSF-M ($n = 20$)	ASC ($n = 20$)	*p*-value
Objective cure	13	15	0.49
Subjective cure	17	17	1.0
MRI measures			
Bladder base – mean (±SD)	1.6 (1.8)	1.1 (1.6)	0.51
Vaginal vault – mean (±SD)	-0.08 (1.8)	-1.4 (1.0)	**0.007**
Anorectal junction – mean (±SD)	2.4 (0.9)	2.5 (1.0)	0.93
Rectocele – mean (±SD)	3.3 (0.6)	3.9 (0.9)	**0.033**
Bladder base MRI stage			
Stages 0 and 1	13	14	0.73
Stage ≥2	7	6	0.73
Vaginal vault MRI stage			
Stages 0 and 1	16	17	1.0
Stage ≥2	4	3	1.0
Anorectal junction MRI stage			
Stage 0	14	14	1.0
Stage 1 or 2	6	6	1.0
Rectocele MRI stage			
Stage 0 or 1	18	11	
Stage 2	2	9	0.0013
MRI cure	12	9	0.52
Apical POP-Q			
stage 0	12	14	0.74
stage 1	7	6	
stage 2	1	0	
Anterior (bladder)			
stage 0	7	8	0.27
stage 1	2	2	
stage 2	7	10	
stage 3	4	0	
Posterior (rectal)			
stage 0	19	11	0.013
stage 1	0	4	
stage 2	1	4	
stage 3	0	1	

Abbreviations: ASC, abdominal sacrocolpopexy; MRI, Magnetic resonance imaging; POP-Q, pelvic organ prolapse quantification; SD, standard deviation; VSF-AM, vaginal sacrospinous fixation with an anterior mesh.

MRI versus Physical Examination – POP-Q

When comparing failure rates between both methods (MRI and physical examination), there was a significant correlation with anterior wall failure: 13 patients had MRI-based failures, and 11 had POP-Q failures ($p = 0.002$) and general failures ($p = 0.007$). The MRI detected more apical failures than physical examination (7 versus 0). In the posterior segment, there were only 2 POP-Q failures versus 12 MRI-based failures with regard to the ARJ ($p = 0.08$), and 11 failures after rectocele pouch MRI-staging ($p = 0.47$). Using subjective failure as a reference, we found no association between the POP-Q findings and the rate of subjective cure ($p = 0.55$); we have also found no association between POP-Q measurements and MRI-based cure in general ($p = 0.6$), in the anterior wall (bladder base; $p = 1.0$), in the apical wall (vaginal vault; $p = 1.0$), or in the posterior wall (rectocele; $p = 0.12$) (►**Table 3**).

Table 3 Comparison among MRI, physical examination (POP-Q) and subjective cure rates

Vaginal wall - n (%)	MRI failure	POP-Q Failure	*p*-value	Subjective failure	*p*-value
General	19 (47.5)	12 (30)	0.007[a]	6 (15)	0.6[e] 0.055[f]
Anterior	13 (32.5)	11 (27.5)	0.02[b]	6 (15)	0.31[g] 1.0[h]
Apical	7 (17.5)	0	*	6 (15)	*
Posterior					
ARJ	12 (30)	2 (5)	0.08[c]	6 (15)	0.6[i]
Rectocele	11 (2.5)	2 (5)	0.47[d]		0.12[j]

Abbreviations: ARJ, anorectal junction; MRI, magnetic resonance imaging; POP-Q, Pelvic Organ Prolapse Quantification System.
Notes:
[a]MRI general failure versus POP-Q general failure (Fisher exact test).
[b]Bladder base to PCL in the MRI (grade ≥ 2) versus POP-Q Ba > 0 (Fisher exact test).
[c]Anorectal junction to PCL in the MRI (grade ≥ 1) versus POP-Q Bp > 0.
[d]Rectocele measure in the MRI (grade ≥ 2) versus POP-Q Bp > 0.
[e]Subjective cure in the ICIQ-VS versus general MRI cure.
[f]Subjective cure in the ICIQ-VS versus POP-Q general failure.
[g]Subjective cure in the ICIQ-VS versus POP-Q Ba > 0 (grade ≥ 2).
[h]Subjective cure in the ICIQ-VS versus BB to PCL in the MRI.
[i]Subjective cure in the ICIQ-VS versus ARJ to PCL in the MRI (grade ≥ 1).
[j]Subjective cure in the ICIQ-VS versus rectocele pouch stage in the MRI (grade ≥ 2).
*Vaginal vault to PCL in the MRI (stage ≥ 2) versus POP-Q C > 0 and subjective cure (ICIQ-VS questions 5a and 6a equal to zero) – homogenous sample, no test was made.
Abbreviations: ARJ, anorectal juntion; Ba, point B in the anterior vaginal wall, in centimeters;BB, bladder base; Bp, point B in the posterior wall, in centimeters; C, point C in the apical wall, in centimeters; ICIQ-VS, international consultation on incontinence questionnaire - vaginal symptoms; MRI, Magnetic resonance imaging; PCL, pubococcygeal line; POP-Q, pelvic organ prolapse quantification.

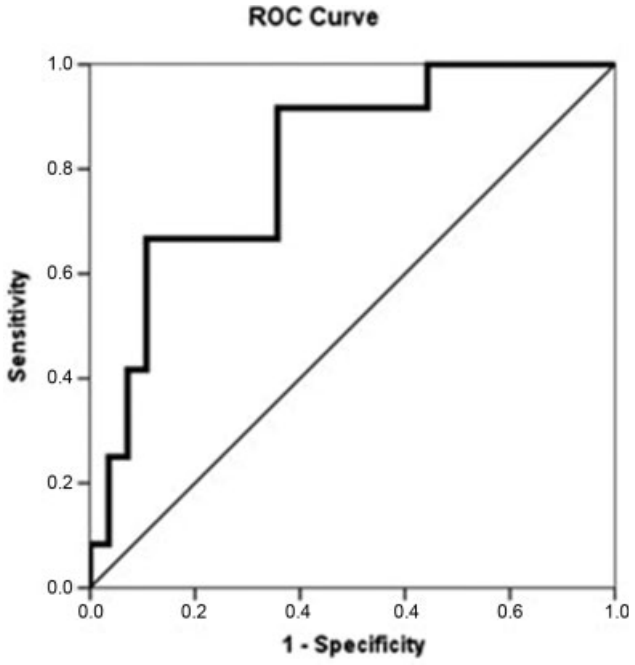

Fig. 3 eLASV measurement (ROC curve). Area under the curve: 0.813; $p = 0.002$; 95%CI: 0.672–0.953; cutoff point: eLASV $\geq$ 33.5 mm3.

Levator Ani Subtended Volume (LASV)

The width of the levator hiatus and the length of the H- and M-lines were measured in static MRI for eLASV calculation, and the numbers were compared by dividing the sample according to POP-Q success. The H- and M-lines were significantly longer among the patients who presented POP-Q failure than among those who achieved objective success (69.6 ± 5.6 mm versus 62.2 ± 7.8 mm respectively; $p = 0.004$; and 23.5 ± 7.8 mm versus 16.7 ± 6.9 mm respectively; $p = 0.004$). The width of the levator hiatus was similar: 38.5 ± 8.1 mm for the patients with failure versus 34.6 ± 5.5 mm for those with success ($p = 0.08$).

The eLASV was calculated for each patient, and it was larger among those with failure than among those with success ($41.1 \pm 16.5\,mm^3$ versus $24.1 \pm 13.6\,mm^3$ respectively; $p = 0.002$). The area under the ROC curve was of 0.813 ($p = 0.002$; confidence interval [CI] = 0.672–0.953), and the optimal cutoff was of $33.5\,mm^3$, with specificity of 89.2% (70.6% to 97.1%), sensitivity of 66.6% (35.4% to 88.7%), and accuracy of 83.5% (66.4% to 92.1%). Among the patients who experienced surgical failure, 66.6% had an eLASV of $\geq 33.5\,mm^3$ versus 10.7% among those who experienced surgical success ($p < 0.001$) (►**Fig. 3**).

Discussion

The present study showed good results for both vaginal and abdominal surgeries, especially regarding subjective outcomes at the mean 27-month follow-up. The MRI staging showed greater failures compared with the POP-Q, and neither correlated well with the symptomatology.

In their nonrandomized study, Ginath et al.[18] compared two surgical approaches (ASC versus Prolift vaginal mesh) and showed equally good postoperative results for both techniques in the POP-Q, but not in the MRI, which revealed no difference between the preoperative and postoperative anatomical positions and angles relative to the PCL. Van der Weiden et al.[19] evaluated 43 women at 6 months after laparoscopic ASC, and found great improvement in prolapse measures for all compartments, but only for the apex in the MRI assessment, resulting in a poor correlation with the POP-Q.[19] Conversely, Brocker et al.[20] studied 69 patients who underwent vaginal mesh repair for POP; during the one-year follow-up, both the dynamic MRI and the clinical examination showed good results, but the MRI showed more prolapse.

The correlation between the POP-Q and the symptoms is frequently poor because the symptoms do not necessarily correlate with the severity of the POP.[21] The MRI assessment seems to be even more dissociated from the symptomatology – MRI scans often describe a great number of prolapses in asymptomatic women.[22] We also found no significant correlation between subjective cure or quality of life questionnaire scores and MRI-based prolapse staging and failure definitions.

Several studies[4,23] have compared physical examination findings with different lines of reference and points of anatomical interest in the MRI, mainly with poor results. The anterior wall seems to show good accordance.[2] Our results were also better for the anterior compartment in terms of a significant association between MRI-based pathological POP and a Ba point > 0 in the POP-Q. We found a rate of 70% of objective cure, a rate of 85% of subjective cure, and a rate of 52.5% of MRI-based cure for the whole sample, without a significant association among symptomatology, POP-Q, and MRI. The MRI staging system showed a greater number of pathological prolapses than the POP-Q and the symptoms in our sample.

The MRI has become an important asset in the evaluation of pelvic-floor dysfunction.[24] The most commonly used line of reference, the PCL, is also the one with the greatest interobserver correlation indexes.[7] This line unites the pubic bone and coccyx, but precise definitions vary among studies. We used the PCL as described by El Sayed et al.[6] in 2017,; that is, a line from the inferior tip of the pubic bone to the anterior aspect of the last visible coccygeal joint.

Another important contribution of the MRI is the proper evaluation of the eLASV and its role in pelvic support. We intended to do a study similar to the research by Wyman et al.[9]; they found a cutoff in the eLASV that correlated with surgical failure: they retrospectively analyzed a cohort of 66 women who underwent laparoscopic uterosacral ligament suspension, and found a significant association between the eLASV and surgical failure at the one-year follow-up, with a cutoff value of $38.5\,mm^3$. In our study, an eLASV $\geq 33.5\,mm^3$ was associated with surgical failure, with good accuracy. However, as this parameter was analyzed postoperatively, we cannot say that this would be a predictor of surgical failure, but as a diagnosis and/or audit of the surgery performed. Our sample might have comprised women with worse preoperative prolapses, and a smaller eLASV could be associated with failure, given that other important factors such as age or parity also play important roles in

surgical outcomes. Apart from that, we evaluated a different surgical modality.

Our study has many strengths. We studied a homogeneous group of women without previous surgical treatment who were randomized according to two surgical POP correction techniques for a mean follow-up >2 years. We have followed the latest recommendations regarding MRIs for prolapse. Our limitations are: we did not use rectal gel or perform MRI defecography, and this might have impaired our evaluation of the posterior wall. Additionally, almost all operations were performed for advanced cases of prolapse, which affected the preoperative MRI examinations of these patients for purposes of comparison. The assessment of the eLASV by postoperative MRI could have produced some bias, and the fact that the ARJ was not adequately visualized may have impaired the measurement of the H-line; this can alter the eLASV assessment as well. However, we do not believe that our surgical techniques directly affected the measurements used for this calculation (that is, the length of the H- and M-lines and the width of the levator hiatus). Finally, we included a limited number of patients, and further studies with larger samples are necessary.

Conclusion

The MRI and POP-Q cure rates were associated, but only in the anterior wall. The MRI staging showed greater failures compared with the POP-Q, and neither correlated well with the symptomatology. Both surgical techniques for advanced prolapse were similar in terms of the objective POP-Q and MRI cure rates. The objective results were poorer in the posterior compartment in the ASC group. The eLASV was larger among the patients whho experienced surgical failure, and when this value was $\geq 33.5\ mm^3$, there was a significant increase in the chance of postoperative failure, but with the limitation that it was only analyzed postoperatively.

Contributions

All authors of the present study made substantial contributions to conception and design, data collection or analysis, and interpretation of data; participated in the writing of the article or critical review of the intellectual content, and provided final approval of the version to be published.

Conflict of Interests

The authors have no conflict of onterests to declare.

References

1 Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al; Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008;300(11):1311–1316. Doi: 10.1001/jama.300.11.1311

2 Gousse AE, Barbaric ZL, Safir MH, Madjar S, Marumoto AK, Raz S. Dynamic half Fourier acquisition, single shot turbo spin-echo magnetic resonance imaging for evaluating the female pelvis. J Urol. 2000;164(05):1606–1613. Doi: 10.1016/S0022-5347(05)67040-1

3 Comiter CV, Vasavada SP, Barbaric ZL, Gousse AE, Raz S. Grading pelvic prolapse and pelvic floor relaxation using dynamic magnetic resonance imaging. Urology. 1999;54(03):454–457. Doi: 10.1016/s0090-4295(99)00165-x

4 Pizzoferrato AC, Nyangoh Timoh K, Fritel X, Zareski E, Bader G, Fauconnier A. Dynamic Magnetic Resonance Imaging and pelvic floor disorders: how and when? Eur J Obstet Gynecol Reprod Biol. 2014;181:259–266. Doi: 10.1016/j.ejogrb.2014.07.025

5 Yang A, Mostwin JL, Rosenshein NB, Zerhouni EA. Pelvic floor descent in women: dynamic evaluation with fast MR imaging and cinematic display. Radiology. 1991;179(01):25–33. Doi: 10.1148/radiology.179.1.2006286

6 El Sayed RF, Alt CD, Maccioni F, Meissnitzer M, Masselli G, Manganaro L, et al; ESUR and ESGAR Pelvic Floor Working Group. Magnetic resonance imaging of pelvic floor dysfunction - joint recommendations of the ESUR and ESGAR Pelvic Floor Working Group. Eur Radiol. 2017;27(05):2067–2085. Doi: 10.1007/s00330-016-4471-7

7 DeLancey JO, Morgan DM, Fenner DE, Kearney R, Guire K, Miller JM, et al. Comparison of levator ani muscle defects and function in women with and without pelvic organ prolapse. Obstet Gynecol. 2007;109(2 Pt 1):295–302. Doi: 10.1097/01.AOG.0000250901.57095.ba

8 Rodrigues Junior AA, Herrera-Hernadez MC, Bassalydo R, McCullough M, Terwilliger HL, Downes K, Hoyte L, et al. Estimates of the levator ani subtended volume based on magnetic resonance linear measurements. Neurourol Urodyn. 2016;35(02):199–205. Doi: 10.1002/nau.22691

9 Wyman AM, Rodrigues AA Jr, Hahn L, Greene KA, Bassaly R, Hart S, et al. Estimated levator ani subtended volume: a novel assay for predicting surgical failure after uterosacral ligament suspension. Am J Obstet Gynecol. 2016;214(05):611.e1–611.e6. Doi: 10.1016/j.ajog.2015.11.005

10 Juliato CRT, Santos-Junior LC, de Castro EB, Dertkigil SS, Brito LGO. Vaginal axis after abdominal sacrocolpopexy versus vaginal sacrospinous fixation-a randomized trial. Neurourol Urodyn. 2019;38(04):1142–1151. Doi: 10.1002/nau.23970

11 de Castro EB, Brito LGO, Juliato CRT. Vaginal hysterectomy with bilateral sacrospinous fixation plus an anterior mesh versus abdominal sacrocervicopexy for the treatment of primary apical prolapse in postmenopausal women: a randomized controlled study. Int Urogynecol J Pelvic Floor Dysfunct. 2020;31(02):365–372. Doi: 10.1007/s00192-019-03948-3

12 Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarsko P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996;175(01):10–17. Doi: 10.1016/s0002-9378(96)70243-0

13 Tamanini JT, Almeida FG, Girotti ME, Riccetto CL, Palma PC, Rios LA. The Portuguese validation of the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS) for Brazilian women with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(10):1385–1391. Doi: 10.1007/s00192-008-0641-8

14 Woodfield CA, Hampton BS, Sung V, Brody JM. Magnetic resonance imaging of pelvic organ prolapse: comparing pubococcygeal and midpubic lines with clinical staging. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(06):695–701. Doi: 10.1007/s00192-009-0865-2

15 Halligan S, Spence-Jones C, Kamm MA, Bartram CI. Dynamic cystoproctography and physiological testing in women with urinary stress incontinence and urogenital prolapse. Clin Radiol. 1996;51(11):785–790. Doi: 10.1016/s0009-9260(96)80006-7

16 Hecht EM, Lee VS, Tanpitukpongse TP, Babb JS, Taouli B, Wong S, et al. MRI of pelvic floor dysfunction: dynamic true fast imaging with steady-state precession versus HASTE. AJR Am J Roentgenol. 2008;191(02):352–358. Doi: 10.2214/AJR.07.3403

17 Nygaard I, Brubaker L, Zyczynski HM, Cundiff G, Richter H, Gantz M, et al. Long-term outcomes following abdominal sacrocolpopexy for

pelvic organ prolapse. JAMA. 2013;309(19):2016–2024. Doi: 10.1001/jama.2013.4919

18 Ginath S, Garely AD, Luchs JS, Shahryarinejad A, Olivera CK, Zhou S, et al. Magnetic resonance imaging of abdominal versus vaginal prolapse surgery with mesh. Int Urogynecol J Pelvic Floor Dysfunct. 2012;23(11):1569–1576. Doi: 10.1007/s00192-012-1783-2

19 van der Weiden RM, Rociu E, Mannaerts GH, van Hooff MH, Vierhout ME, Withagen MI. Dynamic magnetic resonance imaging before and 6 months after laparoscopic sacrocolpopexy. Int Urogynecol J Pelvic Floor Dysfunct. 2014;25(04):507–515. Doi: 10.1007/s00192-013-2254-0

20 Brocker KA, Alt CD, Rzepka J, Sohn C, Hallscheidt P. One-year dynamic MRI follow-up after vaginal mesh repair: evaluation of clinical, radiological, and quality-of-life results. Acta Radiol. 2015; 56(08):1002–1008. Doi: 10.1177/0284185114544241

21 Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol. 2001;185(06):1332–1337, discussion 1337–1338 . Doi: 10.1067/mob.2001.119078

22 Cimsit C, Yoldemir T, Akpinar IN. Prevalence of dynamic magnetic resonance imaging-identified pelvic organ prolapse in pre- and postmenopausal women without clinically evident pelvic organ descent. Acta Radiol. 2016;57(11):1418–1424. Doi: 10.1177/0284 185115589123

23 Broekhuis SR, Fütterer JJ, Barentsz JO, Vierhout ME, Kluivers KB. A systematic review of clinical studies on dynamic magnetic resonance imaging of pelvic organ prolapse: the use of reference lines and anatomical landmarks. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(06):721–729. Doi: 10.1007/s00192-009-0848-3

24 Attenberger UI, Morelli JN, Budjan J, Herold A, Kienle P, Kleine W, et al. The value of dynamic magnetic resonance imaging in interdisciplinary treatment of pelvic floor dysfunction. Abdom Imaging. 2015;40(07):2242–2247. Doi: 10.1007/s00261-015-0476-y

COVID-19: Uncertainties from Conception to Birth

Covid-19: incertezas desde a concepção até o nascimento

Bruno Ramalho de Carvalho[1] Karina de Sá Adami[2] Walusa Assad Gonçalves-Ferri[3] Marise Samama[4] Rui Alberto Ferriani[5] Alessandra Cristina Marcolin[5]

[1] Hospital Sírio-Libanês, Brasília, DF, Brazil
[2] Maternidade Climério de Oliveira, Universidade Federal da Bahia, Salvador, BA, Brazil
[3] Department of Pediatrics, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
[4] Department of Gynecology, Escola Paulista de Medicina, Universidade Federal de São Paulo, SP, Brazil
[5] Department of Gynecology and Obstetrics, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil

Address for correspondence Bruno Ramalho de Carvalho, MD, MSc, SGAS 614, Conjunto C, Sala 177, 70200-740, Edifício VITRIUM - Centro Médico Inteligente, Asa Sul, Brasília, DF, Brazil (e-mail: ramalho.b@gmail.com).

Rev Bras Ginecol Obstet 2021;43(1):54–60.

Abstract

Scientific information on the impact of the new coronavirus (SARS-CoV-2) on the health of pregnant women, fetuses and newborns is considered of limited confidence, lacking good-quality evidence, and drawing biased conclusions. As a matter of fact, the initial impressions that the evolution of COVID-19 was no different between pregnant and non-pregnant women, and that SARS-CoV-2 was not vertically transmitted, are confronted by the documentation of worsening of the disease during pregnancy, poor obstetric outcomes, and the possibility of vertical transmission. The present article aims to compile the data available on the association of COVID-19 and reproductive events, from conception to birth.

Keywords
- COVID-19
- severe acute respiratory syndrome coronavirus 2
- ovary
- testis
- conception
- pregnancy

Resumo

As informações científicas sobre o impacto do novo coronavírus, SARS-CoV-2, na saúde de gestantes, fetos e recém-nascidos são consideradas de confiabilidade limitada, sem evidências de boa qualidade, e levam a conclusões enviesadas. De fato, as impressões iniciais de que a evolução da Covid-19 não era diferente entre mulheres grávidas e não grávidas, e de que o SARS-CoV-2 não era transmitido verticalmente, são confrontadas pela documentação de agravamentos da doença durante a gravidez, resultados obstétricos negativos, e a possibilidade de transmissão vertical. Este artigo tem como objetivo compilar os dados disponíveis sobre a associação entre a Covid-19 e os eventos reprodutivos, desde a concepção até o nascimento.

Palavras-chave
- Covid-19
- síndrome respiratória aguda grave pelo coronavírus 2
- ovário
- testículo
- concepção
- gravidez

received
August 21, 2020
accepted
October 26, 2020

DOI https://doi.org/10.1055/s-0040-1721856.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Introduction

In the last 8 months, the world has been experiencing a pandemic caused by the new coronavirus (SARS-CoV-2). Starting with the first reported cases of pneumonia in the city of Wuhan, Hubei province, China,[1] by August 16, 2020, 21,294,845 COVID-19 cases had already been confirmed, with a total of 761,779 deaths.[2] On that date, the Brazilian Ministry of Health had registered 3,340,197 cases of the disease, and 107,852 deaths.[3]

It is a fact that scientific information on the impact of SARS-CoV-2 on the health of pregnant women, fetuses and newborns is considered of limited confidence, lacking good-quality evidence, and drawing biased conclusions. As a matter of fact, the initial impressions that the evolution of COVID-19 was no different between pregnant and non-pregnant women,[4–6] and that SARS-CoV-2 was not vertically transmitted,[4,7,8] are confronted by the documentation of worsening of the disease during pregnancy, poor obstetric outcomes,[9–14] and the possibility of vertical transmission.[15–20]

Of note, uncertainty is the rule at the moment. Some state that, then, there are no convincing reasons to recommend people to avoid pregnancy.[21] In contrast, it seems that there are at least 5 uncertainties/reasons to advise against pregnancy at this time, if it is possible, namely: 1) there is confounding evidence on the evolution of COVID-19 in pregnant and non-pregnant women; 2) despite the fact that the bulk of the literature suggests the effectiveness of the placental barrier in preventing fetal infection by SARS-CoV-2, fewreports[15,20] indicating vertical transmission sustain medical concerns; 3) it is not clearly known whether infection by SARS-CoV-2 in the first trimester can cause birth defects or pregnancy loss; 4) it is not known whether the newborns of women infected by SARS-CoV-2 will have the same clinical evolution as those born to healthy mothers; and 5) the possibility of SARS-CoV-2 transmission through the sexual route, and the role of its theoretical effect on the gonads and gametes, in vivo and in vitro.

The present review article aims to compile available data on each of the aforementioned uncertainties, providing theoretical background for counseling and caring for women who are planning a pregnancy, those who are pregnant, or those who have given birth during the COVID-19 pandemic.

SARS-CoV-2 in Reproductive Tissues and Gametes

The expression of angiotensin-converting enzyme 2 (ACE2) and other viral entry facilitators in male and female gonads and gametes, as well as the endometrium,[22–25] raises concerns on the interference of SARS-CoV-2 on reproductive health and conception.[26] To date, it is not known if the new coronavirus affects reproductive function via the ACE2 receptors, and which consequences, if any, the infection by the virus would have on the quality of the gametes, embryo development and implantation, or pregnancy in its very beginning.[27]

Indeed, there are reports of human orchitis related to other coronaviruses.[28] Then, the possibility of immediate or long-term SARS-CoV-2-related impairment in the male reproductive functions is a genuine concern. Theoretically, inflammation in the seminiferous epithelium, Leydig and Sertoli cells, and the epididymis could lead to oxidative stress and sperm DNA fragmentation, as well as diminished testosterone secretion and disrupted spermatogenesis.[29]

Regarding conception, the possibility of sexual transmission is another matter of concern. SARS-CoV-2 has already been detected in the small intestine, liver, pancreas, kidney and sweat glands, so, at least theoretically, there are other potential routes of transmission than the respiratory one.[30] The data available on the sexual route of transmission are controversial. In a Chinese cohort study,[31] SARS-CoV-2 was detected in semen samples from infected patients, both in the acute and in the recovery phases. In contrast, other reports did not find the virus in semen collected 8 days after COVID-19 diagnosis,[32] or 30 days.[33] Divergent findings about SARS-CoV-2 in the semen support the need for larger studies, which should not just confirm the presence of the virus in the semen, but provide information about its length of stay and the possibility of transmission by sexual contact.

COVID-19 during Pregnancy

Maternal and fetal complications were documented in previous epidemics caused by other coronaviruses, namely the severe acute respiratory syndrome (SARS)[34] and the Middle East respiratory syndrome (MERS).[35] In addition to historical aspects, physiological adaptations during pregnancy are usually considered to be potential factors of vulnerability to any type of infection. Moreover, some authors suggest that pregnant women are more vulnerable to infective respiratory agents than the general population, and they may respond to COVID-19 with a "cytokine storm," which may lead to severe morbidity.[36] Beyond this, the signs or symptoms related to pregnancy may overlap with other symptoms of COVID-19, thereby making the diagnosis challenging. So, as a precaution, pregnancy and the puerperium are now considered high-risk situations for severe illness from COVID-19.[37,38]

In June 2020, a systematic review[39] of 755 pregnant women presenting with COVID-19 provided only poor-quality evidence, and the authors could not rule out potential worsening of the clinical conditions of pregnant women infected with SARS-CoV-2, or whether the infection is associated with comorbidities or not. Actually, the absence of studies with reliable methodology still greatly limits data interpretation. Thus, it cannot yet be said that the disease evolves in the same way in pregnant and non-pregnant women, nor can pregnancy be excluded from the list of potential risk conditions.

In the United States, the Centers for Disease Control and Prevention (CDC) has recently published a series[12] of 8,207 pregnant women in the United States, associating pregnancy to an increased risk of hospitalization (31.5% in pregnant women *versus* 5.8% in non-pregnant women; adjusted relative risk [aRR] = 5.4; 95% confidence interval [95%CI] = 5.1 to 5.6), admission to the Intensive Care Unit (aRR = 1.5; 95%CI = 1.2 to 1.8), and the need for mechanical ventilation (aRR = 1.7; 95% CI = 1.2 to 2.4) due to COVID-19. Nevertheless, the increase in

morbidity was not reflected in increased mortality, which was similar between pregnant and non-pregnant women (0.2% in both groups; aRR = 0.9; 95%CI = 0.5 to 1.5).

Recent data show that most of the women (~ 85%) contracting SARS-CoV-2 will exhibit mild characteristics of the disease. The rates of severe disease vary between 9.3% and 11.1%, and the rates of critical disease vary between 2% and 6.9%, which are just as similar to the rates for the general population.[40] However, local scenarios of care for pregnant women should also be taken into account to better advise the women about the possibility of becoming pregnant. In Brazil, for example, a country with high rates of maternal mortality when compared with developed countries, 124 pregnant or postpartum women have died due to COVID-19 until June 18, 2020–representing a mortality rate of 12.7% –, a figure that currently surpasses the total number of COVID-19-related maternal deaths reported throughout the rest of the world. These data suggest an aggravation of the bad preexisting conditions of prenatal care due to COVID-19 infection.[10]

In the context of the COVID-19 pandemic, the high rates of preterm birth, cesarean section,[41,42] and preeclampsia,[43] and the increased risk of admissions to the intensive care unit[12] persist as the most common reasons for concern. Outstandingly, the most frequent COVID-19 adverse obstetric outcome seems to be preterm birth, occurring in 41.1% (95%CI: 25.6 to 57.6) of cases.[42] In view of this little-known disease, it is recommended to consider pregnancy a potential aggravating factor for COVID-19, as is customary for other diseases, and, conversely, to consider this infection a cause of negative obstetric and perinatal outcomes. As a precautionary action, it is reasonable to institute unrestricted monitoring measures for pregnant women infected with SARS-CoV-2, and even to suggest that they should be rigorously tested before delivery or before the first contact with the newborns.[39]

Evidence of Vertical Transmission of SARS-CoV-2

Vertical transmission of previous coronaviruses was hypothesized in preliminary studies,[44,45] but such an occurrence was not reported with either SARS or MERS; therefore, it seems that the likelihood of intrauterine maternal-fetal transmission of coronaviruses is low.[46,47]

To date, it cannot be said that the placental barrier is capable of preventing the vertical transmission of SARS-CoV-2. Often times, tests of the amniotic fluid, cord blood, and neonatal throat swab samples were not able to evidence the vertical transmission of SARS-CoV-2, at least in mid-[8] and late pregnancy.[42,47] However, third trimester placentas from COVID-19 patients have been proven to be more likely to present maternal/fetal vascular malperfusion,[48] and the existence of vertical transmission of SARS-CoV-2 has already been demonstrated in some case reports[49,50] and small case series.[51,52] Moreover, the detection of anti-SARS-CoV-2 immunoglobulin M (IgM) in cord and/or early-life neonatal blood supports the suspicion of intrauterine infection, since IgM is not transplacentally transferred from the mother to the fetus.[17]

Recently, in early July 2020, during one of the virtual sessions of the Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), researcher Wafaa Essahib presented evidence of the expression of ACE2 and other viral-entry facilitators in human oocytes and blastocysts, supporting a new hypothesis of transmission of the virus from the mother to the embryo, which would be cause for apprehension for initial pregnancies under COVID-19.[53] Moreover, the expression of the ACE2 receptor has been reported in the placenta, which may increase the risk of vertical transmission of the virus.[54]

It is worth saying that, if maternal-fetal transmission happens, little is known about its impact over embryogenesis, morphogenesis, fetal development, and health.

The Health of the Fetus and the Newborn

Initial data suggested that maternal SARS-CoV-2 infection does not seem to be more harmful in the first trimester than it is throughout the whole pregnancy. Infection was not associated with increased thickness of the nuchal translucency or risk of pregnancy loss.[55] However, other viruses, depending on the gestational age at the moment of infection, have been associated with congenital anomalies and developmental delay later on, like Zika.[56] Thus, the little time since the first studies on the behavior of SARS-CoV-2 is insufficient to evaluate its real impact on neonates.

The RNA of SARS-CoV-2 has already been found in placental and amniotic membrane samples, indicating the possibility of fetal viral exposure during labor and delivery.[57] Placental infection has also been demonstrated as one of the negative outcomes of pregnancy, not just by identification of viral RNA, but by histological findings of subchorial inflammatory infiltrates, increased intervillous fibrin deposition, and funisitis (suggesting inflammatory response from the fetus).[14]

According to the systematic review of 598 newborns, strong evidence of SARS-CoV-2 infection was not available until June 2020, especially considering the lack of reliable information on the care provided during and after delivery, as well as the lack of adequate collection of biological samples from newborns for the SARS-CoV-2 test.[39] Indeed, the data available to date suggest that COVID-19 infection is uncommon among newborns, which are frequently asymptomatic. Furthermore, it was not possible to associate a higher risk of infection to vaginal birth, breastfeeding or close contact with the infected mother.[58]

It is worth highlighting the fact that there has been a decrease in extremely premature births during the COVID-19 pandemic.[59,60] There are still no definite explanations for this unprecedent reduction, but there are two hypotheses: the disease leads to a greater number of early pregnancy losses; or the measures of social distancing and confinement lead to lower exposure of pregnant women to the behavioral and socio-environmental factors linked to prematurity.

Postponing Pregnancy versus Age-related Fertility Loss

Since the deleterious effect of postponing pregnancy by a few months may not be significant,[61–65] even for women of advanced reproductive age or with diminished ovarian reserve,[64] such a decision has been encouraged by some authors.[65,66]

In a very recent retrospective cohort study on in vitro fertilization treatment for women with diminished ovarian reserves, Romanski et al.[65] observed that a delay of up to 180 days did not seem to negatively affect live birth rates, even for women with anti-Mullerian hormone levels < 0.5 - ng/mL, or those older than 40 years of age. The authors recognized a potential selection bias in their study, but considered the results sufficient to reassure that short-term delay in the treatment will not affect its outcomes, in situations that such a delay is deemed necessary or prudent, like the current COVID-19 pandemic.

For cases of infertility that require assisted reproduction, the dilemmas can be even greater. Advice on whether or not to postpone treatment includes information on the lack of knowledge of the effects of COVID-19 on pregnancy, as well as the possible risks of vertical transmissibility and transmission via the gametes, as well as risks of the virus being stored in the gametes and the embryo.[26,66] It should be emphasized that the treatment per se lasts several days, and requires several return visits, and, depending on the region's epidemiological situation, it may be inadvisable for patients to move and expose themselves to medical environments. Besides that, the infection can occur during the treatment period, causing suspension at any stage, which can generate significant emotional distress. Finally, the lack of consensus on screening methods contributes to the uncertainty, since the diagnostic tests contain highly-variable sensitivities and specificities, and unfortunately there is no consensus on which one is the best and safest to detect the disease in real time.[67]

Perspectives for the Future

Pregnancy and Delivery

At this moment, the best knowledge on COVID-19 in pregnancy is based on observational studies, case series and reports, as well as estimates from the surveillance of sanitary authorities in each country. These provide insufficient information to consider changes in the management and definition of the appropriate interventions. Wise strategies minimizing the risk for the pregnancy and poor obstetric outcomes, mainly those associated to preterm birth, pre-eclampsia, and cesarean section, will probably be defined once there is wide knowledge of the disease, which will come with time and experience.

There is no doubt that many aspects remain unclear to date, and randomized clinical trials are expected to provide knowledge from preconception counseling and preventive measures during prenatal care to clinical presentation and management of the infection during pregnancy and the puerperium. Oxford-Horrey et al.[68] opportunely highlight that supportive care must focus on recovery rather than delivery as the main treatment endpoint. Unfortunately, the inclusion of pregnant women in registered trials still seems to be small: among all 3,009 studies registered for COVID-19 in the ClinicalTrials.gov database (https://clinicaltrials.gov) on August 16, 2020, only 66 ($\sim$ 2.2%) included pregnant women, of which only 6 had been completed, 1 had been withdrawn, and 20 were not yet recruiting.

Specifically in Brazil, the high rates of maternal deaths related to COVID-19 might be associated with poor quality in prenatal and obstetric care. Indeed, SARS-CoV-2 may be an aggravating agent of a previous inflammatory status present in hypertensive disease and/or obesity, which are very prevalent in the country. However, social risks and limited access to health care are probably associated to late proper care, potentially contributing to maternal deaths.[69]

Finally, childbirth care under COVID-19 is still one of the main concerning aspects. However, it is worth observing that, to date, there is no evidence of the intrapartum transmission of SARS-CoV-2 to the newborn, and vaginal birth with appropriate precaution measures remains the mode of delivery in mild maternal disease. Moreover, it is essential to reinforce that interventions to shorten the lenght of the second stage of labor and/or to avoid delayed umbilical cord clamping and/or skin-to-skin contact are not supported by good evidence, as well as COVID-19 alone is not an indication for cesarean section. Instead, high rates of cesarean deliveries under COVID-19 are concerning, since they have the potential to promote clinical maternal deterioration.[70]

Fetal and/or Newborn Health

The effects of viremia on the embryo and/or the fetus in the first and second trimesters of pregnancy are poorly known. Actually, women who became pregnant just before or just after the beginning of the pandemic have not yet delivered their babies; therefore, information from the main pregnancy outcomes is still lacking. With regard to neonates, perhaps the great prospect for the future is the clarification of the causes of prematurity. To date, no one can determine if the higher rates of preterm birth under COVID-19 are spontaneous or elective due to maternal clinical complications or fetal compromise. As a matter of fact, it is not known whether children born to mothers infected by the SARS-CoV-2 will have the same clinical evolution as those born to healthy mothers. And such an answer is totally dependent on time.

Availability and Reliability of Diagnostic Tests

COVID-19 screening in early pregnancy has been proposed as strategy to better plan maternal-fetal health surveillance programs in epidemic areas, combining serological tests and nucleic acid testing,[71] mainly for those women presenting for delivery. Those who defend universal screening for parturient women do so based on the benefits of determining hospital isolation practices and bed assignments, informing the neonatal care team, and guiding the use of personal protective equipment.[72] In contrast, the observation of 3,963 women admitted to labor and delivery in California, United States, resulted in a very low prevalence of positive SARS-CoV-2 testing,[73] raising doubts about the benefit of mass testing,

especially in countries like Brazil, in which the testing of large populations still does not seem to be a reality.

Vaccination

There is no doubt that scientific community is watching a race to launch a vaccine against SRAS-CoV-2. There is also no doubt that, with the first vaccine approved in a phase-III study, we will see one of the fastest, if not the fastest, launches of a vaccine in the entire history of active immunization. But there are questions that will be answered only over time: how effective will the vaccine be? Will there be enough distribution to interrupt or, at least, slow the spread of the virus? How safe will vaccinated women be to decide to become pregnant with the virus still spreading? And, finally, since the immune responses to vaccination in pregnant women may not be the same as those observed in non-pregnant women,[74] how will the safety of vaccination in pregnancy will be assessed?

Conclusion

Health professionals and society as a whole have doubts about the impact of COVID-19 on reproductive outcomes, from the impact of SARS-CoV-2 in the gonads and/or gametes to its consequences to the newborn. Data regarding COVID-19 during pregnancy, as it happens with any other pathological condition, are uncertain, possibly due to missingness of pregnancy status, underreporting of cases and disease outcomes, inadequate collection of biological samples for testing, insufficient accuracy of the tests available, and inaccuracy of the mathematical models in predicting the number of asymptomatic individuals. Good quality data are urgently needed to support an adequate counseling to women attempting pregnancy and to those who are already pregnant. With limited evidence available to date, concerning uncertainties from conception to birth inevitably raise the possibility of postponing pregnancy, if possible, to a post-Covid-19 scenario or the one with an effective and broadly-distributed vaccine.

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

References

1 World Health Organization. Pneumonia of unknown cause – China [Internet]. 2020 [cited 2020 Jul 21]. Available from: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/
2 World Health Organization. Coronavirus disease (COVID-19): situation report – 209 [Internet]. 2020 [cited 2020 Aug 21]. Available from: https://apps.who.int/iris/handle/10665/333897
3 Ministério da Saúde. COVID-19 no Brasil [Internet]. 2020 [cited 2020 Aug 16]. Available from: https://susanalitico.saude.gov.br/extensions/covid-19_html/covid-19_html.html#/dashboard/
4 Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809–815. Doi: 10.1016/S0140-6736(20)30360-3
5 Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, Zheng C. Pregnancy and perinatal outcomes of women with Coronavirus Disease (COVID-19) pneumonia: a preliminary analysis. AJR Am J Roentgenol. 2020;215(01):127–132. Doi: 10.2214/AJR.20.23072
6 Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020;20(05):559–564. Doi: 10.1016/S1473-3099(20)30176-6
7 Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020;•••;. Doi: 10.5858/arpa.2020-0901-SA [ahead of print]
8 Yu N, Li W, Kang Q, Zeng W, Feng L, Wu J. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. Lancet Infect Dis. 2020;•••: S1473-3099(20)30320-0. Doi: 10.1016/S1473-3099(20)30320-0 [ahead of print]
9 San-Juan R, Barbero P, Fernández-Ruiz M, López-Medrano F, Lizasoáin M, Hernández-Jiménez P, et al. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: A single-centre cohort study from Spain. EClinicalMedicine. 2020; 23:100407. Doi: 10.1016/j.eclinm.2020.100407
10 Takemoto MLS, Menezes MO, Andreucci CB, Nakamura-Pereira M, Amorim MMR, Katz L, Knobel R. The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. Int J Gynaecol Obstet. 2020;•••;. Doi: 10.1002/ijgo.13300 [ahead of print]
11 Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020;99(07):823–829. Doi: 10.1111/aogs.13867
12 Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(25):769–775. Doi: 10.15585/mmwr.mm6925a1
13 Sentilhes L, De Marcillac F, Jouffrieau C, Kuhn P, Thuet V, Hansmann Y, et al. Coronavirus disease 2019 in pregnancy was associated with maternal morbidity and preterm birth. Am J Obstet Gynecol. 2020;•••:S0002-9378(20)30639-6. Doi: 10.1016/j.ajog.2020.06.022 [ahead of print]
14 Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, Pomar L. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA. 2020;323(21):2198–2200. Doi: 10.1001/jama.2020.7233
15 Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental Pathology in COVID-19. Am J Clin Pathol. 2020;154(01): 23–32. Doi: 10.1093/ajcp/aqaa089
16 Richtmann R, Torloni MR, Oyamada Otani AR, Levi JE, Tobara MC, Silva CA, et al. Fetal deaths in pregnancies with SARS-CoV-2 infection in Brazil: A case series. Case Rep Womens Health. 2020;27:e00243. Doi: 10.1016/j.crwh.2020.e00243
17 Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, Long X. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA. 2020; 323(18):1848–1849. Doi: 10.1001/jama.2020.4861
18 Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Yang J. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18):1846–1848. Doi: 10.1001/jama.2020.4621
19 Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, Benachi A, De Luca D. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020;11(01):3572. Doi: 10.1038/s41467-020-17436-6
20 Patanè L, Morotti D, Giunta MR, Cristina Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020;2(03):100145. Doi: 10.1016/j.ajogmf.2020.100145

21 Rasmussen SA, Jamieson DJ. Caring for women who are planning a pregnancy, pregnant, or postpartum during the COVID-19 pandemic. JAMA. 2020;324(02):190–191. Doi: 10.1001/jama.2020.8883

22 Stanley KE, Thomas E, Leaver M, Wells D. Coronavirus disease-19 and fertility: viral host entry protein expression in male and female reproductive tissues. Fertil Steril. 2020;114(01):33–43. Doi: 10.1016/j.fertnstert.2020.05.001

23 Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, Fei C. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod. 2020;26(06):367–373. Doi: 10.1093/molehr/gaaa030

24 Chadchan SB, Maurya VK, Popli P, Kommagani R. The SARS-CoV-2 receptor, Angiotensin converting enzyme 2 (ACE2) is required for human endometrial stromal cell decidualization. bioRxiv. 2020: 2020.06.23.168252. Preprint. Doi: 10.1101/2020.06.23.168252

25 Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. Medrxiv. 2020

26 Entezami F, Samama M, Dejucq-Rainsford N, Bujan L. SARS-CoV-2 and human reproduction: An open question. EClinicalMedicine. 2020;25:100473. Doi: 10.1016/j.eclinm.2020.100473

27 Segars J, Katler Q, McQueen DB, Kotlyar A, Glenn T, Knight Z, et al; American Society for Reproductive Medicine Coronavirus/COVID-19 Task Force. Prior and novel coronaviruses, Coronavirus Disease 2019 (COVID-19), and human reproduction: what is known? Fertil Steril. 2020;113(06):1140–1149. Doi: 10.1016/j.fertnstert.2020.04.025

28 Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod. 2006;74(02):410–416. Doi: 10.1095/biolreprod.105.044776

29 Dutta S, Sengupta P. SARS-CoV-2 and male infertility: possible multifaceted pathology. Reprod Sci. 2020;•••;. Doi: 10.1007/s43032-020-00261-z [ahead of print]

30 Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol. 2004;203(02):622–630. Doi: 10.1002/path.1560

31 Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with Coronavirus Disease 2019. JAMA Netw Open. 2020;3(05):e208292. Doi: 10.1001/jamanetworkopen.2020.8292

32 Paoli D, Pallotti F, Colangelo S, Basilico F, Mazzuti L, Turriziani O, et al. Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive naso-pharyngeal swab. J Endocrinol Invest. 2020;•••;. Doi: 10.1007/s40618-020-01261-1 [ahead of print]

33 Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, et al. No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. Fertil Steril. 2020;113(06):1135–1139. Doi: 10.1016/j.fertnstert.2020.04.024

34 Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(01):292–297. Doi: 10.1016/j.ajog.2003.11.019

35 Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. J Microbiol Immunol Infect. 2019;52(03):501–503. Doi: 10.1016/j.jmii.2018.04.005

36 Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122. Doi: 10.1016/j.jri.2020.103122

37 Centers for Disease Control and Prevention. Assessing risk factors for severe COVID-19 illness [Internet]. 2020 [cited 2020 Jul 26]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/assessing-risk-factors.html

38 Trapani Júnior A, Vanhoni LR, Silveira SK, Marcolin AC. Childbirth, puerperium and abortion care protocol during the COVID-19 pandemic. Rev Bras Ginecol Obstet. 2020;42(06):349–355. Doi: 10.1055/s-0040-1713587

39 Lopes de Sousa AF, Carvalho HEF, Oliveira LB, Schneider G, Camargo ELS, Watanabe E, et al. Effects of COVID-19 infection during pregnancy and neonatal prognosis: what is the evidence? Int J Environ Res Public Health. 2020;17(11):E4176. Doi: 10.3390/ijerph17114176

40 Api O, Sen C, Debska M, Saccone G, D'Antonio F, Volpe N, et al. Clinical management of coronavirus disease 2019 (COVID-19) in pregnancy: recommendations of WAPM-World Association of Perinatal Medicine. J Perinat Med. 2020;•••:/j/jpme.ahead-of-print/jpm-2020-0265/jpm-2020-0265.xml 10.1515/jpm-2020-0265 [ahead of print]

41 Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. Am J Obstet Gynecol. 2020;223(01):36–41. Doi: 10.1016/j.ajog.2020.04.013

42 Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(02):100107. Doi: 10.1016/j.ajogmf.2020.100107

43 Antoun L, Taweel NE, Ahmed I, Patni S, Honest H. Maternal COVID-19 infection, clinical characteristics, pregnancy, and neonatal outcome: A prospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2020;252:559–562. Doi: 10.1016/j.ejogrb.2020.07.008

44 Gagneur A, Dirson E, Audebert S, Vallet S, Quillien MCL, Baron R, et al. Transmission maternofoetale des coronavirus humains. Etude prospective pilote. Pathol Biol (Paris). 2007;55(10):525–530. Doi: 10.1016/j.patbio.2007.07.013

45 Gagneur A, Dirson E, Audebert S, Vallet S, Legrand-Quillien MC, Laurent Y, et al. Materno-fetal transmission of human coronaviruses: a prospective pilot study. Eur J Clin Microbiol Infect Dis. 2008;27(09):863–866. Doi: 10.1007/s10096-008-0505-7

46 Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) Coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human Coronavirus infections. Viruses. 2020;12(02):194. Doi: 10.3390/v12020194

47 Liu W, Wang J, Li W, Zhou Z, Liu S, Rong Z. Clinical characteristics of 19 neonates born to mothers with COVID-19. Front Med. 2020;14(02):193–198. Doi: 10.1007/s11684-020-0772-y

48 Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, Chen X. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology. 2020;•••;. Doi: 10.1111/his.14215 [ahead of print]

49 Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol. 2020;37(08):861–865. Doi: 10.1055/s-0040-1710050

50 Kirtsman M, Diambomba Y, Poutanen SM, Malinowski AK, Vlachodimitropoulou E, Parks WT, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ. 2020;192(24):E647–E650. Doi: 10.1503/cmaj.200821

51 Zhang ZJ, Yu XJ, Fu T, Liu Y, Jiang Y, Yang BX, Bi Y, et al. Novel coronavirus infection in newborn babies aged <28 days in China. Eur Respir J. 2020;55(06):2000697. Doi: 10.1183/13993003.00697-2020

52 Hu X, Gao J, Luo X, Feng L, Liu W, Chen J, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vertical transmission in neonates born to mothers with Coronavirus Disease 2019 (COVID-19) pneumonia. Obstet Gynecol. 2020;136(01):65–67. Doi: 10.1097/AOG.0000000000003926

53 Maternal-fetal vertical SARS-CoV2 transmission cannot be dismissed. ESHRE Annual Meeting 2020 [cited 2020 Jul 26]. Available

from: https://www.focusonreproduction.eu/article/ESHRE-News-Annual-Meeting-2020-Bahadur
54 Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One. 2020;15(04):e0230295. Doi: 10.1371/journal.pone.0230295
55 Freiesleben NLC, Egerup P, Hviid KVR, Severinsen ER, Kolte AM, Westergaard D, et al. SARS-CoV-2 in first trimester pregnancy - does it affect the fetus? Medrxiv. 2020
56 Moore CA, Staples JE, Dobyns WB, Pessoa A, Ventura CV, Fonseca EB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr. 2017;171 (03):288–295. Doi: 10.1001/jamapediatrics.2016.3982
57 Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM. 2020;2(03):100133. Doi: 10.1016/j.ajogmf.2020.100133
58 Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, Thornton JG. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG. 2020;127(11):1324–1336. Doi: 10.1111/1471-0528.16362
59 Philip RK, Purtill H, Reidy E, et al. Reduction in preterm births during the COVID-19 lockdown in Ireland: a natural experiment allowing analysis of data from the prior two decades. Medrxiv. 2020
60 Hedermann G, Hedley PL, Bækvad-Hansen M, Hjalgrim H, Rostgaard K, Poorisrisak P, et al. Danish premature birth rates during the COVID-19 lockdown. Arch Dis Child Fetal Neonatal Ed. 2020: fetalneonatal-2020-319990
61 Lobo RA. Potential options for preservation of fertility in women. N Engl J Med. 2005;353(01):64–73. Doi: 10.1056/NEJMra043475
62 Heffner LJ. Advanced maternal age–how old is too old? N Engl J Med. 2004;351(19):1927–1929. Doi: 10.1056/NEJMp048087
63 Habbema JD, Eijkemans MJ, Leridon H, te Velde ER. Realizing a desired family size: when should couples start? Hum Reprod. 2015;30(09):2215–2221. Doi: 10.1093/humrep/dev148
64 Eijkemans MJC, Kersten FAM, Lintsen AME, Hunault CC, Bouwmans CAM, Hakkaart-van-Roijen L, et al. Cost-effectiveness of 'immediate IVF' versus 'delayed IVF': a prospective study. Hum Reprod. 2017;32(05):999–1008. Doi: 10.1093/humrep/dex018
65 Romanski PA, Bortoletto P, Rosenwaks Z, Schattman GL. Delay in IVF treatment up to 180 days does not affect pregnancy outcomes in women with diminished ovarian reserve. Hum Reprod. 2020; 35(07):1630–1636. Doi: 10.1093/humrep/deaa137
66 Carvalho BR, Rosa-E-Silva ACJS, Ferriani RA, Reis RMD, Silva de Sá MF. COVID-19 and assisted reproduction: a point of view on the Brazilian scenario. Rev Bras Ginecol Obstet. 2020;42(06): 305–309. Doi: 10.1055/s-0040-1713795
67 Papathanasiou A. COVID-19 screening during fertility treatment: how do guidelines compare against each other? J Assist Reprod Genet. 2020;37(08):1831–1835. Doi: 10.1007/s10815-020-01885-5
68 Oxford-Horrey C, Savage M, Prabhu M, Abramovitz S, Griffin K, LaFond E, et al. Putting it all together: clinical considerations in the care of critically ill obstetric patients with COVID-19. Am J Perinatol. 2020;37(10):1044–1051. Doi: 10.1055/s-0040-1713121
69 Takemoto M, Menezes MO, Andreucci CB, Knobel R, Sousa L, Katz L, et al;Brazilian Group for Studies of COVID-19 and Pregnancy. Clinical characteristics and risk factors for mortality in obstetric patients with severe COVID-19 in Brazil: a surveillance database analysis. BJOG. 2020;•••;. Doi: 10.1111/1471-0528.16470 [ahead of print]
70 Martínez-Perez O, Vouga M, Cruz Melguizo S, Acebal LF, Panchaud A, Muñoz-Chápuli M, Baud D, et al. Association between mode of delivery among pregnant women with covid-19 and maternal and neonatal outcomes in Spain. JAMA. 2020;324(03):296–299. Doi: 10.1001/jama.2020.10125
71 Cosma S, Borella F, Carosso A, Sciarrone A, Cusato J, Corcione S, et al. The "scar" of a pandemic: Cumulative incidence of COVID-19 during the first trimester of pregnancy. J Med Virol. 2020;•••;. Doi: 10.1002/jmv.26267 [ahead of print]
72 Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med. 2020; 382(22):2163–2164. Doi: 10.1056/NEJMc2009316
73 Fassett MJ, Lurvey LD, Yasumura L, Nguyen M, Colli JJ, Volodarskiy M, et al. Universal SARS-Cov-2 screening in women admitted for delivery in a large managed care organization. Am J Perinatol. 2020;37(11):1110–1114. Doi: 10.1055/s-0040-1714060
74 Heath PT, Le Doare K, Khalil A. Inclusion of pregnant women in COVID-19 vaccine development. Lancet Infect Dis. 2020;20(09): 1007–1008. Doi: 10.1016/S1473-3099(20)30638-1

Pre-eclampsia: Universal Screening or Universal Prevention for Low and Middle-Income Settings?

Pré-eclâmpsia: Rastreamento universal ou prevenção universal para países de baixa e média-renda?

Leandro Gustavo De Oliveira[1] Angélica Lemos Debs Diniz[2] Caio Antônio de Campos Prado[3] Edson Vieira Da Cunha Filho[4] Francisco Lázaro Pereira De Souza[5] Henri Augusto Korkes[6] José Geraldo Ramos[7] Maria Laura Costa[8] Mário Dias Corrêa Junior[9] Nelson Sass[10] Ricardo De Carvalho Cavalli[3] Sérgio Hofmeister De Almeida Martins-Costa[7] José Carlos Peraçoli[1]

[1] Department of Gynecology and Obstetrics, Botucatu Medical School, Universidade Estadual Paulista "Júlio de Mesquita Filho," Botucatu, SP, Brazil
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
[3] Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
[4] Gynecology and Obstetrics Training Center, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[5] Department of Tocoginecology, Centro Universitário Lusíada, Santos, SP, Brazil
[6] Department of Obstetrics and Gynecology, Faculty of Medicine, Pontifícia Universidade Católica de São Paulo, Sorocaba, SP, Brazil
[7] Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[8] Department of Gynecology and Obstetrics, Faculty of Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil
[9] Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
[10] Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Address for correspondence Leandro Gustavo De Oliveira, MD, PhD, Distrito de Rubião Junior, s/n°, 18618-970, Botucatu, SP, Brazil (e-mail: leandro.gustavo@unesp.br).

Rev Bras Ginecol Obstet 2021;43(1):61–65.

Abstract

Pre-eclampsia (PE) is a severe disorder that affects up to 8% of all pregnancies and represents an important cause of maternal and perinatal morbidity and mortality. The screening of the disease is a subject of studies, but the complexity and uncertainties regarding its etiology make this objective a difficult task. In addition, the costs related to screening protocols, the heterogeneity of the most affected populations and the lack of highly effective prevention methods reduce the potential of current available algorithms for screening. Thus, the National Specialized Commission of Hypertension in Pregnancy of the Brazilian Association of Gynecology and Obstetrics Federation (Febrasgo, in the Portuguese acronym) (NSC Hypertension in Pregnancy of the Febrasgo) considers that there are no screening algorithms to be implemented in the country to date and advocates that Aspirin and calcium should be widely used.

Keywords
- preeclampsia
- screening
- prevention
- aspirin
- calcium

received
April 1, 2020
accepted
May 7, 2020

DOI https://doi.org/10.1055/s-0040-1713803.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Resumo

A Pré-eclâmpsia (PE) é uma doença grave que acomete ~ 8% das gestações e representa importante causa de morbimortalidade, tanto materna quanto perinatal. O rastreamento da doença é motivo de estudos, porém a complexidade e as incertezas quanto a sua etiologia tornam esse objetivo bastante difícil. Além disso, os custos relacionados com o rastreamento, a heterogeneidade das populações mais afetadas e ainda a falta de métodos de prevenção de grande eficácia reduzem o potencial dos algoritmos de rastreamento. Assim, a Comissão Nacional Especializada sobre Hipertensão na Gravidez da Federação Brasileira das Associações de Ginecologia e Obstetrícia (CNE Hipertensão na Gravidez da FEBRASGO) considera que não há algoritmos de rastreamento que possam ser aplicados no país nesse momento e defende a utilização dos métodos de prevenção como ácido acetilsalicílico e cálcio de maneira ampla.

Palavras-chave

- pré-eclâmpsia
- rastreamento
- prevenção
- ácido acetilsalicílico
- cálcio

Introduction

Pre-eclampsia (PE) is a severe disorder, affecting up to 8% of all pregnancies worldwide. It represents an important cause of maternal and perinatal morbidity and mortality. Most of the adverse outcomes occur in low and middle-income settings.[1]

Regarding Brazil, the latest revised and available data on maternal mortality is from 2018.[2] The maternal mortality ratio for that year was 56 deaths per 100,000 live births. In 2008, the documented ratio was 57 per 100,000 live births, with clear stagnation over 10 years, and with PE accounting for 20% of these deaths. The impact of PE on perinatal outcomes is not correctly estimated, but it is known that 18% of all preterm births in Brazil are related to PE and that ~ 55% of these cases are elective preterm births due to maternal indications related to PE.[3,4] It is possible that many of these indications are iatrogenic due to the lack of a reliable model of risk stratification to be used in clinical practice.

Considering the importance of PE worldwide and mainly in Brazil, screening pregnant women at higher risk for developing the disease is essential. However, the prediction of PE is a difficult task, because of its complex etiology, gaps in its pathophysiology, diversity of clinical presentations and heterogeneity among populations.

Recently, the International Federation on Gynecology and Obstetrics (FIGO) issued its position on universal screening for PE.[5] However, this recommendation is still controversial and the National Specialized Commission of Hypertension in Pregnancy of the Brazilian Association of Gynecology and Obstetrics Federation – (Febrasgo, in the Portuguese acronym) (NSC Hypertension in Pregnancy of the Febrasgo) considers the importance of also presenting its position, to reinforce the local recommendations on PE.

FIGO Recommendations

A recent publication by FIGO recommends universal screening for PE in the 1st trimester of pregnancy using an algorithm that involves maternal characteristics, evaluation of mean arterial blood pressure, uterine artery Doppler and serum levels of Placental Growth Factor (P1GF) and Pregnancy Associated Pregnancy Protein - A (PAPP-A). This recommendation was based primarily on the results of the following studies that screened pregnant women in the first trimester (11–13 weeks):

1) Screening of 58,884 singleton pregnant women. Of these women, 1,426 (2.4%) developed PE. The detection rate was 77% for preterm PE (< 37 weeks) and 54% for total PE, with a 10% false-positive rate.[6]
2) Screening of 35,948 singleton pregnant women. Of these women, 1,058 (2.9%) developed PE. The detection rates for preterm and term PE were 75% and 47%, respectively, with a 10% false-positive rate.[7]
3) Screening of 26,941 singleton pregnant women in 13 maternity hospitals in 6 different countries (United Kingdom, Spain, Italy, Belgium, Greece and Israel) - ASPRE study. The detection rates for preterm and term PE were 77% and 43%, respectively, with a false-positive rate of 9.2%.[8] This study identified 2,971 women at risk for developing preterm PE. Of these pregnant women considered to be at higher risk, 1,776 were randomized and 798 received 150mg of Aspirin for prevention of PE and 822 received placebo. At the end of the study, 13 women developed PE in the study group versus 35 in the placebo group.

To prevent PE, the FIGO recommends the use of Aspirin at a dose of 150mg orally at night and calcium supplementation for women with inadequate calcium intake (< 800mg/day), emphasizing that this prevention should be based on positive screening.

Despite the recommendation based on positive screening, the FIGO recognizes the following risk factors to develop PE: maternal age ≥ 35 years old, nulliparity, previous history of PE, pregnancy interval < 12 months or > 72 months, assisted reproduction, family history of PE (mother and sisters who had PE), obesity (body mass index [BMI] ≥ 30), Afro-Caribbean race and presence of clinical conditions (chronic arterial hypertension, diabetes 1 and 2, kidney disease, systemic

lupus erythematosus and antiphospholipid antibody syndrome). Finally, the FIGO recognizes that areas where the costs of the complete screening for PE are not affordable could implement an alternative screening based on clinical risk factors and assessment of mean arterial blood pressure in the 1st trimester.

Recommendations of the NSC Hypertension in Pregnancy of the Febrasgo

The NSC-Hypertension Brazil is comprised of a group of specialists dedicated to the study and assistance of pregnant women diagnosed with PE in the country. These professionals represent important Universities in Brazil and are responsible for developing guidelines that can be followed at a national level.[9,10] The NSC Hypertension in Pregnancy of the Febrasgo met to discuss the FIGO recommendations regarding universal screening for PE in the 1st trimester, considering the available evidences, as well as the economic impact of such recommendation for a low-income country such as Brazil. After this discussion, the following considerations were established:

Regarding the use of algorithms involving clinical characteristics, biophysical and biochemical markers, it is possible to note a series of studies suggesting that such screening model is not universally accepted. Townsend et al recently evaluated the main reviews on this issue in the medical literature.[11] The authors pointed out a great heterogeneity among the markers used to predict PE and only half of the available reviews assessed the quality of the studies included. Despite lack of quality assessment, some predictors presented better performances. Body mass index $>$ 35 kg/m2 presented specificity of 92% (95% confidence interval [CI], 89–95%) and sensitivity of 21% (95% CI, 12–31%); BMI $>$ 25 - kg/m2 had specificity of 73% (95% CI, 64–83%) and sensitivity of 47% (95% CI, 33–61%); first-trimester uterine Doppler with pulsatility or resistance index $>$ 90th had specificity of 93% (95% CI, 90–96%) and a sensitivity of 26% (95%CI, 23–31%) and PlGF concentration presented specificity of 89% (95% CI, 89–89%) and sensitivity of 65% (95% CI, 63–67%). This review of the reviews concluded that no single marker can be used in the clinical practice, but the combination of different markers appears to be promising. However, none of the proposed screening models has undergone external validations. Di Martino et al evaluated the performance of the algorithm suggested by the group of researchers related to the recommendations published by the FIGO.[12] After applying this algorithm to 11,632 Italian pregnant women, the authors demonstrated a detection rate of 58.2% for early PE ($<$ 34 weeks) and 41.8% for late PE ($\geq$ 34 weeks). The studies cited in the FIGO's recommendation presented detection rates of no more than 77% for early PE and were clearly unable to identify women who later developed late or term PE.[6–8]

It is important to consider the weight of each marker proposed in screening models, costs and logistics required to incorporate each one in places with restricted structural conditions or few financial resources. When considering the weight of each marker, O'Gorman et al demonstrated that maternal characteristics had a detection rate of 53% (40–65%) for PE before 32 weeks and that the addition of mean blood pressure assessment raised this rate to 65% (52–76%).[7] Bearing in mind the weight of each marker used for PE screening leads us to question whether there is sufficient benefit to invest financial resources in an attempt to raise detection rates that would go from 65% to 77%. So far, the NSC Hypertension in Pregnancy of the Febrasgo does not recognize this benefit. In practical terms, the ASPRE study initially screened 26,941 pregnant women and, among these women, the total number that would develop preterm PE whether no intervention had been implemented would be $\sim$ 70 women (0,26%).[8] Once again, the NSC Hypertension in Pregnancy of the Febrasgo does not consider the existence of a balance among benefits of detection, costs and logistics required to recommend universal screening based on the suggested algorithm, mainly in the Brazilian regions where there are no financial resources.

Another question that deserves an answer at this point is whether there is any contraindication in recommending Aspirin and calcium for more pregnant women than those screened by expensive algorithms. Recent studies indicate that the benefits of using low-dose Aspirin go beyond the prevention of PE. Andrikopulou et al demonstrated that the use of Aspirin in nulliparous women without morbidities led to important reduction in preterm births before 34 weeks of gestation.[13] A recent trial (ASPIRIN) demonstrated that the introduction of Aspirin between 6 and 13 weeks plus 6 days for nulliparous women led to considerable reduction in preterm births and perinatal mortality.[14]

Mallampati et al studied the outcomes related to the universal use of Aspirin, without clinical or laboratory screening.[15] The authors demonstrated a significant reduction in the incidence of PE, mainly preterm PE, from 311 to 148 cases per 1,000 pregnancies. There was also a significant reduction in costs when the universal prescription was compared with the screening by biomarkers and ultrasound ($\sim$ US$192.16 per patient). Additionally, the implementation of biomarkers and ultrasound for PE screening increased costs by US$19,216,251 per 100,000 pregnant women. These results still need better analyses, mainly regarding adverse events or side effects, but they are initially very interesting.

Calcium supplementation for women with low calcium intake has been recognized by the World Health Organization (WHO).[16] In Brazil, calcium intake by women at childbearing age is $\sim$ 500mg/day, that is, below current recommendations.[17] Sun et al demonstrated in a systematic review that the supplementation with low doses of calcium (from 600mg/day) significantly reduced the incidence of PE ($p < 0{,}001$), even in low-risk populations (risk ratio [RR]: 0.32; 95%CI: 0.18–0.59) and mainly in developing countries (RR: 0.41; 95%CI: 0.29–0.58).[18] Therefore, the NSC Hypertension in Pregnancy of the Febrasgo understands that recommending Aspirin and calcium supplementation for pregnant women with clinical risk factors for PE and all nulliparous women, especially those in the public health system in Brazil, can be an important strategy to improve maternal and perinatal outcomes.

Regarding the recommendation to use Aspirin at a dose of 150mg/day, we emphasize that the ASPRE study did not compare different doses and received criticisms in this regard.[8,19,20] Brazil has 100mg tablets that are supplied by the public health system. This concentration is already higher than that recommended in North America, which is 85mg/day. Thus, the NSC Hypertension in Pregnancy of the Febrasgo does not find subsidies to recommend an increase in the Aspirin doses at the moment and since the country does not have different formulations available in the public health system, the NSC Hypertension in Pregnancy of the Febrasgo maintains the recommendation of Aspirin at 100-mg/day. The drug should be started at 12 weeks of gestation, and some authors claim that the benefits are achieved with its introduction up to 16 weeks of gestation. However, a recent meta-analysis confirms that the benefits are consistent whether the medication is commenced up to 20 weeks of pregnancy.[21] Therefore, this is the recommendation from the NSC Hypertension in Pregnancy of the Febrasgo.

Final Considerations

The NSC Hypertension in Pregnancy of the Febrasgo emphasizes the importance of maintaining the investigation of effective methods for screening PE, mainly according to the characteristics of each population. The various phenotypes of PE suggest that different populations may present different risk factors and such interpretation needs to be considered. The FIGO itself, in its publication, recognizes that the screening methods must be adequate for each setting and that the existing resources must be respected. Thus, the NSC Hypertension in Pregnancy of the Febrasgo maintains, at this time, the recommendation for screening PE based on clinical and epidemiological characteristics. Finally, the NSC Hypertension in Pregnancy of the Febrasgo reinforces its position that the main impact in reducing morbidity and mortality due to PE, in our scenario, is to improve the quality of antenatal care, risk identification and timely diagnosis, to ensure proper management to the different clinical presentations of PE.

Contributions

All authors contributed equally for the production of the present manuscript and fulfilled with the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE).

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors thank the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO) for supporting the CNE-Hypertension Brazil.

References

1 Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(03):130–137. Doi: 10.1053/j.semperi.2009.02.010

2 Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Saúde e Vigilância de Doenças Não Transmissíveis [Internet]. Painel de monitoramento da mortalidade materna. 2019 [cited 2019 Dec 10]. Available from: http://svs.aids.gov.br/dantps/centrais-de-conteudos/paineis-de-monitoramento/mortalidade/materna/

3 Passini R Jr, Tedesco RP, Marba ST, et al; Brazilian Network of Studies on Reproductive and Perinatal Health. Brazilian multicenter study on prevalence of preterm birth and associated factors. BMC Pregnancy Childbirth. 2010;10:22. Doi: 10.1186/1471-2393-10-22

4 Souza RT, Cecatti JG, Passini R Jr, et al; Brazilian Multicenter Study on Preterm Birth study group. The burden of provider-initiated preterm birth and associated factors: evidence from the Brazilian Multicenter Study on Preterm Birth (EMIP). PLoS One. 2016;11(02):e0148244. Doi: 10.1371/journal.pone.0148244

5 Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145(Suppl 1):1–33. Doi: 10.1002/ijgo.12802

6 Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther. 2013;33(01):8–15. Doi: 10.1159/000341264

7 O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol. 2016;214(01):103.e1–103.e12. Doi: 10.1016/j.ajog.2015.08.034

8 Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol. 2017;50(04):492–495. Doi: 10.1002/uog.18816

9 Ramos JGL, Sass N, Costa SHM. Preeclampsia. Rev Bras Ginecol Obstet. 2017;39(09):496–512. Doi: 10.1055/s-0037-1604471

10 Peraçoli JC, Borges VTM, Ramos JGL, et al. Pre-eclampsia/Eclampsia. Rev Bras Ginecol Obstet. 2019;41(05):e1–e2. Doi: 10.1055/s-0040-1702167

11 Townsend R, Khalil A, Premakumar Y, et al; IPPIC Network. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol. 2019;54(01):16–27. Doi: 10.1002/uog.20117

12 Di Martino D, Masturzo B, Paracchini S, et al. Comparison of two "a priori" risk assessment algorithms for preeclampsia in Italy: a prospective multicenter study. Arch Gynecol Obstet. 2019;299(06):1587–1596. Doi: 10.1007/s00404-019-05146-4

13 Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. Am J Obstet Gynecol. 2018;219(04):399.e1–399.e6. Doi: 10.1016/j.ajog.2018.06.011

14 Hoffman MK, Goudar SS, Kodkany BS, et al; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10220):285–293. Doi: 10.1016/S0140-6736(19)32973-3

15 Mallampati D, Grobman W, Rouse DJ, Werner EF. Strategies for prescribing aspirin to prevent preeclampsia: a cost-effectiveness analysis. Obstet Gynecol. 2019;134(03):537–544. Doi: 10.1097/AOG.0000000000003413

16 World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: WHO; 2011

17 Camargo EB, Moraes LF, Souza CM, et al. Survey of calcium supplementation to prevent preeclampsia: the gap between evidence and practice in Brazil. BMC Pregnancy Childbirth. 2013;13:206. Doi: 10.1186/1471-2393-13-206

18 Sun X, Li H, He X, et al. The association between calcium supplement and preeclampsia and gestational hypertension: a systematic review and meta-analysis of randomized trials. Hypertens Pregnancy. 2019;38(02):129–139. Doi: 10.1080/10641955.2019. 1593445

19 Askie L, Duley L. Associations between the timing and dosing of aspirin prophylaxis and term and preterm pre-eclampsia. BMJ Evid Based Med. 2018; Jun 7. pii: bmjebm-2018–110931 . Doi: 10.1136/bmjebm-2018-110931
20 Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019;2019(10):. Doi: 10.1002/14651858.CD004659.pub3
21 Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. Am J Obstet Gynecol. 2017; 216(02):121–128.e2. Doi: 10.1016/j.ajog.2016. 10.016

Does Big Mean Evil? Giant, but Benign Uterine Leiomyoma: Case Report and Review of the Literature

Será que grande significa maligno? Leiomioma gigante, porém benigno: Relato de caso e revisão de literatura

Luiz Gustavo Oliveira Brito[1,2] Natalia Lysei Ueno[2] Maira Rossmann Machado[1]

[1] Department of Obstetrics and Gynecology, Faculdade de Ciências Médicas da Universidade de Campinas, Campinas, SP, Brazil
[2] Department of Gynecology and Obstetrics, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil

Address for correspondence Luiz Gustavo Oliveira Brito, MD, MsC, PhD, Rua Alexander Fleming, 101, Campinas, SP, 13083-881, Brazil (e-mail: lgobrito@unicamp.br).

Rev Bras Ginecol Obstet 2021;43(1):66–71.

Abstract

Uterine leiomyoma is the most prevalent benign type of gynecological tumor. It affects more than 80% of women worldwide and, within this group, more than 50% may be asymptomatic. However, large fibroid volumes may be associated with symptoms of extrinsic compression, and most of the cases do not present atypical cells. We present the case of a 49-year-old woman who underwent a total abdominal hysterectomy of a 13.5-kg uterine leiomyoma with no malignancies at histopathology and review the literature about giant uterine leiomyomas and their clinical repercussion. We concluded that large volumes do not always pose a threat regarding malignancy; however, future molecular studies are needed to investigate giant uterine fibroids.

Keywords
- uterine leiomyoma
- giant tumors
- gynecological tumors

Resumo

Leiomioma uterino é o tumor benigno ginecológico de maior prevalência. Ele afeta mais de 80% das mulheres no mundo e, deste grupo, mais de 50% podem ser assintomáticas. Contudo, miomas de grande volume podem ser associados com sintomas de compressão extrínseca, e a maioria dos casos não apresentam células atípicas. Nós apresentamos o caso de uma mulher de 49 anos que foi submetida a histerectomia total abdominal de um espécime de 13,5 quilos sem malignidades ao exame histopatológico. Também revisamos a literatura sobre leiomiomas uterinos de grande volume e sua repercussão clínica. Concluímos que grandes volumes nem sempre representam um risco relacionado à malignidade; contudo, estudos moleculares futuros são necessários para investigar leiomiomas uterinos gigantes.

Palavras-chave
- leiomioma
- neoplasias ginecológicas
- tumores ginecológicos

received
May 25, 2020
accepted
September 22, 2020

DOI https://doi.org/10.1055/s-0040-1721351.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

Introduction

Uterine leiomyoma is a benign gynecological tumor originated from smooth muscle cells that affects up to 80% of women worldwide. From these, only 20 to 30% resent symptoms.[1] Multiple risk factors are associated with leiomyoma development, with the most common ones being nulliparity, obesity, early menarche, African descent, and age, all of them secondary to an extended exposure to estrogens or genetic predisposition.[1]

Leiomyomas are classified as giant when their weight exceeds 11.4 kg.[2] They are included in the category of giant tumors, which is a concept that can also include ovarian tumors. Giant leiomyomas, in addition to the usually reported increase in abdominal size, presents other common clinical signs are mainly related to extrinsic compression. Examples of these signs and symptoms are worsening of the renal function, bowel obstruction, venous stasis, respiratory discomfort, thrombosis, and lymphedema.[1] Most of the cases only cause severe symptoms after a long period of growth. Herein, we describe the case of a patient with a growing abdominopelvic mass, the pre and postoperative results, and the immediate postoperative surgical evolution. Moreover, we present a review of the literature. The inclusion criteria for this review were all case reports on patients over 18 years old with uterine weight over 10 kg. We excluded all case reports with no data reporting weight and those whose authors did not answer about the weight of the specimen. The search strategy was composed of the following structure: ("uterine leiomyoma" OR "uterine fibroids" OR "uterine tumors") (large OR giant), and the search was performed on January 3rd, 2020 in the PubMed database with 577 results. Manuscript language was not considered a barrier for inclusion in this review. References were also consulted for analysis, as well as similar studies that were suggested in the PubMed website. Of these studies, 19 case reports that described giant leiomyomas were selected for analysis, and ►**Table 1** displays detailed data for 14 of them.[2–20]

Case Report

A 49-year-old nulliparous, obese woman with chronic hypertension sought medical care due to an increase in the size of her abdomen (►**Fig. 1**) for one year. She was amenorrheic for about a year without the use of contraceptives, and, 6 months prior to her consultation, she had been submitted to an abdominal computerized tomography (CT), which showed a uterine mass measuring $25.7 \times 29.0 \times 29.5$ cm (volume 11,432.9 cc). The patient presented with complaints of frequent urination and urinary incontinence, with a urinary infection diagnosed on screening laboratory evaluation. Physical examination revealed a palpable abdominopelvic mass located up to 2 cm below the xiphoid process. Gynecological examination was unaltered, and no malignancy was found in the pap smear.

As there were no previous radiological exams evaluating the uterine growth rate and we could not rule out leiomyosarcoma for this patient preoperatively (a preoperative endometrial sample was attempted – Pipelle de Cormier) without sufficient material, a total abdominal hysterectomy with bilateral salpingo-oophorectomy was scheduled. One week before surgery, the patient underwent a magnetic resonance imaging (MRI), and the size of the tumor did not present any alterations. No hypothesis for leiomyosarcoma was performed. One day before the surgery, the patient was complaining of progressive abdominal pain, constipation, and urinary retention. Low-molecular weight heparin (enoxaparin) was administered prophylactically prior to surgery. A median incision was performed, and surgery (total hysterectomy plus prophylactic salpingectomy) occurred with no abnormalities, with an estimated blood loss of 600 ml, measured by compress weighing. An enormous uterine mass, weighing 13.5 kg, was removed (►**Fig. 2**). Ureterolysis was performed to confirm that both ureters were intact.

Intraoperative histological analysis of the mass revealed no atypia, and the specimen was sent to pathology. No complications occurred in the immediate postoperative period, and the patient was discharged two days after the surgery. Gross macroscopy did not find any abnormalities, except for a giant uterine fibroid, with abundant vasculature in the periphery of the lesion. No areas of degeneration were seen. Histopathological examination evidenced leiomyoma with no atypia or degeneration and unaltered adnexa. The patient was discharged with no complications.

Discussion

Giant leiomyomata are rare, and not frequently reported in the literature. They are of special interest when presenting with a fast growth rate, which suggests malignancy, as uterine cancers usually present with signs and symptoms similar to benign tumors of the uterus and there are no specific criteria for the suspicion of leiomyosarcoma.[1] The first report of these cases occurred in 1888, with the highest reported uterine tumor (63.6 kg), which was operated by Hunt et al.[3] after an autopsy. Behrend[4] operated a 60 kg tumor, and the patient died due to pneumonia 48 hours later.[4] Singhabhandhu et al.[5] have described the largest uterine tumor removed with survival of the patient (45.5 kg).

A case series ($n = 2$) published by Oelsner et al.[7] has performed a literature review, and 57 reported cases were found up to 2003. After 2003, our review has identified 13 cases plus the one described in the present article, thus comprising 71 cases. Our table summarizes most of the recent cases, and, after 2003, the largest reported uterine leiomyoma weighed 28.1 kg.[18] The main complaint is the progressive enlargement of the abdomen, and, in some cases, serious malnutrition was observed, as well as complications related to other organs that were damaged due to the expanding abdominopelvic tumor. One of the reported cases[15] presented with a coexisting endometrial tumor, and only one case after the 2003 review evolved with death.[19]

Rev Bras Ginecol Obstet Vol. 43 No. 1/2021 © 2021. The Author(s).

Table 1 Giant leiomyomas (over 11.4 kg) – data obtained from the literature

Author	Uterine weight	Age (years)	Duration of symptoms	Symptoms	Preoperative assessment to rule out malignancy	Surgery and complications	Observations
Behrend[4]	60.7 kg (133.8 lb)	35	9 years	Enlargement of the abdomen	Not performed	Removal of the tumor, no details	Patient died from pneumonia 48 hours after the surgery
Oelsner et al.[7]	Two cases: 43.176 kg and 13.116 kg	49 and 54	10 and 7 years	1st case - Slow progressive enlargement of the abdomen, respiratory insufficiency with intubation prior to surgery. 2nd case - abdominal pain and enlargement, weight loss, cachexia	1st case – urgent laparotomy and no pre-op performed 2nd case – tumor size was big and patient could not undergo CT	1st case – TAH-BSO 2nd case – mass removal + TAH-BSO	1st case evolved well. 2nd case evolved with grand mal convulsions
Reddy et al.[8]	17.69 kg (39 lb)	67	20 years	Increasing abdominal distension + low back pain. Tumor with air-fluid levels preop image	Only CT – no endometrial bx	TAH-BSO	Fibroid with septic degeneration – cefuroxime + metronidazole
Pérez and Ramón[9]	27 kg	40	12 months	Weight loss, increasing abdominal distension	Normal tumor markers (did not specify). CT-guided fine-needle aspiration biopsy (mesenchymal tumor).	TAH-BSO + segment of jejunum	No malignancies – post op uneventful
Nappi et al.[10]	27.7 kg		18 months	Abdominal enlargement, weight gain of 25 kg	MRI + US – multilocular mass, undetermined origin. Normal CEA, CA-125, AFP. No endometrial bx	TAH-BSO + omentectomy	None
Amber et al.[11]	26.94 kg	47	3 years	Cachexia, giant abdominal mass	CT with contrast – suspicious of leiomyosarcoma. AFP, CA 19–9 and CEA with normal levels. CA-125 slightly elevated.	TAH-BSO, appendectomy and partial omentectomy	Reoperated after 24 hours – hemorrhagic shock – Discharge 3POD
Semczuk et al.[12]	15.2 kg	50	Not reported	Bilateral hydronephrosis by abdominal tumor	No pre-op assessment.	TAH-BSO. Bilateral double-J catheters insertion before surgery	Coexisting with endometrial cancer deriving from a polyp
Savulescu et al.[13]	18.1 kg	45	10 months	Increased abdominal size, constipation, urinary loss, urinary frequency, back pain	US and CT. No endo bx.	TAH-BSO	Discharge at POD #6;

Table 1 (*Continued*)

Author	Uterine weight	Age (years)	Duration of symptoms	Symptoms	Preoperative assessment to rule out malignancy	Surgery and complications	Observations
Mate et al.[15]	13.5 kg	71	Not informed	Increased abdominal distension, cachexia	CT. Normal CEA, AFP, B-HCG. CA-125 94 U/mL.	TAH-BSO	No complications
Orazulike et al.[16]	15.5 kg	43	14 years	Increasing abdominal distention + pelvic pain	Only ultrasound. Normal CA-125. No endometrial biopsy	TAH-BSO	Discharged POD #7
Ezugwu et al.[17]	16.8 kg	31	8 years	Progressive abdominal swelling, infertility, weight loss and dyspnea	Transabdominal US. Authors considered doing CA-125, CT and MRI but did not have funds to request for patient. No endo bx	Myomectomy	Elective cesarean section at 38 weeks
Moris and Vernadakis[18]	28.1 kg	39	4 months	Progressive constipation, increasing abdominal size, back pain, urinary frequency	Transabdominal US and CT – no ascites, metastases, or enlarged pelvic or para-aortic lymph nodes. No endo bx	Midline incision – ASH-BSO – Postop uneventful – 10th day	None
Sonoo et al.[19]	17.4 kg	37	3 years	Fatigue for 2 weeks – Hyperkalemia (10.3) and arrived in CPA	Post-mortem laparotomy – not performed any pre-op	Post-mortem laparotomy for mass resection	Death
Lim et al.[20]	27.8 kg	53	Not reported	Massive uterine mass complicating restrictive lung disease		TAH-BSO	Coagulopathy and hemorrhagic shock

Abbreviations: AFP, α-fetoprotein; ASH-BSO, supracervical abdominal hysterectomy + bilateral salpingo-oophorectomy; Bx, biopsy; CEA, carcinoembryonic antigen; MRI, magnetic resonance imaging; TAH-BSO, total abdominal hysterectomy + bilateral salpingo-oophorectomy; US, ultrasound.

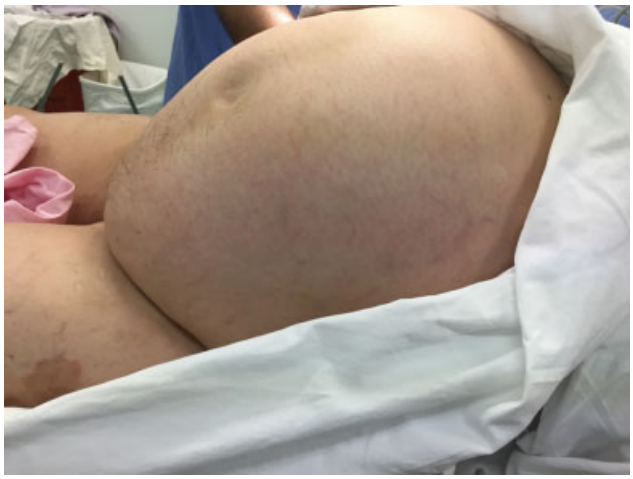

Fig. 1 Giant mass occupying all abdomen.

Surgery can be challenging in these cases. It is quite difficult to consider a minimally invasive approach in a large abdomen, as most of the incisions were xiphopubic. Within the selected cases, only one case was performed myomectomy—it was a nulliparous woman.[17] As the uterine tumor presents large dimensions, the standard treatment for uterine sarcomas (total hysterectomy + bilateral salpingo-oophorectomy) is suggested and performed. A multidisciplinary approach with other specialties (general surgeon, plastic surgeon, urology) may be needed to help the gynecological surgeon during this procedure.

The present case report does not show an association between tumor size and malignancy. We need to understand the biological behavior of significantly enlarged leiomyomas with molecular approach. A study comparing large leiomyomas versus simple uterine leiomyomas has shown that there are large growth rates are present in fibroids from adolescent women.[21] There is a systematic review studying uterine leiomyoma in adolescents, and the biological behavior of these tumors in women under 20 years seems to be different, because they present higher growth rates in adolescents than in adults.[22] In summary, there is a need for further elucidation on the relationship between giant uterine fibroids and their growth rate and the associated malignancy potential.

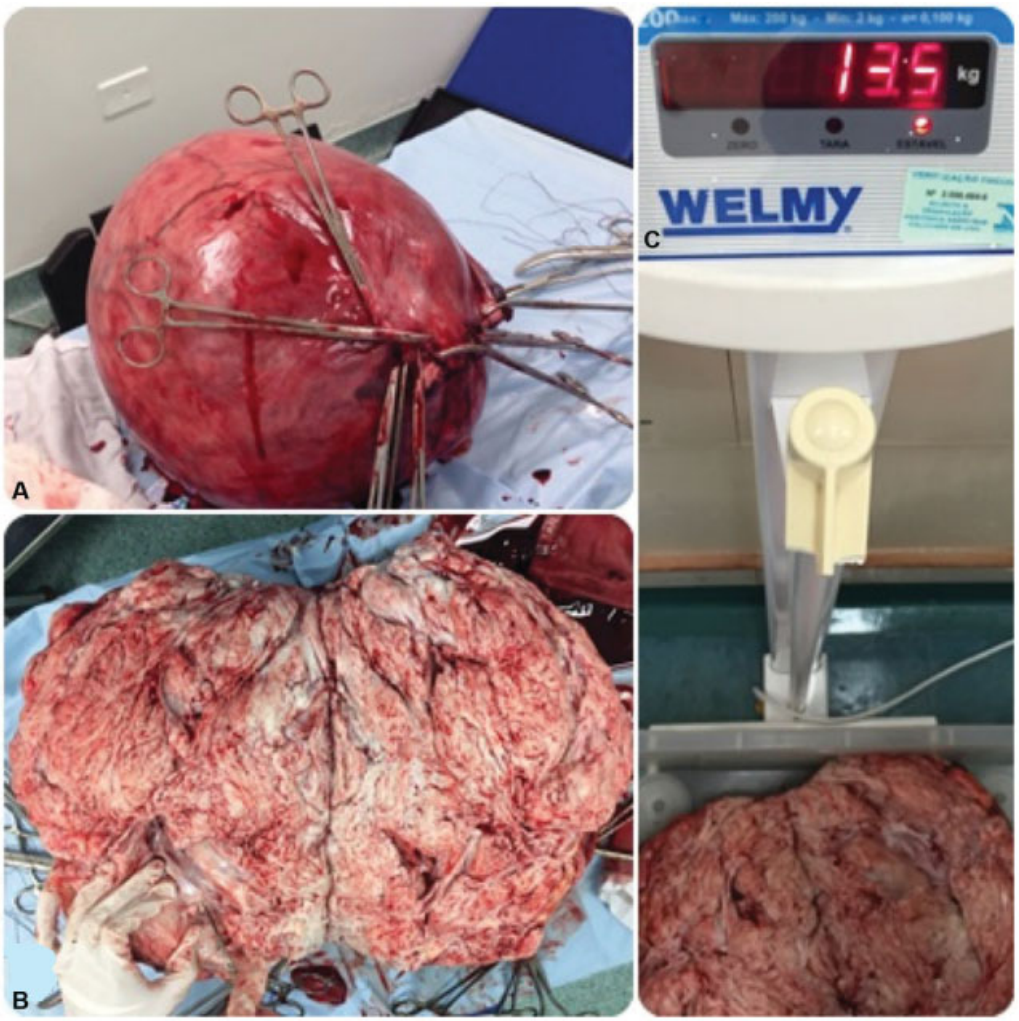

Fig. 2 (**A**) Voluminous uterus extracted after hysterectomy. (**B**) Macroscopic aspect of a leiomyoma (cut section). (**C**) Specimen weighing 13.5 kg.

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

Acknowledgments
We acknowledge the patient that gave her written consent to have her case reported. This case report has been approved by the Institutional Review Board.

References

1 Moroni R, Vieira C, Ferriani R, Candido-Dos-Reis F, Brito L. Pharmacological treatment of uterine fibroids. Ann Med Health Sci Res. 2014;4(Suppl 3):S185–S192. Doi: 10.4103/2141-9248.141955
2 Jonas HS, Masterson BJ. Giant uterine tumors: case report and review of the literature. Obstet Gynecol. 1977;50(1, Suppl)2s–4s
3 Hunt SH. Fibroid weighing one hundred and forty pounds. Am J Obstet Dis Women Child. 1888;21(01):62–63
4 Behrend M. Report of a case of fibromyoma of the uterus weighing 133 pounds removed at operation. Am J Obstet Gynecol. 1930;20 (05):699–702. Doi: 10.1016/S0002-9378(30)90197-4
5 Singhabhandhu B, Akin JT Jr, Ridley JH, Gray SW, Skandalakis J. Giant leiomyoma of the uterus: report of a case and review of the literature. Am Surg. 1973;39(07):391–397
6 Evans AT III, Pratt JH. A giant fibroid uterus. Obstet Gynecol. 1979; 54(03):385–386
7 Oelsner G, Elizur SE, Frenkel Y, Carp H. Giant uterine tumors: two cases with different clinical presentations. Obstet Gynecol. 2003; 101(5 Pt 2):1088–1091. Doi: 10.1016/s0029-7844(02)02621-2
8 Reddy BV, Lee J, Cunningham PL. Giant uterine leiomyoma with air-fluid levels. J Am Coll Surg. 2004;198(05):844–845. Doi: 10.1016/j.jamcollsurg.2003.11.027
9 Pérez M, Ramón JM. Large abdominal mass due to a giant uterine leiomyoma. Mayo Clin Proc. 2006;81(11):1415. Doi: 10.4065/ 81.11.1415
10 Nappi L, Matteo M, Giardina S, Rosenberg P, Indraccolo U, Greco P. Management of uterine giant myoma. Arch Gynecol Obstet. 2008; 278(01):61–63. Doi: 10.1007/s00404-007-0523-1
11 Amber I, Kennedy G, Martinez H, Pearson JM, Jimenez E. A leiomyoma in a cachectic woman presenting as a giant abdominal mass. J Radiol Case Rep. 2009;3(10):23–29. Doi: 10.3941/jrcr.v3i10.324
12 Semczuk A, Skorupski P, Olcha P, Skomra D, Rechberger T, Gogacz M. Giant uterine leiomyomas causing bilateral hydronephrosis coexisting with endometrial cancer in polyp: a case study. Eur J Gynaecol Oncol. 2009;30(03):344–346
13 Săvulescu F, Iordache I, Albiţa O, Hristea R, Dumitru C, Iordache A, et al. Giant uterine leiomyoma. Chirurgia (Bucur). 2011;106(05):665–668
14 Aydin C, Eriş S, Yalçin Y, Sen Selim H. A giant cystic leiomyoma mimicking an ovarian malignancy. Int J Surg Case Rep. 2013;4 (11):1010–1012. Doi: 10.1016/j.ijscr.2013.08.018
15 Máté S, Szatmári E, Sipos N, Széll J, Szánthó A, Rigó J Jr. [Giant uterine leiomyoma causing acute symptoms]. Orv Hetil. 2013;154 (10):387–390. Doi: 10.1556/oh.2013.29563
16 Orazulike NC, Green KI, Uzoigwe SA. Giant uterine fibroids: consequences of delay in presentation. Eur J Obstet Gynecol Reprod Biol. 2015;194:251–252. Doi: 10.1016/j.ejogrb.2015.06.034
17 Ezugwu EC, Iyoke CA, Ezugwu FO, Ugwu G. Successful pregnancy following myomectomy for giant uterine fibroid in an infertile woman. J Reprod Infertil. 2014;15(04):233–236
18 Moris D, Vernadakis S. Giant uterine leiomyoma mimicking pregnancy. Mayo Clin Proc. 2014;89(06):e53–e54. Doi: 10.1016/j.mayocp.2013.06.029
19 Sonoo T, Tokunaga K, Fukuda T, Nakamura K. Cardiac arrest induced by a giant uterine leiomyoma. BMJ Case Rep. 2015; 2015:bcr2015213370. Doi: 10.1136/bcr-2015-213370
20 Lim PT, Tan CH, Chia HL, Phoon J. Management of a giant uterine leiomyoma. BMJ Case Rep. 2018;2018:bcr2017224052. Doi: 10.1136/bcr-2017-224052
21 Kogan EA, Zharkov NV, Askolskaya SI. Popov, Krot MA, Demura TA. [Growth mechanisms and morphological structural features of large uterine leiomyoma]. Arkh Patol. 2018;80(05):16–22. Doi: 10.17116/patol20188005116
22 Moroni RM, Vieira CS, Ferriani RA, Reis RM, Nogueira AA, Brito LG. Presentation and treatment of uterine leiomyoma in adolescence: a systematic review. BMC Womens Health. 2015;15:4. Doi: 10.1186/s12905-015-0162-9

Psychological Follow-up During Prenatal Care of Pregnant Women: Insights During the covid-19 pandemic

Magda Spinello Consul Da Silva[1] Edward Araujo Júnior[1] Julio Elito Júnior[1]

[1] Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Rev Bras Ginecol Obstet 2021;43(1):72–73.

Address for correspondence Edward Araujo Júnior, PhD, Rua Napoleão de Barros, 875, Vila Clementino, São Paulo, SP, 04024-002, Brazil (e-mail: araujojred@terra.com.br).

Dear Editor,

The puerperal pregnancy cycle is considered a period of crisis marked by emotional changes in women and men, and may evolve healthily or present psychological disorders that will compromise psychological, physical and marital health. Psychological prenatal care is the monitoring of the pregnant and/or of the couple during pregnancy, the postpartum period and the puerperium until at least the 3rd month. The follow-up is for any and all pregnancies in obstetric physiological, pathological, fetal medicine and pregnancy losses. The main objective of psychological support involves preparing the couple to experience motherhood and fatherhood, to develop an active posture of the pregnant and the father, the strengthening of the marital relationship, the facilitation of the maternal-paternal-filial bond and the prevention of postpartum depression and puerperal psychosis.[1]

As for the specific objectives, these will be elaborated according to the physical emotional experiences of each patient's pregnancy. It is a personalized interdisciplinary psychological monitoring that aims to provide humanized assistance to women at such a special time and with so many changes.[2] Pregnancy is contemplated by different feelings and transformations each quarter, which means that the stages of psychological prenatal care are adapted to each moment of the evolution of pregnancy. The use of an initial interview and the investigation through psychological anamnesis are important instruments for the knowledge of the psychic functioning of the pregnant woman and the couple. Anguish and anxiety mark the gestational and postpartum 1st quarter. Stimulating the free expression of these feelings is one of the most important aspects to be highlighted for facilitating the experience of the puerperal pregnancy cycle. The need for information regarding physical and emotional changes, fetal development, childbirth, neonatal care and breastfeeding are extremely relevant during the approach with the pregnant woman. During psychological counselling, it is important to encourage appropriate body activities according to each case. Meditation, massage and abdominal breathing are also tools taught to the woman and the couple to encourage motherhood, facilitating the moment of delivery and favoring the emotional strengthening of parents with the unborn child.[3]

Pregnancy is the pinnacle of a female psychosexual development. The changes that may occur are inherent to the puerperal pregnancy cycle, for both men and women; they lead to increased expectations and anxiety, feelings that can be aggravated during this Covid-19 pandemic period.[4,5] Social distance is mandatory in the midst of the need for health care to the future parents; however, considering the technological advances that have been happening in the last decades, psychological prenatal care remains viable through the use of videoconferencing applications and software such as WhatsApp, Skype and Zoom.[6]

Videoconferences allow the obstetric psychologist to perform the service in all its completeness, and the only difference is in the adaptation of some dynamics - visual resources such as video tutorials or illustrated documents can be used to assist the pregnant woman and the couple in performing physical exercises, massages and meditation, for instance. The current moment sets a great challenge in the hands of professionals, who suddenly see themselves in the need of finding new protocols to reinvent the way of dealing with patients. With the use of virtual resources, obstetric psychology sees itself as an opportunity to experience a new way of guiding pregnant women during the day of setting up their maternity.

Conflict of Interests

The authors have no conflict of interests to declare.

received
June 30, 2020
accepted
August 14, 2020

DOI https://doi.org/10.1055/s-0040-1718451.
ISSN 0100-7203.

© 2021. Federação Brasileira das Associações de Ginecologia e Obstetrícia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)

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

References

1 Benute GR, Nozzella DC, Prohaska C, Liao A, de Lucia MC, Zugaib M. Twin pregnancies: evaluation of major depression, stress, and social support. Twin Res Hum Genet. 2013;16(02):629–633. Doi: 10.1017/thg.2012.153

2 Kliemann A, Böing E, Crepaldi MA. [Factors for anxiety and depression during pregnancy: systematic review of empiric articles]. Mudanças Psicol Saúde. 2017;25(02):69–76

3 Araújo WS, Romero WG, Zandonade E, Amorim MHC. Effects of relaxation on depression levels in women with high-risk pregnancies: a randomised clinical trial. Rev Lat Am Enfermagem. 2016;24(00):e2806. Doi: 10.1590/1518-8345.1249.2806

4 Silva IL, Lucena Filho EL. [Mental health and social assistance: challenges during COVID - 19]. Rev Psicol Saberes.. 2020;9(19): 138–146

5 Castro P, Narciso C, Matos AP, Werner H, Araujo Júnior E. Pregnant, uninfected, stressed, and confined in the COVID-19 period: what can we expect in the near future? Rev Assoc Med Bras (1992). 2020;66(04):386–387. Doi: 10.1590/1806-9282.66.4.386

6 Estrela FM, Silva KKA, Cruz MA, Gomes NP. Gestantes no contexto da pandemia da Covid-19: reflexões e desafios. Physis. 2020;30 (02):e300215. Doi: 10.1590/s0103-73312020300215

Good practices for ultrasound examinations in gynecology and obstetrics during the COVID-19 pandemic

Number 1 - Janeiro 2021

DOI: https://doi.org/10.1055/s-0041-1723082

The National Specialty Commission for Ultrasonography in GO 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:

- Routine ultrasound examinations by specialists are an essential part of prenatal care and should be performed even in the extraordinary situation of the COVID-19 pandemic.
- The routine of obstetric and gynecological ultrasound services during COVID-19 pandemic period was changed to increase the protection of the patient, her fetus and her family, as well as of health professionals involved in care.
- The impossibility of maintaining the recommended distance during the ultrasound examination requires rigorous and systematic precautions, because patients and health professionals are exposed to COVID-19 infection.
- Given the risk of COVID-19 transmission, the performance of ultrasound examinations in gynecology and obstetrics must be based on a priority assessment and in accordance with Febrasgo protocols.
- COVID-19 infection within health services must be avoided at all costs. Part of this strategy involves the surveillance of employees in the sector and the systematic use of personal protective equipment (PPE).

Recommendations:

- Obstetric and gynecological ultrasound services must prevent the scheduling of appointments in person.
- Obstetric and gynecological ultrasound services should prepare informative material on infection prevention in the form of leaflets, use iconographic material in the various environments of the ultrasound sector and apply questionnaires about COVID-19 to patients to define the infection status.
- Patients must undergo screening before entering an ultrasound unit in order to check if they are already infected or have any suspicion for COVID-19.
- The ultrasound sector should provide information about specific training on hygiene, use of PPE and equipment handling for healthcare professionals, including doctors, nurses, technicians, cleaning, maintenance and administrative staff, among others.
- Symptomatic patients not severely immunosuppressed: reschedule after ten days from the onset of symptoms.
- Patients living with people with symptoms of COVID-19: reschedule after 14 days.
- Positive polymerase chain reaction (PCR) patients who remain asymptomatic, not severely immunosuppressed: exempt from the scheduled appointment and reschedule ten days after the first positive real-time PCR (RT-PCR) test for COVID-19.
- Patients with positive PCR who remain asymptomatic and severely immunosuppressed: exempt from the scheduled appointment and reschedule 20 days after the first positive RT-PCR test for COVID-19.
- Aiming to reduce the time of direct contact with the patient, make videos of anatomical regions or capture specific screenshots and take biometric measurements offline. An experienced ultrasonographer may be chosen to perform the exams, thereby reducing the exam time and the need for a second opinion.

Background

The COVID-19 pandemic period changed the routine of obstetric and gynecological ultrasound services,[1] as well as the routine in all other women's health care services.[2,3] Such changes involve a series of protective measures that will be highlighted in this regulation.

Based on the care, safety and prevention of COVID-19, procedures to improve the protection of the patient, her fetus and her family and of health professionals involved in the care are mentioned. Routine ultrasound examinations by specialists are an essential part of prenatal care and should be performed even in the extraordinary situation of the COVID-19 pandemic. Precautions must be rigorous and systematic in the practice of this clinical activity, mainly because there is exposure of the patient and health professionals, given the impossibility of maintaining the recommended distance during the procedure.[1]

The information found in this document is based on the best practices recommended by National and International Diagnostic Imaging Societies and guided by two main axes:

1. Prevention against the expansion of COVID-19 during the performance of ultrasound examinations of women;
2. Protection of the patient and health care professionals in the ultrasound sector in order to maintain a safe workflow from the scheduling to the performance of exams. Note that conducts provided here can be adapted depending on the availability of resources and infrastructure.

Routine of obstetric and gynecological ultrasound exams in the context of the COVID-19 pandemic

How should the scheduling of exams in gynecology and obstetrics be during the COVID-19 pandemic?

The guidelines to avoid scheduling in person are as follows:[4-6]

- Exams must be scheduled by phone or the internet;
- The professional of the service unit, previously guided by doctors, should contact the patient on the eve of the exam to check about symptoms and risk factors for COVID-19 (Chart 1);
- Scheduling times should have a safe interval in between to avoid the crowding of patients in the waiting room;
- If patients have already done tests before, they should be instructed to bring them;
- If patients spontaneously appear at the medical ultrasound unit without prior appointment, they must return with a rescheduling and be informed that their prenatal care will not be affected;
- In cases that a rescheduling is impossible, when these patients present some type of symptom, possibly related to a respiratory infection, such as cough, fever or sore throat, they must undergo screening immediately for guidance to the best solution.

In the screening of patients for elective exams, what is the procedure to avoid COVID-19 transmission?

Before entering an ultrasound unit to do their exams, patients must undergo screening in order to check if they are already infected or have any suspicion for COVID-19.

This screening should be done with all preventive care:

- Mandatory use of masks;
- Control of the entry, exit and transit of patients;
- Reservation of a specific place in the waiting room;
- Access to information on respiratory etiquette.

Informative material on the prevention of infection should be prepared in the form of leaflets, iconographic material should be used in the various environments of the ultrasound sector and questionnaires about COVID-19 should be applied to patients to define the infection status.

Patients should be investigated for symptoms related to the risk of COVID-19 (Chart 1).[7] At this time, their temperature should be measured. In case of cough, high fever or shortness of breath, these patients must undergo specific screening for COVID-19 and evaluation by a health professional in accordance with local protocols.[6]

Chart 1. Guidelines for screening patients for coronavirus infection in elective exams

"Before service, you must answer some questions. For everyone's protection, it is important that you answer honestly". It is important to ask one question at a time and wait for each answer.
• Do you have the flu? • Are you coughing? • Do you have a runny nose? • Do you have a sore throat? • Do you feel body ache? • Can you smell food and other things? • Can you taste food? • Do you have a fever? • Do you have chills? • Do you have the flu? • Do you feel shortness of breath? • Do you have diarrhea? • Have you had contact with someone who tested positive for COVID-19 in the past 14 days? • Have you had contact with someone who has been hospitalized for flu or pneumonia in the past 14 days?

Source: Adapted from the Ministry of Health (2020).[7]

What are the recommendations for screening patients with possible coronavirus infection in elective exams?

- Symptomatic patients not severely immunosuppressed: reschedule after ten days from the onset of symptoms.[8]

- Patients living with people with symptoms of COVID-19: reschedule after 14 days.[8]
- Patients with positive PCR who remain asymptomatic and not severely immunosuppressed: exempt from the scheduled appointment and reschedule ten days after the first positive RT-PCR test for COVID-19.[8]
- Patients with positive PCR who remain asymptomatic and severely immunosuppressed: exempt from the scheduled appointment and reschedule 20 days after the first positive RT-PCR test for COVID-19.[8]

In such cases, follow-up can be done by direct communication with the patient or preferably by remote technology means.

How to assess the priority of ultrasound exams in the context of the COVID-19 pandemic?

Exams must be analyzed using three types of priority:[6]

- Exams that must be done immediately without delay;
- Exams that can be postponed without harm to the patient's care;
- Exams that can be suspended during the pandemic period.

From this choice of priorities, the following points must also be considered:

- The routine of ultrasound examinations covering specific periods of pregnancy in the course of the first or second semester;[9,10]
- Any history of genetic or structural abnormalities,[9] placental insufficiency (preeclampsia, fetal growth restriction),[11,12] previous preterm birth, twin pregnancy,[13] as well as any previous maternal diseases harmful to pregnancy;[14]
- If there are any risk factors that arose during the pregnancy period.

In these cases, the recommendations for performing obstetric and gynecological ultrasounds are as follows:

- Select an experienced ultrasonographer to perform these exams, thereby minimizing the need for a second opinion;
- Follow Febrasgo protocols to determine the time of exams in the first and second trimester of pregnancy and for the performance of gynecological exams;
- If possible, for reduced time of direct contact with the patient, make videos of anatomical regions or capture specific screenshots and take biometric measurements offline.

What is the routine of obstetric exams for patients without preexisting maternal or fetal comorbidities?

- In the first trimester (preferably between 11 and 14 weeks), the following should be evaluated: location of pregnancy, viability, number of fetuses and chorionicity, date of pregnancy, fetal anatomy and screening for aneuploidy and preeclampsia.[6]
- Perform morphological ultrasound at week 20-22 for the assessment of fetal static, cardiac activity, biometrics, basic fetal anatomy, fetal wellbeing and placental location.[6]
- Perform fetal growth screening exams during the third trimester.[6]

Patients with comorbidities should use the guidelines provided in the previous item. However, the monitoring must be more rigorous and follow the specific protocols for each condition.[6,15]

How to proceed with ultrasound exams in hospitalized patients with suspected or confirmed cases of COVID-19 infection?

The ultrasound examination must be done by an experienced doctor, preferably at the bedside. The following must be evaluated: fetal statics, cardiac activity, biometrics, amniotic fluid volume, placenta and umbilical artery doppler velocimetry. Another important point is the assessment of fetal growth within four weeks after recovery.

How should the waiting environment for exams be organized in patients with and without suspected/confirmed COVID-19?

Ultrasound sector waiting room

In the waiting room environment, the distance of two meters between seats must be preserved with a maximum of one person in the examination room. Children or other relatives should not be allowed in this area. Patients should be advised to go unaccompanied to the examination site. To reduce the risk of transmission among health professionals, it is recommended that people who fit into a risk group do not stay in the waiting room, which is for exclusive use of scheduled patients.

Creation of an isolation room

The isolation room is recommended for patients with suspected COVID-19 or confirmed cases who need to perform a gynecological or obstetric examination in the ultrasound sector. These patients should be examined in an exclusive room with a bathroom.[3] It is important to ensure thorough cleaning of the equipment used.

Cleaning of the ultrasound room and its devices[6]

Cleaning with appropriate disinfectant should be performed every morning in the morning, including the ultrasound monitor, computer keyboard and mouse, stretcher rails, transducer support, gel container, door handles, buttons, light switches, chairs and countertops.

Reduce the number of accessories on site that are not being used. These surplus accessories must be removed and kept in a clean, closed place. As for transducers connected to the ultrasound, only one transabdominal and one transvaginal are sufficient, used as required.

In the case of patients with suspected/probable/confirmed infection, the equipment should preferably be separated and used exclusively. It should always be sanitized, preferably with single-use gel packets, avoiding the usual containers. Prefer the use of disposable gloves and equipment.

What are the precautions with equipment and how should PPE be used in the ultrasound sector?

Some care is essential for professionals who have direct contact with patients or even with potentially infectious materials. This directly involves the use and access to PPE:[5]

- Pay attention to the time of use and removal of PPE; with gloves, for example, in order to avoid self-contamination and that of third parties, as the chance of contamination is greater if removal of this equipment is inappropriate;
- Discard and perform the proper maintenance of non-disposable PPE.

Likewise, information on specific training on hygiene and instrument handling for health professionals should be provided, including doctors, nurses, technicians, cleaning, maintenance and administrative staff, among others.

Some important guidelines:[15]

- Make sure the ultrasound professional is experienced and has undergone infection control training;
- Pay strict attention to hand hygiene, before and after contact with the patient. If you cannot wash your hands, use a disinfectant or an appropriate sanitizing product;
- Give preference to single-use gel packets instead of using the gel directly from containers;
- Use the transducer cover for non-endoluminal probes;
- Always aim at reducing the exam duration.

Use of more specific equipment to treat patients with COVID-19 - confirmed or suspected/symptomatic/asymptomatic:[5,6,15]

- Mask:
  - The patient must wear a face mask to avoid and/or reduce transmission by droplets;
  - The professional must follow the same hygiene rules and mandatorily use the facial mask;
  - Remove the mask carefully and always proceed with hand hygiene.
    a. Wash your hands with water and soap/detergent for at least 20 seconds;
    b. Use specific products with alcohol in the concentration of 60%-95%;
    c. The ultrasound operator should preferably use a three-layer surgical mask.
- Eye protection

For eye protection, the use of a disposable facial protector that can protect the front and sides of the face is recommended. It should always be used when professionals are in the patient's room and in the service area.

Two important aspects to be highlighted:

- Glasses and contact lenses for personal use are not considered an appropriate eye protection;
- Eye protection must always be removed when leaving the service area.

- Gloves

Appropriate care with gloves must include the following:

- Always be clean when entering the service room;
- Be removed and discarded when leaving the service area;
- Hands should be cleaned after removing the gloves;
- During the ultrasound examination, disposable gloves, preferably latex-free, should be used, which will be changed after the care of each patient.[15]

- Aprons

Disposable and non-disposable gowns can be used in patient care areas. Disposable gowns that can be placed in an appropriate disposal container before leaving the service area should be preferred.

Environmental infection control

It is mandatory to follow procedures for cleaning and disinfecting the ultrasound environment consistently and correctly. The control of environmental infection must aim at reusable materials that will be disinfected according to instructions provided by the manufacturer and supported by its installation and use policies. This also includes the care and management of objects and clothing of the team of professionals. Unusable material must be discarded according to health surveillance rules.

How to deal with employees and collaborators of the health team with COVID-19?

In case of confirmed cases of COVID-19 infection in the hospital service unit, recommendations are the following:

- Put part of the health team to work remotely in order to avoid the simultaneous contamination of

a relevant part of professionals and thereby, not impact the maintenance of services;
- For professionals who already show symptoms of COVID-19 infection, flexible medical leave policies consistent with public health guidelines should be implemented.

Final considerations

This regulation covers different procedures that must be followed in the pandemic period of COVID-19 for the performance of obstetric and gynecological ultrasounds in order to monitor and preserve the health of pregnant women and their fetuses, and of all professionals involved.

References

1. Wataganara T, Ruangvutilert P, Sunsaneevithayakul P, Sutantawibul A, Chuchotirot M, Phattanachindakun B, et al. Minimizing cross transmission of SARS-CoV-2 in obstetric ultrasound during COVID-19 pandemic. J Perinat Med. 2020;48(9):931-42. doi: 10.1515/jpm-2020-0228
2. American College of Obstetricians and Gynecologists (ACOG). Novel Coronavirus 2019 (COVID-19): Practice Advisory [Internet]. 2020 [cited 2020 Nov 12]. Available from: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019
3. International Federation of Gynecology and Obstetrics (FIGO). Safe motherhood and COVID-19 [Internet]. 2020 [cited 2020 Nov 12]. Available from: https://www.figo.org/safe-motherhood-and-covid-19
4. Colégio Brasileiro de Radiologia e Diagnóstico por Imagem. Recomendações gerais de prevenção de infecção pelo COVID-19 para clínicas e serviços hospitalares de diagnóstico por imagem [Internet]. 2020 [cited 2020 Jul 25]. Available from: https://cbr.org.br/recomendacoes-gerais-de-prevencao-de-infeccao-pelo-covid-19-para-clinicas-e-servicos-hospitalares-de-diagnostico-por-imagem/
5. Poon LC, Abramowicz JS, Dall'Asta A, Sande R, Ter Haar G, Maršal K, et al. ISUOG Safety Committee Position Statement on safe performance of obstetric and gynecological scans and equipment cleaning in context of COVID-19. Ultrasound Obstet Gynecol. 2020;55(5):709-72. doi: 10.1002/uog.22027
6. Declaração do Consenso ISUOG sobre a organização de serviços de ultrassonografia obstétrica de rotina e especializados no contexto da COVID-19 [Internet]. 2020 [cited 2020 Nov 25]. Available from: https://www.isuog.org/uploads/assets/ab697155-d3fa-4818-abad79c3fecd8291/ISUOG-Consensus-StatementCOVID19Portuguese.pdf
7. Ministério da Saúde. Secretaria de Atenção Primária à Saúde. Departamento de Ações Programáticas e Estratégicas. Manual de recomendações para a assistência à gestante e puérpera frente à pandemia de Covid-19 [Internet]. Brasília (DF): Ministério da Saúde; 2020 [cited 2020 Nov 25]. Available from: http://189.28.128.100/dab/docs/portaldab/documentos/corona/manual_recomendacoes_gestantes_covid19.pdf
8. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Nota técnica GVIMS/GGTES/Anvisa No. 07/2020. Orientações para prevenção e vigilância epidemiológica das infecções por SARS-CoV-2 (COVID-19) dentro dos serviços de saúde. (Complementar à nota técnica GVIMS/GGTES/ANVISA No. 04/2020) [Internet]. 2020 [cited 2020 Dec 5]. Available from: https://www20.anvisa.gov.br/segurancadopaciente/index.php/alertas/item/nota-tecnica-gvims-ggtes-anvisa-n-07-2020-atualizada-em-17-09-2020?category_id=244
9. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2013;41(1):102-13. doi: 10.1002/uog.12342
10. Salomon LJ, Alfirevic Z, da Silva Costa F, Deter RL, Figueras F, Ghi T, et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019;53(6):715-23. doi: 10.1002/uog.20272
11. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol. 2019;53(1):7-22. doi: 10.1002/uog.20105
12. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(2):233-9. doi: 10.1002/uog.12371
13. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol. 2016;47(2):247-63. doi: 10.1002/uog.15821
14. Organização Pan-Americana da Saúde, Ministério da Saúde, Federação Brasileira das Associações de Ginecologia e Obstetrícia, Sociedade Brasileira de Diabetes. Tratamento do diabetes mellitus gestacional no Brasil. Brasília (DF): OPAS; 2019.
15. Royal College of Obstetricians and Gynaecologists. Guidance for antenatal screening and ultrasound in pregnancy in the evolving coronavirus (COVID-19) pandemic: information for healthcare professionals: Version 1.1 [Internet]. 2020 [cited 2020 Nov 22]. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/2020-07-10-guidance-for-antenatal-screening.pdf

Fernando Maia Peixoto Filho[1]
[1]Universidade Federal de Uberlândia, Uberlândia, MG, Brazil.

Adriana Gualda Garrido[2]
[2]Faculdade de Medicina, Universidade Federal de Brasília, Brasília, DF, Brazil.

Anselmo Verlangieri Carmo[3]
[3]Universidade Federal de Mato Grosso, Cuiabá, MT, Brazil.

Eduardo Becker Júnior[4]
[4]Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

Guilherme de Castro Rezende[5]
[5]Faculdade da Saúde e Ecologia Humana, Vespasiano, MG, Brazil.

Heron Werner Junior[6]
[6]Universidade do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Joffre Amin Junior[7]
[7]Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Jorge Roberto Di Tommaso Leão[8]
[8]Universidade do Estado do Amazonas, Boca do Acre, AM, Brazil.

Luciano Marcondes Machado Nardozza[9]
[9]Universidade Federal de São Paulo, São Paulo, SP, Brazil.

Luiz Eduardo Machado[10]
[10]Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil.

Manoel Alfredo Curvelo Sarno[11]
[11]Universidade Federal da Bahia, Salvador, BA, Brazil.

Patricia El Beitune[12]
[12]Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.

Pedro Pires Ferreira Neto[13]
[13]Universidade de Pernambuco, Recife, PE, Brazil.

Sergio Kobayashi[14]
[14]Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

Fabricio da Silva Costa[15]
[15]Faculdade de Medicina, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.

Conflict of interest: none to declare.

National Specialty Commission for Ultrasonography in GO of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO)

President:
Fabricio da Silva Costa

Vice-President:
Eduardo Becker Júnior

Secretary:
Heron Werner Júnior

Members:
Adriana Gualda Garrido
Anselmo Verlangieri Carmo
Fernando Maia Peixoto Filho
Guilherme de Castro Rezende
Joffre Amim Junior
Jorge Roberto Di Tommaso Leão
Luciano Marcondes Machado Nardozza
Luiz Eduardo Machado
Manoel Alfredo Curvelo Sarno
Patricia El Beitune
Pedro Pires Ferreira Neto
Sergio Kobayashi