ISSN 0100-7203
eISSN 1806-9339

RBGO Gynecology & Obstetrics

Revista Brasileira de Ginecologia e Obstetrícia
Number 9 • Volume 45 • Pages 501–554 • September 2023

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)

Associate 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 Cristina Pinheiro Fernandes Araujo
Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
Ana Katherine da Silveira Gonçalves de Oliveira
Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
Andréa Cronemberger Rufino
Universidade Estadual do Piauí, Floriano, PI, Brazil
Andréa Pires Souto Damin
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Andréa da Rocha Tristão
Universidade Estadual Paulista "Júlio de Mesquita 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
Cassio Cardoso Filho
Universidade Estadual de Campinas, Campinas, SP, 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
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
Fernanda Garanhani de Castro Surita
Universidade Estadual de Campinas, Campinas, SP, 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
Helmer Herren
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Helena Borges Martins da Silva Paro
Universidade de São Paulo, São Paulo, SP, Brazil
Hélio Humberto Angotti Carrara
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Ilza Maria Urbano Monteiro
Universidade Estadual de Campinas, Campinas, 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 Estadual de Campinas, 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
Rossana Pulcineli Vieira Francisco
Universidade de São Paulo, São Paulo, 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
Rogério Bonassi Machado
Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil
Silvana Maria Quintana
Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Sophie Françoise Mauricette Derchain
Universidade Estadual de Campinas, Campinas, SP, Brazil
Sue Yazaki Sun
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Valéria Cristina Sandrim
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil

Editorial Board

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, Austrália
Giuseppe Rizzo
Università degli Studi di Roma "Tor Vergata", Roma, Itália
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 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, Canadá
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
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, Japão
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
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
Silvia Daher
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Shaun Patrick Brennecke
University of Melbourne Parkville, Victoria, Austrália
Técia Maria de Oliveira Maranhão
Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

Toshiyuki Hata
University Graduate School of Medicine, Kagawa, Japão

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
Jan Pawel Andrade Pachnicki (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 45, Number 9/2023

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Thieme Revinter Publicações Ltda

online www.thieme-connect.com/products

Febrasgo Position Statement

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

Cover design: © Thieme
Cover image source: © Thieme

© 2023. Federação Brasileira de Ginecologia e Obstetrícia. 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.thieme.com/rbgo.**

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

The Insertion of Intrauterine Devices in the Immediate Postpartum Period Remains an Important Missed Opportunity to Prevent Unplanned Pregnancies in Brazil

Adalberto Kiochi Aguemi[1] Mirna Namie Okamura[1] Cristina Aparecida Falbo Guazzelli[2] Maria Regina Torloni[2]

[1] Secretaria Municipal de Saúde de São Paulo, São Paulo, SP, Brazil
[2] Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Rev Bras Ginecol Obstet 2023;45(9):e501–e502.

Unplanned pregnancy continues to be a public health problem in Brazil, particularly for the most vulnerable segment of the population. According to data from the Birth in Brazil study, 55% of pregnancies are unplanned, a proportion that reaches 65.3% among adolescents. Although the copper IUD is a highly effective long-term contraceptive method, it is still little used in Brazil for several reasons, including access barriers in outpatient clinics. The offer of IUD insertion immediately after childbirth or abortion is a window of opportunity to avoid unplanned pregnancies.

In 2017, the Ministry of Health launched a project to expand access to this method by encouraging the offer and insertion of copper IUDs in the immediate postpartum and post-abortion periods in Brazilian maternity hospitals for all women willing to use this contraceptive. Despite this initiative, in 2021 the postpartum IUD insertion rate in Brazilian maternity hospitals was less than 1.5% compared with 18% in Mexico in 2014,[1] where the unplanned pregnancy rate was 36%. These data show the need for advances in existing strategies to expand the use of IUDs in Brazilian maternity hospitals, including a continuous public policy by the Ministry and Departments of Health, in addition to studies on the various factors involved in this process.

A study conducted in Brazilian maternity hospitals on the knowledge, attitude and practice of physicians in the use of IUDs in the immediate postpartum and post-abortion periods is published in this issue of RBGO,[2] and points to some of the barriers and facilitators present in our environment. For example, ~42% of physicians said they had not received any training on IUD insertion in the immediate postpartum (IPP) or immediate post-abortion (IPA). In the previous 12 months, 19.7%, 22.8% and 53.5% of respondents stated they had not inserted an IUD during a cesarean section, immediately after a vaginal delivery and an abortion, respectively. However, this proportion may be lower in Brazilian maternity hospitals, as 95% of maternity hospitals in the study were teaching hospitals. More than 70% of participants consider women's resistance to the method as an important or very important barrier to IUD insertion in the IPP or IPA periods in the public hospital where they work. More than 60% pointed to the unavailability of copper IUDs in the obstetric center and the lack of hospital protocols as important or very important barriers to IUD insertion in the IPP or IPA periods. Other important or very important barriers mentioned by most participants were the lack of experience of physicians and fear of IUD expulsion (in insertions after vaginal or cesarean deliveries), fear of infection or perforation (in insertions after vaginal delivery or abortion) and lack of support from hospital managers (for IUD insertion in the IPA period).

These findings indicate the need to reassess and improve the quality of training currently offered by educational institutions and the involvement of managers to offer refresher courses and training. The addition of a practical training module, including a clinical demonstration (on real patients) and tutor supervision in the obstetrics center for a few days or weeks after the theoretical module could reduce the lack of experience and increase the confidence of physicians in IUD insertion in the IPP and particularly in the IPA period in Brazilian public hospitals. The involvement, performance and support of clinical directors and hospital managers are essential to overcome the main organizational barriers to IUD insertion in the IPP or IPA periods reported by study participants.

It is important that physicians guide and clarify the woman's and partner's doubts during antenatal care about the possibility of IUD insertion in the IPP period, thus increasing the possibility of adherence to this contraceptive method.

Address for correspondence Adalberto Kiochi Aguemi, Rua General Jardim, 36, 01223-010, Vila Buarque, São Paulo, SP, Brazil (e-mail: adalbertoaguemi@gmail.com).

DOI https://doi.org/10.1055/s-0043-1774737.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

Reducing unplanned pregnancies is a priority for entities and health professionals committed to improving maternal and child indicators. The challenge is to change this reality to visualize a promising future.

Conflicts of Interest
None to declare.

References

1 Potter JE, Hubert C, White K. The availability and use of postpartum LARC in Mexico and among Hispanics in the United States. Matern Child Health J. 2017;21(09):1744–1752. Doi: 10.1007/s10995-016-2179-6
2 Knowledge, attitude and practice of Brazilian physicians about immediate postpartum and postabortion IUD insertion. Rev Bras Ginecol Obstet. 2023;45(09):e523–e533

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Prediction of Rupture by Complete Blood Count in Tubal Ectopic Pregnancies Treated with a Single-Dose Methotrexate Protocol

Predição de ruptura por hemograma completo em gestações ectópicas tubárias tratadas com protocolo de dose única de metotrexato

Yıldız Akdaş Reis[1] Arife Akay[1] Elif Gülşah Diktaş[1] Merve Özkan[1] Neslihan Öztürk[1] Doğukan Özkan[1] Betül Tokgöz Çakır[1] Salim Erkaya[1]

[1] Obstetrics-Gynecology Department, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital, Ankara, Turkey

Rev Bras Ginecol Obstet 2023;45(9):e503–e510.

Address for correspondence Yıldız Akdaş Reis, Obstetrics-Gynecology Department, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital, Ankara, Turkey (e-mail: yildizakdasreis@hotmail.com).

Abstract

Objective The availability of reliable and inexpensive markers that can be used to determine the risk of rupture during methotrexate (MTX) treatment in ectopic pregnancies (EPs) is considerable. The aim of the present study is to investigate the role of systemic inflammatory markers such as leukocytes (or white blood cells, WBCs), the neutrophil-to-lymphocyte ratio (NLR), and platelet distribution width (PDW), which are among the parameters of the complete blood count (CBC), in the prediction of rupture of EPs under MTX treatment.

Materials and Methods A total of 161 patients with tubal EP who underwent a single-dose methotrexate (MTX) protocol were retrospectively analyzed, and the control group (n = 83) included patients cured by MTX, while the ruptured group (n = 78) included patients who were operated on for tubal rupture during the MTX treatment. The features of EP, beta-human chorionic gonadotropin (β-hCG) levels, sonographic findings, and CBC-derived markers such as WBC, NLR, and PDW, were investigated by comparing both groups.

Results The NLR was found to be higher in the ruptured group, of $2.92 \pm 0.86\%$, and significantly lower in the control group, of $2.09 \pm 0.6\%$. Similarly, the PDW was higher ($51 \pm 9\%$) in the ruptured group, and it was significantly lower a ($47 \pm 13\%$) in the control group ($p < 0.05$). Other CBC parameters were similar in both groups ($p > 0.05$).

Conclusion Systemic inflammation markers derived from CBC can be easily applied to predict the risk of tubal rupture in Eps, since the CBC is an inexpensive and easy-to-apply test, which is first requested from each patient during hospitalization.

Keywords
- ectopic pregnancy
- methotrexate
- neutrophil-to-lymphocyte ratio
- platelet distribution width

received
March 16, 2023
accepted
May 5, 2023

DOI https://doi.org/10.1055/s-0043-1772485.
ISSN 0100-7203.

© 2023. Federação Brasileira 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 disponibilidade de marcadores confiáveis e baratos que podem ser usados para determinar o risco de ruptura durante o tratamento com metotrexato (MTX) em gestações ectópicas (GEs) é considerável. O objetivo do presente estudo é investigar o papel de marcadores inflamatórios sistêmicos, como leucócitos (ou glóbulos brancos, glóbulos brancos), a relação neutrófilo-linfócito (NLR) e largura de distribuição de plaquetas (PDW), que estão entre os parâmetros do hemograma completo (hemograma), na predição de ruptura de PEs sob tratamento com MTX.

Materiais e Métodos Foram analisados retrospectivamente 161 pacientes com EP tubária submetidas a protocolo de dose única de metotrexato (MTX), sendo que o grupo controle (n = 83) incluiu pacientes curadas com MTX, enquanto o grupo roto (n = 78) incluíram pacientes operadas por ruptura tubária durante o tratamento com MTX. As características de EP, beta-gonadotrofina coriônica humana (β-hCG), achados ultrassonográficos e marcadores derivados de CBC, como WBC, NLR e PDW, foram investigados comparando os dois grupos.

Resultados A RNL foi maior no grupo roto, de 2,92 ± 0,86%, e significativamente menor no grupo controle, de 2,09 ± 0,6%. Da mesma forma, o PDW foi maior (51 ± 9%) no grupo roto, e foi significativamente menor a (47 ± 13%) no grupo controle ($p < 0,05$). Outros parâmetros do hemograma foram semelhantes em ambos os grupos ($p > 0,05$).

Conclusão Marcadores inflamatórios sistêmicos derivados do hemograma podem ser facilmente aplicados para predizer o risco de ruptura tubária na Eps, uma vez que o hemograma é um exame de baixo custo e fácil aplicação, solicitado primeiramente a cada paciente durante a internação.

Palavras-chave

- gravidez ectópica
- metotrexato
- proporção de neutrófilos para linfócitos
- largura de distribuição de plaquetas

Introduction

Ectopic pregnancy (EP) is defined as the implantation of the fertilized ovum outside the uterine cavity, frequently in the fallopian tubes, and it occurs in 2% of all pregnancies.[1] Although the rate of deaths associated with EP have decreased, 9% to 13% of all pregnancy-related deaths are associated with EP, particularly in developing countries.[2] Methotrexate (MTX), a folinic acid antagonist, is preferred as a cost-effective, first-line therapy in tubal EPs if the patient is hemodynamically stable.[3] However, the success rate of the MTX treatment in EP ranges from 65% to 95%.[4–6] Sporadically, the failure of the treatment results in rupture of the EP, which can lead to hemodynamic instability or even death caused by intraabdominal bleeding; therefore, it is crucial to predict rupture.

Conditions that lead to faultiness of implantation signals due to reasons, such as tubal damage caused by infection or inflammation, alter tubal transport and microenvironment, increase receptivity in the tubal epithelium, and are thought to predispose to EP, that is, inflammation is an important factor in the formation and maintenance of EP.[7,8] Many studies[7,9,10] have also shown that the expression of several chemokines and cytokines increases in the tube in which the EP is located. Furthermore, complete blood counts (CBCs) were accepted as serial and basic parameters indicative of systemic inflammation and stress.[11] Markers of CBC, such as the neutrophil-to-lymphocyte ratio (NLR)[12] and the platelet-to-lymphocyte ratio (PLR)[13] are known as inexpensive and easily calculable inflammatory markers that correlate with the prognosis of systemic inflammatory diseases.

Rupture of the EP may occur during MTX therapy and may have dramatic consequences. Therefore, there is a need for inexpensive, sensitive, and easy-to-apply markers for patients undergoing MTX therapy. The present study aims to investigate whether CBC-derived markers such as leukocytes (white blood cells, WBCs), NLR, PLR, and platelet distribution width (PDW) predict EP rupture.

Materials and Methods

We performed a retrospective evaluation of the data of the patients hospitalized between January 1st, 2014, and January 12th, 2019, with the diagnosis of tubal EP in the Early Pregnancy Service of our institution, and who underwent the single-dose MTX protocol. In our clinic, the diagnosis and treatment of EP are made according to the 2018 American College of Obstetricians and Gynecologist (ACOG) guidelines.[3] The diagnosis of tubal EP is made if the β-HCG level is above 1,500-3,500 mIU/mL, an intrauterine pregnancy is not observed and a tubal ectopic focus is observed on transvaginal ultrasonography (TVUSG), or if the level of beta-human chorionic gonadotropin (β-HCG) is below 1,500 mIU/mL to 3,500 mIU/mL, an irregular β-HCG increase is observed below the minimum threshold (35% to 55%) when serial β-HCG concentration measurements are made at 48-hour intervals, an intrauterine pregnancy is not detected, and a tubal ectopic

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

focus is detected on TVUSG in the follow-up. In addition, an MTX protocol consisting of a single dose of 50 mg/m^2 (body surface area) was administered intramuscularly in stable EPs that fulfilled the ACOG criteria and had no contraindications. Accordingly, we excluded cases with the following characteristics: intrauterine pregnancy, evidence of immunodeficiency, moderate to severe anemia, leukopenia or thrombocytopenia, sensitivity to MTX, active pulmonary disease, active peptic ulcer disease, clinically significant hepatic dysfunction, clinically significant renal dysfunction, breastfeeding, active infection, and chronic inflammatory diseases (as they affect hematological parameters). Tubal EPs in which the villus structure is proven not to be in the intrauterine cavity by endometrial sampling, or pregnancies with a histopathology report of tubal EP after surgery, that were hemodynamically stable and were compatible with follow-up and were not clinically ruptured were included in the study. Furthermore, in our clinic, the patients followed up according to the ACOG recommendations. The treatment is as follows: in the single-dose MTX regimen, measure the hCG level on days 4 and 7; if the decrease is greater than 15%, measure β-hCG levels weekly until they reach a non-pregnant level but decrease below 15%. If the β-hCG levels flatten or rise during follow-up, a second dose of MTX is administered, and the measurement of the β-hCG level is repeated. After the single-dose MTX protocol, patients who were followed up until the β-HCG level was zero and did not experience rupture were considered cured. The patients who underwent emergency surgery after the single-dose MTX protocol were found to have ruptured from the tubal region and were histopathologically confirmed were considered ruptured.

The sample was divided into group 1 (cases), which included patients who experienced rupture during the MTX treatment, and group 2 (controls), which was composed of patients successfully treated with MTX. Group 1 was composed of 78 patients. Among the patients cured with the single-dose MTX protocol, the cases with the same age, body mass index (BMI), gestational age, baseline β-hCG, and EP size as the cases in group 1 were selected as the control group. Therefore, differences in these parameters were prevented from affecting the CBC. In addition, when creating the control group, if there were two different cases with similar values for these parameters (there were about five cases), both were included in the control group to avoid bias. As a result, the control group (group 2) was composed of 83 patients cured with the single-dose MTX protocol. In addition, EPs caused by assisted reproductive methods were excluded from the study. Patients with a pregnancy of unknown location, those with non-tubal EPs, patients with inflammatory, hematological, or connective tissue disease, as well as smokers, and the cases whose age, BMI, gestational age, baseline β-hCG, and EP size did not match one of the controls were not included in the study. Approval from the local ethics committee and the necessary consent from the patients were obtained for the study.

Moreover, venous blood is routinely taken from each patient in an anticoagulant tube containing ethylenediaminetetraacetic acid (EDTA) at the time of hospitalization, and the CBC performed with the BC-6000 (Mindray, Shenzhen, China) device in the blood laboratory shows a total of 23 parameters. The first hemogram parameters at the time of hospitalization, WBCs, hemoglobin (Hb), platelets (PLTs), mean corpuscular volume (MCV), NLR, PLR, reticulocyte distribution width (RDW), PDW, and mean platelet volume (MPV) were determined for this study

Age, BMI, obstetric history (gravidity, parity, and ectopic pregnancy), previous history of abdominal surgery and pelvic inflammatory disease, levels and follow-ups of β-hCG, diameter and features of EP material, results and failures of treatment modalities, and all other features were obtained retrospectively from patient files and the electronic patient registry system. All of these parameters for both study groups were compared.

The statistical analyses were made with the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 21.0, and we adopted a confidence level of 95%. If the kurtosis and skewness values obtained from the measurements are between +3 and -3, they are considered sufficient for the normal distribution. The categorical variables were expressed as numbers and percentages, and the numerical variables, as minimum, maximum, mean, and standard deviation (SD) values. Statistical significance was set as $p < 0.05$. In two independent groups, the parametric variables were analyzed with the *t*-test and non-parametric variables, with the Mann–Whitney test. The relationships involving the categorical variables were analyzed with the Chi-squared test. Hematologic markers (WBC, Hb, PLT, NLR, PLR, MPV, MCV, PDW, RDW) were expressed as mean and SD values, and the receiver operating characteristic (ROC) curve was used to show the sensitivity and specificity of each marker. The detection value of each biomarker increases until it is close to 1 when the area under the curve (AUC) is greater than 0.5. The Pearson correlation test was used to assess the relationship regarding free peritoneal fluid, NLR, and PDW.

Results

There were 83 cases in the control group cured with a single-dose MTX protocol and 78 cases in the ruptured group. There was no significant difference in terms of demographic parameters between the groups. History of pelvic inflammatory disease (PID) was significantly higher in the control group (6% versus 0% in the ruptured group; $p = 0.028$) and the odds ratio (OR) was determined as 5. However, the history of abdominal surgery was insignificantly () higher in the ruptured group (39% versus 28% in the control group; $p = 0.148$), and the OR was found to be of 1.6. The demographic characteristics of the groups are presented in ►**Table 1**.

In consistency with the study design, no significant difference was observed between the two groups in terms of age, BMI, gestational age, EP size, and β-hCG values on admission ($p > 0.05$). The mean amount of free peritoneal fluid before treatment in the ruptured group was of 58.44 ± 29.31 mm, and it was found to be significantly higher than the control group ($p = 0.000$). The length of hospital stay

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 1 Demographics of the study groups

		Groups		Chi-squared	*p*	OR
		Control	Ruptured			
		N = 83: n(%)	N = 78: n(%)			
Gravidity	1	26(31.3)	17(21.8)	9.045	0.060	
	2	22(26.5)	14(17.9)			
	3	22(26.5)	20(25.6)			
	4	6(7.2)	16(20.5)			
	> 5	7(8.4)	11(14.1)			
Parity	0	36(43.4)	25(32.1)	4.079	0.253	
	1	28(33.7)	25(32.1)			
	2	15(18.1)	24(30.8)			
	3–4	4(4.8)	4(5.1)			
Number of previous D&C	0	80(96.4)	73(93.6)	0.666	0.415	1.826
	1–3	3(3.6)	5(6.4)			
Number of previous EP	0	73(88)	66(84.6)	0.379	0.538	1.327
	1	10(12)	12(15.4)			
Number of previous stillbirths	0	80(96.4)	76(97.4)	0.147	0.701	0.702
	1–2	3(3.6)	2(2.6)			
Level of schooling	Illiterate	1(1.2)	2(2.6)	2.949	0.566	
	Primary school	18(21.7)	14(17.9)			
	Secondary school	11(13.3)	17(21.8)			
	High school	29(34.9)	22(28.2)			
	University	24(28.9)	23(29.5)			
History of pelvic inflammatory disease	Not available	78(94)	78(100)	4.849	0.028*	0.500
	Available	5(6)	0(0)			
History of abdominal surgery	Not available	59(71.1)	47(60.3)	2.096	0.148	1.621
	Available	24(28.9)	31(39.7)			
Contraceptive method	Not available	72(86.7)	74(94.9)	7.379	0.194	
	IUD	5(6)	3(3.8)			
	Male condom	0(0)	1(1.3)			
	Coitus interruptus	4(4.8)	0(0)			
	COCs	1(1.2)	0(0)			
	BTL	1(1.2)	0(0)			
Application complaint	Not available	14(16.9)	6(7.7)	7.417	0.115	
	Pelvic pain	13(15.7)	14(17.9)			
	Vaginal bleeding	39(47)	32(41)			
	Pelvic pain + vaginal bleeding	9(10.8)	19(24.4)			
	Menstrual delay	8(9.6)	7(9)			

Abbreviations: BTL, bilateral tubal ligation; COCs, combined oral contraceptives; D&C, dilation and curettage; EP, ectopic pregnancy; IUD, intrauterine device; OR, odds ratio (OR).
Note: *$p < 0.05$; Chi-squared test.

was found to be significantly shorter in the ruptured group (9.44 ± 6.36 days versus 11.84 ± 7.14 days in the control group). There was no significant difference between the control and ruptured groups in terms of β-hCG values on admission ($2{,}675.81 \pm 2{,}288.22$ versus $2{,}629.31 \pm 2{,}047.12$ mIU/mL respectively). The characteristics of the groups according to the obstetric and hematological parameters are presented in ►**Table 2**. Upon assessing the CBC, there were no significant differences in Hb, PLT, PLR, MCV, RDW, and MPV values between the two groups ($p > 0.05$); WBC was significantly higher in the control group ($8{,}753 \pm 2{,}435 \times 1/\mu l$ versus $7{,}982 \pm 2{,}271 \times 1/\mu l$ in the ruptured group; $p = 0.040$), while the ruptured group presented significantly higher values for NLR ($2.92 \pm 0.86\%$ versus

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 2 Obstetric and hematological features of the study groups

	Groups		Test statistic	*p*
	Control	Ruptured		
	Mean ± SD	Mean ± SD		
Age (years)	29.69 ± 5.55	29.71 ± 5.55	−0.021	0.983
Body mass index	25.06 ± 4.01	25.15 ± 4.65	−0.137	0.891
EP size (mm)	18.43 ± 7.64	19.34 ± 7.9	−0.736	0.463
Day of gestational age	42.33 ± 13.32	41.97 ± 13.4	0.157	0.875
Mean amount of free peritoneal fluid (mm)	27.1 ± 19.69	58.44 ± 29.31	−4.656	0.000*
Length of hospital stay (days)	11.84 ± 7.14	9.44 ± 6.36	2.225	0.027*
β-hCG on hospitalization (mlU/mL)	2675.81 ± 2288.23	2629.31 ± 2047.12	0.136	0.892
Hb (g/dL)	12.65 ± 1.14	12.79 ± 1.1	−0.788	0.432
WBCs (×1/μL)	8,753.49 ± 2,435.02	7,982.69 ± 2,271.04	2.074	0.040*
PLTs (×1/μL)	274,000 ± 56,013.5	257,756.41 ± 65,488.21	1.695	0.092
PLR (%)	132.56 ± 41.15	134.82 ± 40.18	−0.351	0.726
NLR (%)	2.09 ± 0.6	2.92 ± 0.86	−7.117	0.000*
MCV (fL)	85.87 ± 7.19	86.97 ± 5.56	−1.076	0.284
MPV (fL)	8.03 ± 0.86	8.04 ± 1.06	−0.105	0.917
PDW (%)	47.08 ± 13.17	51.28 ± 9.09	−2.366	0.019*
RDW (%)	14.32 ± 1.26	14.07 ± 1.25	1.277	0.203

Abbreviations: β-hCG, beta-human chorionic gonadotropin; EP, ectopic pregnancy; Hb, hemoglobin; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PLTs, platelets; RDW, reticulocyte distribution width; SD, standard deviation; WBCs, white blood cells (leukocytes).
Note: *$p < 0.05$; *t*-test.

2.09 ± 0.6% in the control group; $p = 0.000$) and PDW (51 ± 9% versus 47 ± 13% among the controls; $p = 0.019$). There was a moderate positive correlation between NLR and the number of days until rupture in the case group ($r = 0.585$; $p < 0.05$), but no significant correlation was found with PDW ($r = 0.381$; $p = 0.221$).

The results of the ROC curve analyses of the hematological markers are shown in ►**Table 3**. The AUC for NLR was of 0.800, as seen in ►**Figure 1**, which is a significantly higher area ($p < 0.05$), with 2.13% representing the optimal cut-off value. The AUC for PDW was of 0.601, as seen in ►**Figure 1**, which is a significantly higher area ($p < 0.05$), with 49.05% representing the optimal cut-off value. According to ►**Table 3** and ►**Figure 2**, no significant AUC was found regarding the values for β-hCG on hospitalization, WBC, Hb, PLR, RDW, MCV, and MPV.

Table 3 Results of the ROC curve analyses of hematological markers

	Area	Standard error	*p*	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
NLR	0.800	0.034	0.000	0.733	0.867
PDW	0.601	0.045	0.026	0.514	0.689
β-HCG on admission	0.493	0.046	0.872	0.403	0.582
Hb	0.486	0.046	0.760	0.396	0.576
WBCs	0.584	0.045	0.064	0.496	0.672
PLTs	0.576	0.045	0.095	0.488	0.665
MCV	0.464	0.046	0.429	0.374	0.553
MPV	0.524	0.046	0.595	0.434	0.614
RDW	0.560	0.045	0.185	0.472	0.649
PLR	0.489	0.046	0.810	0.399	0.579

Abbreviations: β-hCG, beta-human chorionic gonadotropin; Hb, hemoglobin; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PLTs, platelets; RDW, reticulocyte distribution width; ROC, receiver operating characteristic; WBCs, white blood cells (leukocytes).
Note: *$p < 0.05$; ROC curve.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

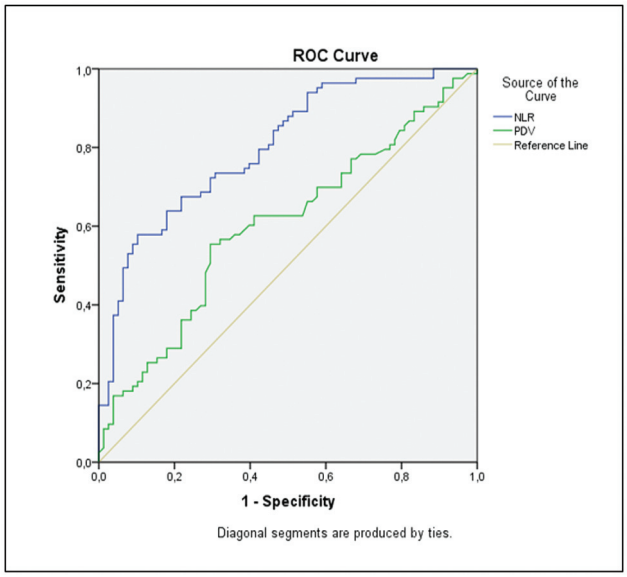

Fig. 1 The receiver operating characteristic (ROC) curve for neutrophil-to-lymphocyte ratio (NLR) and platelet distribution width (PDW).

Discussion

The MTX therapy can be safely administered in the treatment of EP; unfortunately, it may fail, resulting in tubal rupture of the ampullary EP. However, many factors affect the failure of the MTX treatment, such as the general health of the ectopic pregnancy,[14] pretreatment levels of β-hCG,[15] EP size,[16] and gestational age,[17] but the values found or these variables were similar in the two groups in the present study. In addition, systemic inflammatory markers derived from the CBC can affect many parameters. Cho et al.[18] stated that hematological inflammatory markers such as NLR may be an indicator of the aging process, and obesity is associated with chronic inflammation.[19] However, in the present study, the ages and BMIs of both groups were similar, and patients with systemic comorbidities were also excluded. Although we ruled out all these variables that may affect inflammatory markers and rupture rate, we determined that one of the two groups with similar characteristics ruptured, while the other was cured. In the present study, we investigated whether CBC-derived inflammatory markers could be used to predict the failure of the MTX therapy and the resulting life-threatening EP rupture despite all of these similarities.

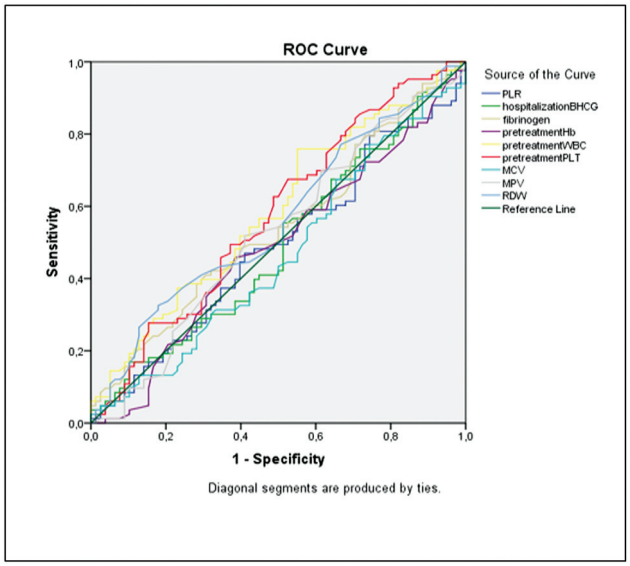

Fig. 2 The ROC curve for other hematological markers.

The history of PID was significantly higher in the control group, but the relationship between the history of PID and rupture is still inconsistent according to studies in the literature.[14,20] Similarly, the size of the pelvic effusion was not significant in terms of rupture in these studies,[14,20] and the size of the effusion was higher in the ruptured group in the present study. Similarly to the study by Cohen et al.,[21] in the present study, the mean time between the beginning of the MTX and rupture was of 7 ± 3.19 days. In an attempt to predict rupture, studies have generally investigated the properties of EP.[14,21,22] However, in the present study, we aimed to investigate the relationship between CBC parameters routinely obtained from all hospitalized patients and the prediction of rupture of tubal EP undergoing the MTX treatment. There are several similar and recently-published;[23–26] however, the characteristics of the EP differ among the groups in these studies, such as baseline β-hCG levels. Nonetheless, parameters such as NLR, PLR, RDW, and MPV are as effective to the success of the MTX treatment as baseline β-hCG in these studies.[23–26]

In the present study, the NLR and PDW were higher in the ruptured group compared to the control group, while the WBC was lower: $7982 \pm 2271 \times 1/\mu l$ versus $8753 \pm 2435 \times 1/\mu l$ respectively; $p < 0.05$. In the study by Kan et al.[23] with 142 patients, the ruptured group presented significantly higher values for NLR (4.62 ± 3.13 versus 2.67 ± 1.43; $p < 0.05$) and PLR (162.94 ± 63.61 versus 115.84 ± 41.15; $p < 0.05$). Moreover, Kanmaz et al.,[24] who investigated the monitoring of hematological markers in 434 patients undergoing the MTX showed that, in addition to monitoring β-hCG levels in the group in which the treatment was successful, the NLR values, which were monitored on the 1st, 4th and 7th days after a single dose of MTX were lower ($p = 0.012$; $p = 0.035$; and $p = 0.001$ respectively). However, in the aforementioned study, there was no significant difference between the groups in terms of PDW and PLT values on the 1st, 4th, and 7th days ($p > 0.05$).[24] In the study by Cekmez et al. with 115 patients, the cut-off values for MPV and NLR were determined as 10.1 fL and 1.82% respectively, and they showed similar sensitivity and specificity in estimating the success of the MTX treatment.[25] In this study, in a homogeneous group, with a high AUC, the cut-off value for NLR was found to be of 2.3% and for PDW, of 49.05%. Additionally, Akkaya and Uysal[26] found that WBC, Hb, MCV, PLT, PLR, and PDW values were similar in the surgical and MTX groups, while RDW and MPV were significantly increased in the MTX group. In the present study, other hematological markers such as Hb, MCV, PLT, and PLR were found to be similar in both groups ($p > 0.05$). Although a positive correlation between β-hCG values and the risk of rupture has been reported in many

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

studies in the literature, a precise threshold for the risk of rupture cannot be determined; therefore, Galstyan and Kurzel.,[27] in a study with 183 patients, did not report a reliable β-hCG value to predict the risk of rupture in EP. In the present study, there was a moderate positive correlation between NLR and the number of days since the beginning of the MTX treatment until rupture in the case group, but no significant correlation was found with PDW.

The decision for surgical treatment or medical management of an EP should be guided by a patient choice based on initial clinical, laboratory, and radiological data, as well as a discussion about the benefits and risks of each treatment. A clinical decision is made when an EP is ruptured, and its clinical features include: hemodynamic instability, pelvic pain, tenderness in the abdominal examination, signs of intraperitoneal bleeding, decrease in Hb values or the need for blood transfusion, and detection of intraabdominal fluid with coagulum by radiological imaging methods. According to the ACOG guidelines, the presence of intraabdominal fluid alone is not an absolute contraindication for MTX and is not sufficient for surgery.[3] In a study[28] on EP risk in patients with isolated free peritoneal fluid on transvaginal ultrasound, 42% of patients with isolated free peritoneal fluid were diagnosed with EP. Accordingly, if the fluid is echogenic or the volume is large, the risk of EP diagnosis increases; EP was detected in 22% of the patients with moderate anechoic fluid, and in 73% of the patients with large volumes of fluid or any echogenic fluid.[28] Patients with isolated free peritoneal fluid are at moderate risk of developing EP, but free fluid in the abdomen may represent the blood, serous fluid, or pus, and serous fluid is often found in asymptomatic healthy women. Moreover, in an ultrasound-based prediction model for the determination of the amount of hemoperitoneum in EP by Fauconnier et al.,[29] tubal rupture was only detected in 40% of the cases. In this study,[29] peritoneal free fluid was detected at a rate of 21/78 (26.9%) in the MTX group, and of 34/83 (40.9%) in the ruptured group. However, in the present study, free peritoneal fluid, NLR, and PDW were found to be significantly higher in the ruptured group ($p < 0.05$). The correlation of free peritoneal fluid with NLR and PDW is presented in ►**Table 4**. A low positive correlation was only observed between free peritoneal fluid and NLR.

In the present study, NLR and PDW were higher in the ruptured group, while WBC was higher in the control group. Extravasation of WBCs is an important feature of the inflammatory response, and Kan et al.[23] found that the WBC count for EP was significantly higher than for intrauterine pregnancies, suggesting that an increase in WBC count is associated with the development of EP. The higher increase in WBC in the control group in the present study suggests that it may have played an important role in suppressing the maternal immune response against a semiallogeneic fetus and limiting the invasiveness of the trophoblast.[30] However, the direction in which the increase is shifted (left or right) is more important in clinical use, rather than an increase in WBC count, because neutrophilia indicates systemic inflammatory events, whereas lymphopenia reflects an inadequate response in cellular immunity.[31] The reason why an increase in NLR indicates a poor prognosis is based on the mechanism by which neutrophils dominate and suppress cytotoxic T-cells through cytokines and chemokines in inflammatory processes.[31] In this case, the increase in the NLR is an indirect indicator of the immune response of he host, and it was found to be higher in the ruptured group in the present study. However, the underlying mechanisms for the relationship between inflammation and the outcome of the EP treatment need further study.

The strengths of the present study are that it was conducted with a homogeneous group (the groups were similar in terms of age, BMI, gestational age, baseline β-hCG, and EP size), with the exclusion of factors influencing systemic inflammation, at a tertiary center. The limitation of the study is its retrospective design. In conclusion, we can state that systemic inflammatory markers obtained from CBC are convenient and affordable tools to establish the difference in MTX response in patients with similar characteristics and in estimating the risk of tubal rupture in EPs.

Conclusion

The present study shows that systemic inflammatory markers such as NLR and PDW may be suitable tools to detect the risk of tubal rupture during the MTX treatment for EP. These markers can help physicians estimate which cases will or will not benefit from the treatment right at the beginning. We think these systemic inflammatory markers, which are easily obtained from the CBC without additional cost, should be evaluated and considered in larger cohort studies.

Table 4 Correlation of free intraabdominal fluid with NLR and PDW

		Free peritoneal fluid	Neutrophil-to-lymphocyte ratio (NLR)	Platelet distribution width (PDW)
Free peritoneal fluid (mm)	Pearson Correlation	1	0.373**	0.164
	Sig. (2-tailed)		0.005	0.233
	Sum of squares and cross-products	49,227.527	715.609	3,877.282
	Covariance	911.621	13.252	71.802
	N	55	55	55

Notes: *Correlation is significant at 0.05 (2-tailed); **correlation is significant at 0.01 (2-tailed).

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Contributions

YAR: project development, data collection or management, and writing and editing of the manuscript. AA: data collection or management, data analysis, and writing and editing of the manuscript. NÖ, MÖ, and HDÖ: data collection or management, project development. EGD, BTÇ: project development and writing and editing of the manuscript. SE: supervision and writing and editing of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

We would like to thank all participants and their families who dedicated their precious time to participate in this research program. We are also thankful for the tireless efforts of the members of the research team.

References

1 Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, Syverson CJ. Pregnancy-related mortality surveillance–United States, 1991–1999. MMWR Surveill Summ. 2003;52(02):1–8
2 Goyaux N, Leke R, Keita N, Thonneau P. Ectopic pregnancy in African developing countries. Acta Obstet Gynecol Scand. 2003;82 (04):305–312
3 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy. Obstet Gynecol. 2018;131(03):e91–e103
4 Edozien LC. Non-surgical management of ectopic pregnancy: appropriate risk management must be in place. Arch Gynecol Obstet. 2011;283(05):925–927
5 Lipscomb GH, Givens VA, Meyer NL, Bran D. Previous ectopic pregnancy as a predictor of failure of systemic methotrexate therapy. Fertil Steril. 2004;81(05):1221–1224
6 Wu J, Ludlow JP, De Vries B, Black K, Beale P. Single-dose methotrexate treatment for ectopic pregnancy and pregnancy of unknown location and progesterone as a predictor of success. Aust N Z J Obstet Gynaecol. 2014;54(05):469–474
7 Li P, Zhu WJ, Ma ZL, Wang G, Peng H, Chen Y, et al. Enhanced beta-catenin expression and inflammation are associated with human ectopic tubal pregnancy. Hum Reprod. 2013;28(09):2363–2371
8 Balasubramaniam ES, Van Noorden S, El-Bahrawy M. The expression of interleukin (IL)-6, IL-8, and their receptors in fallopian tubes with ectopic tubal gestation. Fertil Steril. 2012;98(04):898–904
9 Eskicioğlu F, Özdemir AT, Turan GA, Gür EB, Kasap E, Genç M The efficacy of complete blood count parameters in the diagnosis of tubal ectopic pregnancy. Ginekol Pol. 2014;85(11):823–827
10 Daikoku T, Song H, Guo Y, Riesewijk A, Mosselman S, Das SK, Dey SK. Uterine Msx-1 and Wnt4 signaling becomes aberrant in mice with the loss of leukemia inhibitory factor or Hoxa-10: evidence for a novel cytokine-homeobox-Wnt signaling in implantation. Mol Endocrinol. 2004;18(05):1238–1250
11 Liu D, Huang X, Xu Z, Chen M, Wu M. Predictive value of NLR and PLR in missed miscarriage. J Clin Lab Anal. 2022;36(03):e24250
12 Kim SK, Park JY, Jee BC, Suh CS, Kim SH. Association of the neutrophil-to-lymphocyte ratio and CA 125 with the endometriosis score. Clin Exp Reprod Med. 2014;41(04):151–157
13 Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(07):1204–1212
14 Dudley PS, Heard MJ, Sangi-Haghpeykar H, Carson SA, Buster JE. Characterizing ectopic pregnancies that rupture despite treatment with methotrexate. Fertil Steril. 2004;82(05):1374–1378
15 Nowak-Markwitz E, Michalak M, Olejnik M, Spaczynski M. Cutoff value of human chorionic gonadotropin in relation to the number of methotrexate cycles in the successful treatment of ectopic pregnancy. Fertil Steril. 2009;92(04):1203–1207
16 Gnisci A, Stefani L, Bottin P, Ohannessian A, Gamerre M, Agostini A. Predictive value of hemoperitoneum for outcome of methotrexate treatment in ectopic pregnancy: an observational comparative study. Ultrasound Obstet Gynecol. 2014;43 (06):698–701
17 Mirbolouk F, Yousefnezhad A, Ghanbari A. Predicting factors of medical treatment success with single dose methotrexate in tubal ectopic pregnancy: a retrospective study. Iran J Reprod Med. 2015;13(06):351–354
18 Cho S, Cho H, Nam A, Kim HY, Choi YS, Park KH, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril. 2008;90(06):2073–2079
19 Pilch W, Piotrowska A, Wyrostek J, Czerwińska-Ledwig O, Ziemann E, Antosiewicz J, et al. Different Changes in Adipokines, Lipid Profile, and TNF-Alpha Levels between 10 and 20 Whole Body Cryostimulation Sessions in Individuals with I and II Degrees of Obesity. Biomedicines. 2022;10(02):269
20 Chen S, Chen X-F, Qiu P, Huang YX, Deng GP, Gao J. Association Between White Blood Cells at Baseline and Treatment Failure of MTX for Ectopic Pregnancy. Front Med (Lausanne). 2021; 8:722963. Doi: 10.3389/fmed.2021.722963
21 Cohen A, Bar-On S, Cohen Y, Sandel O, Fouks Y, Michaan N, et al. Ruptured ectopic pregnancies following methotrexate treatment: clinical course and predictors for improving patient counseling. Reprod Sci. 2022;29(04):1209–1214
22 Lee JH, Kim S, Lee I, Yun J, Yun BH, Choi YS, et al. A risk prediction model for medical treatment failure in tubal pregnancy. Eur J Obstet Gynecol Reprod Biol. 2018;225:148–154
23 Kan Ö, Gemici A, Alkilic A, Cetindag EN, Cakir C, Dur R, Altay M. The Effect of Preoperative Neutrophil-To-Lymphocyte Ratio and Platelet-To-Lymphocyte Ratio on Predicting Rupture Risk in Tubal Ectopic Pregnancies. Gynecol Obstet Invest. 2019;84(04):378–382
24 Kanmaz AG, Inan AH, Beyan E, Budak A. Role of various complete blood count parameters in predicting the success of single-dose Methotrexate in treating ectopic pregnancy. Pak J Med Sci. 2018; 34(05):1132–1136
25 Cekmez Y, Göçmen A, Sanlıkan F, Türkmen SB. Role of mean platelet volume and neutrophil/lymphocyte ratio to predict single-dose methotrexate treatment success in tubal ectopic pregnancy. Clin Exp Obstet Gynecol. 2016;43(04):509–511
26 Akkaya H, Uysal G. Can hematologic parameters predict treatment of ectopic pregnancy? Pak J Med Sci. 2017;33(04):937–942
27 Galstyan K, Kurzel RB. Serum beta-hCG titers do not predict ruptured ectopic pregnancy. Int J Fertil Womens Med. 2006;51 (01):14–16
28 Dart R, McLean SA, Dart L. Isolated fluid in the cul-de-sac: how well does it predict ectopic pregnancy? Am J Emerg Med. 2002;20 (01):1–4. Doi: 10.1053/ajem.2002.30101
29 Fauconnier A, Mabrouk A, Salomon LJ, Bernard JP, Ville Y. Ultrasound assessment of haemoperitoneum in ectopic pregnancy: derivation of a prediction model. World J Emerg Surg. 2007;2:23. Doi: 10.1186/1749-7922-2-23
30 King A, Loke YW. On the nature and function of human uterine granular lymphocytes. Immunol Today. 1991;12(12):432–435. Doi: 10.1016/0167-5699(91)90014-K
31 Faria SS, Fernandes PC Jr, Silva MJ, Lima VC, Fontes W, Freitas-Junior R, et al. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience. 2016;10:702. Doi: 10.3332/ecancer.2016.702

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Comparison of Cavum Septum Pellucidum Size in Euploid and Aneuploid Fetuses

Comparação do tamanho do cavum septum pellicidium em fetos euploides e aneuploides

Merve Ozturk Agaoglu[1] Zahid Agaoglu[1] Filiz Halici Ozturk[1] Sevki Celen[2] Turhan Caglar[2]

[1] Department of Perinatology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey.
[2] Department of Perinatology, Etlik City Hospital, Ankara, Turkey.

Address for correspondence Merve Ozturk Agaoglu, MD, Department of Perinatology, Turkish Ministry of Health Ankara City Hospital Universiteler Mahallesi Bilkent Cad. No: 1 Cankaya, Ankara, Turkey (e-mail: drmerveoz@gmail.com).

Rev Bras Ginecol Obstet 2023;45(9):e511–e516.

Abstract

Objective The aim of the present study is to compare the cavum septum pellucidi (CSP) z-score in euploid and aneuploid fetuses and to investigate the performance of the CSP width/length and CSP width/biparietal diameter (BPD) ratios as a diagnostic marker in aneuploidy.

Methods A total of 54 patients, 20 aneuploid and 35 euploid fetuses, between 18 and 37 weeks of gestation, were included in this retrospective study. The CSP width z-score was compared between the two groups. Receiver operating characteristic (ROC) curves were calculated for the CSP width/length and CSP width/BPD ratios to predict aneuploidy.

Results The median CSP width was 4.8 mm (range, 1.8 to 8.5 mm) in the euploid group, and 5.4 mm (range 3.1 to 8.4 mm) in the aneuploid group. Cavum septum pellucidi width z-score, CSP width/length ratio, and CSP width/BPD ratio were significantly higher in fetuses with aneuploidy than in fetuses with normal karyotype ($p = 0.001$; $p = 0.013$; $p = 0.028$). In the ROC analysis, the CSP width/length ratio had the optimal cutoff value of 0.59, with 72.0% sensitivity and 58.0% specificity, and for the CSP width/BPD ratio, the cutoff value was 0.081 with 83.0% sensitivity and 61.0% specificity for detection of aneuploidy.

Conclusion CSP width z-score was found to be increased in aneuploid fetuses. The CSP width /BPD ratio can be used as a new marker for predicting aneuploidy.

Keywords
- aneuploidy
- cavum septum pellucidum
- karyotype

Resumo

Objetivo O objetivo do presente estudo é comparar o escore z do cavum septum pellucidi (CSP) em fetos euploides e aneuploides e investigar o desempenho das relações largura/comprimento do CSP e largura do CSP/diâmetro biparietal (BPD) como marcador diagnóstico de aneuploidia. como marcador de diagnóstico de aneuploidia.

received
June 3, 2023
accepted
July 24, 2023

DOI https://doi.org/10.1055/s-0043-1775847.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

Métodos Um total de 54 pacientes, 20 fetos aneuploides e 35 fetos euploides, entre 18 e 37 semanas de gestação, foram incluídos neste estudo retrospectivo. O escore z da largura da CSP foi comparado entre os dois grupos. As curvas ROC (Receiver Operating Characteristic) foram calculadas para as relações largura/comprimento da PEC e largura da PEC/BPD para prever a aneuploidia.

Resultados A largura mediana da CSP foi de 4,8 mm (variação de 1,8 a 8,5 mm) no grupo euploide e de 5,4 mm (variação de 3,1 a 8,4 mm) no grupo aneuploide. O escore z da largura do cavum septum pellucidi, a relação largura/comprimento do CSP e a relação largura do CSP/BPD foram significativamente maiores em fetos com aneuploidia do que em fetos com cariótipo normal ($p < 0,001$; $p < 0,013$; $p < 0,028$). Na análise ROC, a relação largura/comprimento da CSP teve o valor de corte ideal de 0,59, com 72,0% de sensibilidade e 58,0% de especificidade, e para a relação largura da CSP/BPD, o valor de corte foi de 0,081, com 83,0% de sensibilidade e 61,0% de especificidade para a detecção de aneuploidia.

Conclusão Verificou-se que o escore z da largura da CSP estava aumentado em fetos aneuploides. A relação A relação largura da CSP /BPD pode ser usada como um novo marcador para prever a aneuploidia.

Palavras-chave
- aneuploidia
- cariótipo
- septo do cavum pelúcido

Introduction

The cavum septum pellucidum (CSP) is an intracranial structure on axial images of the fetal head examined during routine obstetric examinations as recommended in the guidelines for fetal neurosonography.[1,2] It is a hypoechoic, roughly rectangular formation in the midline, in front of the third ventricle. The CSP can be detected between 16 weeks and birth. Although it resolves after delivery when the 2 lamellae of the cavum form the septum pellucidum, it is observed in the majority of preterm newborns and in around 50% of full-term infants.[3–5] In the studies performed, the absence of CSP has been highlighted as an indication of the presence of several midline abnormalities, including corpus callosum dysgenesis, holoprosencephaly, and agenesis of the septum pellucidum.[6–8]

Routine anatomical screening recommended to detect aneuploidy in the 2nd trimester mainly includes autosomal trisomies and triploidy. The most common aneuploidies are trisomy 21, 18, 13, and triploids. Although there are specific findings for each trisomy, cardiovascular and cranial system anomalies are the most common system anomalies.[9–12] Recently, it has been noted that CSP tends to be larger than normal in fetuses with chromosomal abnormalities, and studies have been conducted on CSP measures associated with fetuses with trisomy 18, 21, and 13.[13] However, the results are inconclusive because there are not enough studies in this area.

Our study aimed to compare the size of CSP in euploid and aneuploid fetuses and to investigate the ratio of CSP width/length and CSP width/biparietal diameter (BPD) in both groups.

Methods

A total of 54 patients, 20 aneuploid and 34 euploid fetuses, admitted to the perinatology outpatient clinic of the tertiary center between May 2019 and September 2019 were included in the study. The stored ultrasound data of fetuses between 18 and 37 weeks were retrospectively analyzed. All patients gave informed consent for ultrasound examination and consented to digital data storage. The hospital ethics committee approved the study. The study was conducted in accordance with the Declaration of Helsinki.

We searched the databases of our center for pregnancies diagnosed with prenatal trisomy 21, 18, triploidy, or Turner syndrome by amniocentesis or chorionic villus sampling and who underwent ultrasonography after 20 weeks of gestation. Pregnancies known to result in neonates with normal outcomes and aneuploid pregnancies between 20 and 37 weeks of gestation were included in our analysis.

Patients were included in the study if the proximal and distal hemispheres were seen in the same size cross-section of the fetal head, the standard anatomic points required to measure the fetal head, and the image containing the CSP. Other inclusion criteria were pregnancies in which an ultrasound examination was performed in the 1st trimester. Twin pregnancies, fetal growth restriction, anomalies with the absence of CSP, such as holoprosencephaly or agenesis of the corpus callosum, or fetuses with other cranial anomalies were excluded from the analysis. All ultrasound examinations were performed with a GE Voluson E8 convex transabdominal probe (1.75 to 4.95 MHz), and measurements were made on the acquired images and stored in the database.

Maternal characteristics, gestational age at the time of examination, BPD (mm), occipitofrontal diameter (mm), size of CSP (mm), fetal karyotype, and lateral ventricle measurement (mm) were recorded in the control and case groups. The length and width of CSP were measured on images stored in the patient registry, and the CSP width was measured at the center of CSP as described

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

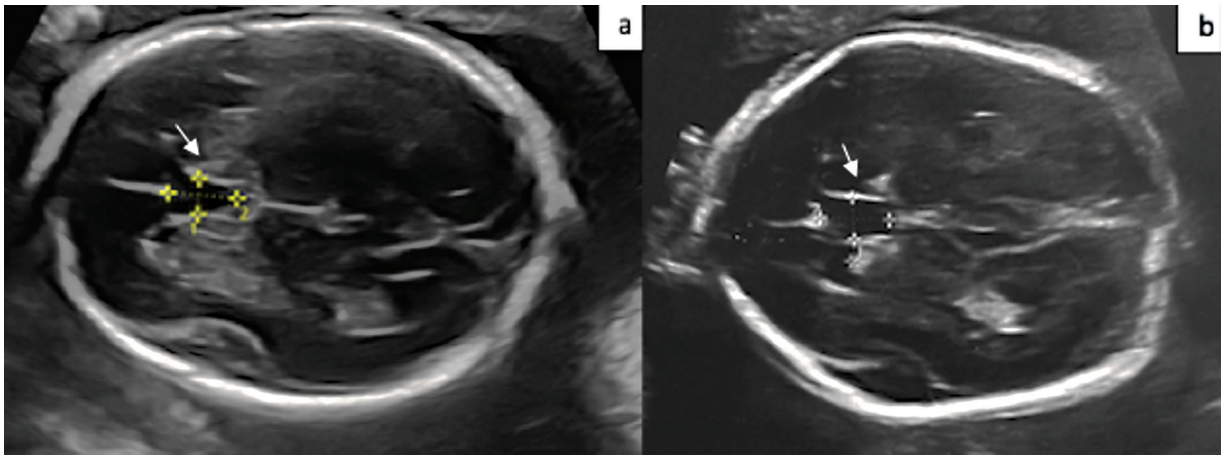

Fig. 1 Two-dimensional ultrasound images of the cavum septi pellucidi (white arrow) in a euploid fetus (a) and in a fetus with trisomy 18 (b).

by Abele et al.[13] The CSP length was measured between the callosal sulcus anteriorly and the fornix posteriorly (►**Fig. 1**).

The measurement of the width of CSP was converted to a z-score according to the table defined by Zhou et al. so that it was not affected by gestational week.[14] The CSP ratio was calculated by dividing the width of the CSP by its length, and then the other ratio, the CSP width/BPD ratio, was calculated. The two groups were compared based on maternal characteristics, CSP size, and the associated ratios. IBM SPSS Statistics for MAC, version 22.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analyses. Frequency tables and descriptive statistics were used to analyze the results. Visual (histograms, probability plots) and analytical methods were used to determine whether the variables were normally distributed or not. For the nonparametric distribution, the Mann-Whitney U test was used to compare the groups. The Spearman correlation coefficient was used to examine the relationship between groups that did not have a normal distribution. Receiver operating characteristic (ROC) analysis was used to assess the predictive performance of the CSP width/length and of the CSP width/BPD ratio for aneuploidy. P-values < 0.05 were considered statistically significant.

Results

The present study included 54 pregnancies, 34 with euploid fetuses, and 20 aneuploid fetuses. There were 9 (45%) fetuses with trisomy 21, 8 (40%) fetuses with trisomy 18, 2 (10%) fetuses with triploidy, and 1 (5%) fetus with Turner syndrome. In the aneuploid group, the median maternal age was 36, significantly higher than in the euploid group (30 versus 36; $p = 0.004$). The median gestational age at ultrasound examination was similar for both groups (27 versus 23.3; $p = 0.771$) (►**Table 1**).

The median CSP width was 4.8 mm (range, 1.8 to 8.5 mm) in the euploid group, and 5.4 mm (range 3.1 to 8.4 mm) in the aneuploid group. A statistical difference was detected between euploid and aneuploid groups by terms of CSP width z-score ($p = 0.001$) (►**Table 2**).

A significantly lower CSP z-score was found in fetuses with aneuploidy than in the control group. In the fetuses with trisomy 21, 18, and triploidy, the median CSP width was 4.8 mm (range 3.1 to 7.5 mm), 6.9 mm (range 4.8 to 8.4 mm), and 5.0 mm (range 4.8 to 5.2 mm), respectively. The CSP width/length ratio and the CSP width/BPD ratio was higher in fetuses with aneuploidy compared with fetuses with normal karyotype ($p = 0.013$; $p = 0.028$). In the ROC analysis,

Table 1 Maternal and fetal ultrasound characteristic in the euploid and aneuploid groups

	Euploid group ($n = 34$)	Aneuploid group ($n = 20$)	*p-value*
Age, years old	30 (24–40)	36 (26–45)	0.004
Gravida	3 (1–6)	2.5 (1–5)	0.558
Parity	1 (0–3)	1.5 (0–3)	0.124
Gestational age at ultrasound examination, week	27 (20–34)	23.3 (20–34)	0.771
BPD (mm)	67.0 (47–84)	58.7 (45–91)	0.100
HC (mm)	248 (168–302)	214 (161–329)	0.265
OFD (mm)	89 (58–108)	75.9 (53–115)	0.168

Abbreviations: BPD, biparietal diameter; HC, head circumference; OFD, occipitofrontal diameter.
Data shown as median (min-max).
$p < 0.05$ is considered statistically significant.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 2 Comparison of CSP width and CSP ratios in euploid and aneuploid groups

	Euploid group ($n = 34$)	Aneuploid group ($n = 20$)	*p-value*
CSP width (mm)	4.8 (2.3–8.5)	5.4 (3.1–8.4)	0.173
CSP width Z-score	- 0.5 (-2.0–2.0)	1.0 (- 1.0–3.0)	0.001
CSP length (mm)	9.0 (5–12)	8.7 (5–15)	0.589
CSP width/CSP length	0.57 (0.32–0.85)	0.62(0.49–0.88)	0.013
CSP width/BPD (mm)	0.080 (0.05–0.11)	0.088 (0.06–0.15)	0.028
Lateral ventricule (mm)	5.8 (3.5–8.0)	6.6 (5.0–9.6)	0.045

Abbreviations: BPD, biparietal diameter; CSP, cavum septum pellucidi.
Data shown as median (min-max).
$p < 0.05$ is considered statistically significant.

Table 3 Diagnostic values of CSP width/length, CSP width/BPD ratios to differentiate aneuploidy

Value	CSP width/length	CSP width/BPD
Cutoff	0.59	0.081
Area under the receiver operating curve	0.69	0.72
Sensitivity	72	83
Specificity	58	61

Abbreviations: BPD, biparietal diameter; CSP, cavum septum pellucidi.

the CSP width/length ratio had the optimal cutoff value of 0.59, with 72.0% sensitivity and 58.0% specificity, and for the CSP width/BPD ratio, the cutoff value was 0.081, with 83.0% sensitivity and 61.0% specificity for detection of aneuploidy (►**Table 3**) (►**Fig. 2**).

In the aneuploid group, a significant strong positive correlation was found between CSP width z-score and CSP width /BPD ratio ($p = 0.00$; $r = 0.875$). In contrast, the CSP width z-score did not correlate with the CSP width/length ratio in the aneuploid group ($p = 0.302$).

Discussion

In the present study, we investigated CSP z-score, and CSP ratios in aneuploid fetuses as a diagnostic tool to distinguish aneuploid fetuses. We found a higher CSP z-score in aneuploid fetuses compared with the euploid group. Moreover, the CSP width/BPD ratio, a new marker, was significantly higher in aneuploid fetuses.

The International Society of Ultrasound in Obstetrics and Gynecology recommendations for baseline evaluation of the central nervous system include the visualization of the CSP.[1,2] The CSP serves as a reference for establishing the proper axial plane when evaluating BPD. Previous research has established reference ranges for CSP width.[13–16] Large CSP has been recognized as a marker for fetal neural developmental abnormalities, often affecting the septohippocampal and limbic systems.[13] Several studies have shown that a CSP of > 1 cm is an important indicator of neurological impairment and may be associated with an increased risk of cognitive delays and behavioral problems.[17,18] Abele et al reported that the width of CSP due to chromosomal abnormalities was large, particularly in trisomy 18.[13] The CSP was found to be enlarged in 92, 40, and 41% of fetuses

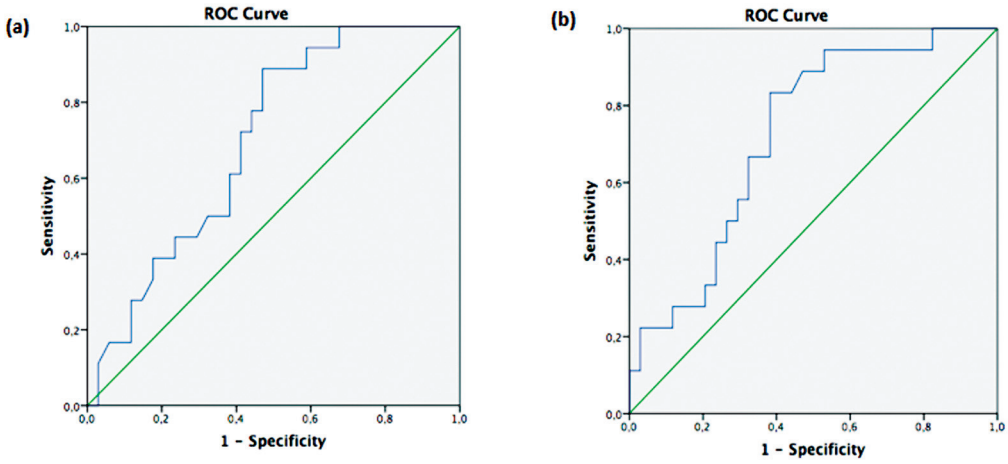

Fig. 2 ROC curve of CSP width/length (a) and CSP width/BPD ratio (b) to differentiate aneuploidy.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

with trisomy 18, 13, and 21, respectively. In another study, Chaoui et al. investigated the relationship between del.22q11 and CSP size and found that 67.5% of fetuses with del.22q11 had an enlarged CSP.[19] Based on the publication on the relationship between the size of the CSP and genetic abnormalities, we investigated CSP size in aneuploid fetuses and determined a new ratio that is independent of head size. Our study revealed that the CSP width /BPD ratio can help identify aneuploid fetuses, with higher specificity than the CSP width/length ratio in aneuploid fetuses. The pathophysiological mechanism of CSP enlargement in fetuses with aneuploidy is not clearly defined. Considering that larger lateral ventricles are usually found in aneuploid fetuses, cerebrospinal fluid filling of the CSP by the anterior horns of the lateral ventricles could explain the enlargement of the CSP associated with fetal aneuploidy.[19] In another study, it was suggested that it might be caused by an abnormality in one of the surrounding structures of the CSP or by an abnormality causing increased diffusion of cerebrospinal fluid within the septum pellucidum.[13] The relationship between CSP size and intracranial structures has been discussed in many recent studies. Shen et al. reported that in partial agenesis of the corpus callosum, CSP was enlarged and the width of the CSP is greater than its length.[20] Karl et al. also defined the CSP length/width as a CSP ratio and found that < 1.5 was associated with partial corpus callosum agenesis.[21] They concluded that the CSP ratio has the potential to identify fetuses at high risk for partial corpus callosum agenesis. In our study, we found that a CSP width/length ratio > 0.59 was significant in determining aneuploid fetuses. A recent study examined the efficacy of the ratio of CSP width to anterior-posterior cerebellar diameter (APCD) as a diagnostic tool for prenatal trisomy 18 diagnosis.[22] A higher CSP/APCD ratio would support the diagnosis, especially in cases with trisomy 18 syndrome with few abnormalities.

The strength of our study is that we have presented the CSP width/BPD ratio, a new practical and gestational week-independent marker to predict aneuploidy. The limitation of our study is its retrospective design. Because of the retrospective design, we were unable to follow-up and evaluate the size of the CSP in the neonatal period.

Conclusion

It is important to examine the dimensions of the CSP and its relationship to other structures as part of basic prenatal screening. An easily measurable abnormal CSP width/length ratio and the more specific CSP width/BPD ratio can serve as a simple indicator for the possible presence of aneuploidy. To the best of our knowledge, this is the first study to address CSP width/BPD ratio in aneuploid fetuses. Although previous studies show that CSP is increased in aneuploid fetuses, prospective studies are needed to demonstrate the applicability of the CSP width/BPD ratio for predicting aneuploidy in clinical practice.

Contributions

MOA, substantial contributions, including: Formal analysis of data, writing and drafting of the initial manuscript, and review and editing of the manuscript. ZA, substantial contributions, including: developing the methodology of the study, supervision/oversight of the study, data curation of the study, supervision of formal data analysis, and review and editing of the manuscript. FHO, substantial contributions, including: developing the methodology of the study, data curation, and review and editing of the manuscript. SC, substantial contributions, including: conceptualization/ design of the study, developing methodology of the study, data curation, investigation, supervision/oversight of the study, acquisition, and review and editing of the manuscript. TC, substantial contributions, including: conceptualization/ design of the study, developing the methodology of the study, data curation, investigation, supervision/oversight of the study, supervision of formal analysis, and review and editing of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Karl K, Kainer F, Heling KS, Chaoui R. Fetal neurosonography: extended examination of the CNS in the fetus. Ultraschall Med. 2011;32(04):342–361
2 Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram'. Ultrasound Obstet Gynecol. 2007;29(01): 109–116
3 Farruggia S, Babcock DS. The cavum septi pellucidi: its appearance and incidence with cranial ultrasonography in infancy. Radiology. 1981;139(01):147–150
4 Cerisoli M, Sandri F, Pilu G, Giulioni M, Bovicelli L, Salvioli GP, et al. Ultrasound recognition of the cavum septi pellucidi and the cavum vergae in the newborn. J Nucl Med Allied Sci. 1984;28 (03):163–166
5 Mott SH, Bodensteiner JB, Allan WC. The cavum septi pellucidi in term and preterm newborn infants. J Child Neurol. 1992;7(01): 35–38
6 Malinger G, Lev D, Kidron D, Heredia F, Hershkovitz R, Lerman-Sagie T. Differential diagnosis in fetuses with absent septum pellucidum. Ultrasound Obstet Gynecol. 2005;25(01):42–49
7 Pilu G, Segata M, Ghi T, Carletti A, Perolo A, Santini D, et al. Diagnosis of midline anomalies of the fetal brain with the three-dimensional median view. Ultrasound Obstet Gynecol. 2006;27(05):522–529
8 Cagneaux M, Guibaud L. From cavum septi pellucidi to anterior complex: how to improve detection of midline cerebral abnormalities. Ultrasound Obstet Gynecol. 2013;42(04):485–486
9 Viora E, Zamboni C, Mortara G, Stillavato S, Bastonero S, Errante G, et al. Trisomy 18: Fetal ultrasound findings at different gestational ages. Am J Med Genet A. 2007;143A(06):553–557
10 Cho RC, Chu P, Smith-Bindman R. Second trimester prenatal ultrasound for the detection of pregnancies at increased risk of Trisomy 18 based on serum screening. Prenat Diagn. 2009;29(02):129–139
11 Wagner P, Sonek J, Hoopmann M, Abele H, Kagan KO. First-trimester screening for trisomies 18 and 13, triploidy and Turner syndrome by detailed early anomaly scan. Ultrasound Obstet Gynecol. 2016;48(04):446–451
12 Emer CS, Duque JA, Müller AL, Gus R, Sanseverino MTV, Silva AA, et al. [Prevalence of congenital abnormalities identified in fetuses

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

with 13, 18 and 21 chromosomal trisomy]. Rev Bras Ginecol Obstet. 2015;37(07):333–338
13 Abele H, Babiy-Pachomow O, Sonek J, Hoopmann M, Schaelike M, Kagan KO. The cavum septi pellucidi in euploid and aneuploid fetuses. Ultrasound Obstet Gynecol. 2013;42(02):156–160
14 Zhou X, Lin MF, Wu LH, Huang LH, Xie HN. Enlarged cavum septi pellucidi Z-scores in fetuses with trisomy 18. J Matern Fetal Neonatal Med. 2022;35(05):981–986
15 Falco P, Gabrielli S, Visentin A, Perolo A, Pilu G, Bovicelli L. Transabdominal sonography of the cavum septum pellucidum in normal fetuses in the second and third trimesters of pregnancy. Ultrasound Obstet Gynecol. 2000;16(06):549–553
16 Jou HJ, Shyu MK, Wu SC, Chen SM, Su CH, Hsieh FJ. Ultrasound measurement of the fetal cavum septi pellucidi. Ultrasound Obstet Gynecol. 1998;12(06):419–421
17 Bodensteiner JB, Schaefer GB, Craft JM. Cavum septi pellucidi and cavum vergae in normal and developmentally delayed populations. J Child Neurol. 1998;13(03):120–121
18 Bronshtein M, Weiner Z. Prenatal diagnosis of dilated cava septi pellucidi et vergae: associated anomalies, differential diagnosis, and pregnancy outcome. Obstet Gynecol. 1992;80(05): 838–842
19 Chaoui R, Heling KS, Zhao Y, Sinkovskaya E, Abuhamad A, Karl K. Dilated cavum septi pellucidi in fetuses with microdeletion 22q11. Prenat Diagn. 2016;36(10):911–915
20 Shen O, Gelot AB, Moutard ML, Jouannic JM, Sela HY, Garel C. Abnormal shape of the cavum septi pellucidi: an indirect sign of partial agenesis of the corpus callosum. Ultrasound Obstet Gynecol. 2015;46(05):595–599
21 Karl K, Esser T, Heling KS, Chaoui R. Cavum septi pellucidi (CSP) ratio: a marker for partial agenesis of the fetal corpus callosum. Ultrasound Obstet Gynecol. 2017;50(03):336–341
22 He M, Du L, Xie H, Lei T, Zheng Q, Wu L. The ratio of cavum septi pellucidi width to anteroposterior cerebellar diameter: A novel index as a diagnostic adjunct for prenatal diagnosis of trisomy 18. J Obstet Gynaecol Res. 2019;45(07):1245–1250

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

The Effect of Mindfulness-Based Stress Reduction Counseling on Blood Glucose and Perceived Stress in Women with Gestational Diabetes

O efeito do aconselhamento para redução do estresse baseado na atenção plena sobre a glicose no sangue e o estresse percebido em mulheres com diabetes gestacional

Moslemi Zadeh Zeinabeh[1] Ahmadi Atefeh[1] G. Hazanfar Pour Masumeh[1] Dehesh Tania[1] Sanjari Mojgan[1] Alidousti Katayoun[1]

[1] Kerman University of Medical Sciences, Kerman, Iran

Rev Bras Ginecol Obstet 2023;45(9):e517–e523.

Address for correspondence Alidousti Katayoun, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran (e-mail: alidoosti@kmu.ac.ir).

Abstract

Objective Gestational diabetes can cause maternal and neonatal morbidity. Psychological factors, especially stress, play a meaningful role in diabetes management. Therefore, the present study aimed to investigate the effect of Mindfulness-Based Stress Reduction counseling on blood sugar and perceived stress in women with gestational diabetes.

Methods The present quasi-experimental interventional study was performed on 78 women with gestational diabetes. In the intervention group, a Mindfulness-Based Stress Reduction counseling program was conducted by the researcher in 8 sessions of 90 minutes twice a week. The Cohen stress questionnaire was filled in both groups. Also, fasting blood sugar and 2-hour blood sugar levels were measured in both groups. Statistical analysis was performed using the independent T-Test, the paired T-Test, the Mann-Whitney and Wilcoxon Tests using IBM SPSS Statistics for Windows version 20 version (IBM Corp., Armonk, NY, USA).

Results The mean age of pregnant women in the intervention group was 28.84 ± 6.20 years old and 29.03 ± 5.42 years old in the control group. There was a significant mean difference between the fasting blood sugar score ($p = 0.02$; - 6.01; and - 11.46) and the 2-hour fasting blood sugar score ($p < 0.001$;12.35; and - 5.3) and the perceived stress score ($p < 0.001$; 35.57; and - 49.19) existed between the intervention and control groups after the intervention.

Keywords
- perceived stress
- mindfulness-based stress reduction
- gestational diabetes
- blood sugar

received
May 11, 2022
accepted
August 1, 2023

DOI https://doi.org/10.1055/s-0043-1775810.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

Conclusion The results of the present study showed that mindfulness-based stress reduction counseling is effective in reducing blood sugar levels and reducing perceived stress in women with gestational diabetes treated with diet.

Introduction

Diabetes is defined as a chronic metabolic disorder affecting carbohydrates, proteins, and fats, which is caused by a deficiency or resistance to insulin and hyperglycemia. Gestational diabetes is a disorder of glucose tolerance which is first started or diagnosed during pregnancy and is the most common metabolic disorder during pregnancy that can predispose the mother and fetus to serious and fatal complications. Children of women with gestational diabetes appear to be at increased risk for obesity and glucose intolerance and have a greater risk of developing diabetes in late adolescence. Moreover, the risk of fetal malformations is 4 to 10 times more common in mothers with uncontrolled gestational diabetes.[1] The prevalence of gestational diabetes in the world is $\sim$ 1 to 14% of all pregnancies.[2] Among many studies that have been done in recent years on the etiology, course, prognosis, and treatment of diabetes, psychological factors have received special attention. One of the most important psychological factors affecting the incidence of physical health disorders, such as diabetes, is stress.[3] Stress is defined as an individual's appraisal of the degree to which situations in her/his life are overwhelming. Stress can lead to non-adherence to dietary recommendations and thus indirectly affect the patient's blood sugar. Due to stress, a person with diabetes may forget to take care of their food intake or take their medication, which will affect their blood sugar level. In general, stress is one of the factors increasing blood sugar level, leading to elevated mortality and prenatal complications in pregnancy. Pregnant women with gestational diabetes experience more stress than nond2iabetic pregnant women.[4] One of the most important components of gestational diabetes treatment is awareness, training, and recognition of patients' mental health problems. Counseling and education are an effective way to reduce the adverse effects of stress on the behavior of women with diabetes. Therefore, many psychological interventions are used simultaneously with medical interventions to manage the disease and its related complications. Mindfulness is one of the key components of the third wave of psychological treatment models. Mindfulness-based therapies are considered the third wave of cognitive therapy. Mindfulness meditation activates an area of the brain that creates positive emotions and beneficial effects on the body's immune function. As a result, events are perceived less distressing than they are at the moment, new thoughts are formed, and unpleasant emotions are reduced.[5] Previous studies reported the efficacy of mindfulness in reducing blood sugar level, stress, and depression and in increasing self-confidence in different groups of patients.[4,6,7] However, no study has yet investigated the effect of this intervention on the management of blood sugar in pregnant women. Women with gestational diabetes face many obstacles and challenges, including psychological stress, lack of information about the disease and its management, and fear of the disease. On the other hand, stress plays an important role in the onset, course, and prognosis of gestational diabetes and has adverse effects on blood sugar level in women with gestational diabetes. Therefore, the present study was performed to determine the effect of mindfulness-based stress reduction (MBSR) therapy on blood sugar level and stress in pregnant women with gestational diabetes who were under dietary treatment of diabetes and referred to urban health centers.

Methods

The present educational intervention study was conducted to investigate the effect of MBSR counseling on the blood sugar and perceived stress of the patients. In this study, 80 pregnant women who were in the first half of pregnancy ($<$ 20 weeks) and under treatment with gestational diabetes diet were included. These patients were selected among those who referred to health centers of Sirjan, Kerman province, Iran, provided that they met the inclusion criteria. Patients were excluded from the study due to pregnancy-related complications and none of the patients had to start pharmacological treatment. But 2 patients in the intervention group did not want to continue the counselling session so, finally, the study was performed on 78 patients.

Inclusion Criteria

- Age between 18 and 45 years old;
- Being in the first half of pregnancy (given that the counseling procedure lasted for a month and there was a possibility of prescribing a medication or insulin by an endocrinologist and also to prevent serious complications induced by diabetes in the second half of pregnancy, we recruited patients who were in the first half of their pregnancy);
- Willingness to participate in the research;
- Singleton pregnancy;
- Being literate (at least elementary education);
- No history of gestational diabetes in previous pregnancies;
- No history of medical diseases (that is, cardiovascular and respiratory diseases) and pregnancy complications in previous pregnancies (such as preeclampsia, polyhydramnios, abnormal bleeding, placenta previa, recurrent miscarriage, giving birth to a high birthweight baby $>$ 4 kg or fetal macrosomia, and stillbirth);

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

- No history of hospitalization in psychiatric department, use of psychotropic medications, and known personality and mental disorders;
- Suffering from gestational diabetes in the first half of pregnancy (fasting blood sugar [FBS] > 93 mg/dL or 2-hour PPBS > 120 mg/dL (75 g OGTT) according to national guidelines of the Ministry of Health).

Discontinuation Criteria

- More than two absences in training sessions;
- Occurrence of diseases and complications related to pregnancy (such as cardiovascular, lung, and renal diseases, abortion, and preeclampsia) during the study;
- Starting drug treatment or insulin therapy in pregnancy;
- Occurrence of major stressful events during the research (new illness in spouse or children, death of a loved one, accident, migration, or bankruptcy);

Sample size was estimated to be 40 patients in each group according to a previous study, using sample size formula for two independent samples, taking into account the error of 5% and a power of 80%, and anticipating a 10% dropout rate.

Measurements

To collect data, a demographic questionnaire and perceived stress scale developed by Cohen et al., were used. In addition, glucose kit (Pars Azmon product, made in Iran) was used to measure the blood sugar level of the patients.

Demographic Questionnaire

The demographic questionnaire used in the present study extracted data on patients' age, body mass index (BMI), number of pregnancies, gestational age, birth-to-conception interval, education level, occupation, and the spouse's education level and occupation.

Perceived Stress Scale Developed by Cohen

In the present study, the perceived stress scale developed by Cohen et al., was used to assess patients' perceived stress. This questionnaire has 14 questions, which are used to measure the general stress perceived in the past month. This questionnaire also assesses someone's thoughts and feelings about stressful events as well as their ability to control, overcome, and cope with such experienced stress. This questionnaire is suitable for determining the extent to which people recognize their stress in the face of unpredictable and uncontrollable life events. The questionnaire is scored based on a 5-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). Questions 4, 5, 6, 7, 9, 10, and 13 are scored in reverse (never = 4 to very often = 0). The minimum score is zero and the maximum score is 56. A higher score indicates greater perceived stress.[4,6]

Blood Glucose Measurement Kit and Test Basis

Pars Azmon kits were used to measure FBS and two-hour PPBS in the central laboratory of Sirjan. The glucose kit measures blood sugar using the enzymatic and colorimetric method (GOD-PAP) and does single point measurement using the photometric method.

Procedure

After receiving ethics code (Kmu.ac.ir.1398.126), cluster sampling was done. For this purpose, out of 19 health centers, 6 centers were randomly selected as clusters by drawing lots. Then, from 6 centers, we randomly selected (by drawing lots) 3 centers as intervention group and 3 centers as control group. In the next step, among pregnant women with gestational diabetes who met the inclusion criteria, 40 were randomly assigned to each group. Gestational diabetes diagnosing was based on FBS and two-hour PPBS tests in pregnancy according to the national guidelines of the ministry of health of Iran. If the pregnant woman's FBS was > 93 mg / dL or blood sugar 2 hours after receiving 75 mg of glucose (two-hour PPBS) was > 120 mg / dL, she was diagnosed with gestational diabetes. For FBS and 2-hour PPBS tests (75g OGTT), two cc of blood was taken from pregnant women by the staff of Sirjan Central Laboratory. The FBS test was taken in the early morning and before eating breakfast. Two-hour PPBS test was done 2 hours after taking 75 g glucose. Then, FBS and two-hour PPBS were measured by laboratory kits using the ELISA method (Pars Azmon kits, Tehran, Iran). After receiving informed consent from each patient and assuring them about the confidentiality of their information, the study was initiated. Before intervention, both groups filled out the questionnaires. The MBSR sessions were held by one of the researchers, who had an MSc in counseling in midwifery and received mindfulness training exclusively. The intervention group underwent eight MBSR sessions in groups (each group consisted of 10 to 12 patients). The sessions were held twice a week and each session lasted for 90 minutes. During this period, the control group received only routine pregnancy care. The content of the training sessions is provided in ►**chart 1**. One week after the intervention, the perceived stress scale (post-test) was completed by both groups. The patients' FBS and 2-hour PPBS were measured after the intervention. The study lasted 9 months from May, 2019 until January, 2021 (►**Fig. 1**).

Statistical Analysis

IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA) was used for data analysis. Descriptive statistic such as frequency, mean, and percentage were used. Inferential statistics (independent samples *t*-test, paired *t*-test, chi-squared test, and the analysis of covariance) were also used. The statistically significant level was ≤ 0.05.

The present manuscript was derived from a master counselling in midwifery thesis (project code No. 97000964) and was approved by the Ethics Committee of Kerman University of Medical Sciences, Iran (code of ethics No. Kmu.ac.ir.1398.126). Written informed consent was obtained to enter the study and it was easy for participants to withdraw from the study whenever they were willing. At the request of the ethics committee, the study was conducted in accordance with the Declaration of Helsinki and Ethics Publication on Committee (COPE). Special codes were used for each of the participants to ensure the confidentiality of information.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Chart 1 Summary of sessions of counseling based on MBSR approach for reduction of Blood Sugar and Perceived-Stress in women with Gestational Diabetes Treated with diet

session	Content
1	Greeting and declaration of counseling rules, definition of the concepts of mindfulness and the main variables, description of the internal and external flow of the mind, eating raisins, homework.
2	Reviewing previous homework, mindful thinking, mindful examination of body and sitting meditation, homework.
3	Reviewing previous homework, focus on being present, practice seeing and hearing consciously in 3 minutes, focus on 5 senses in 5 minutes, homework.
4	Reviewing previous homework, stress and the body's reaction, practicing thoughts-emotions-body senses-behavior relationships, 3 minutes of concentration on an unpleasant event, mindful walking, homework.
5	Reviewing previous homework, effective responses to stress, 3-minute Breathing Space (3MBS), meditation in daily life, homework.
6	Reviewing previous homework, conscious mind interactions, take care of yourself, practicing speaking and listening consciously, practicing consecutive thoughts in an hour, getting feedback from participants from practicing, presenting homemade homework .
7	Reviewing previous homework, being more careful, mindful Yoga, making the unpleasant event enjoyable, providing homework
8	Reviewing previous homework, mountain meditation, summarization of all sessions, homework.

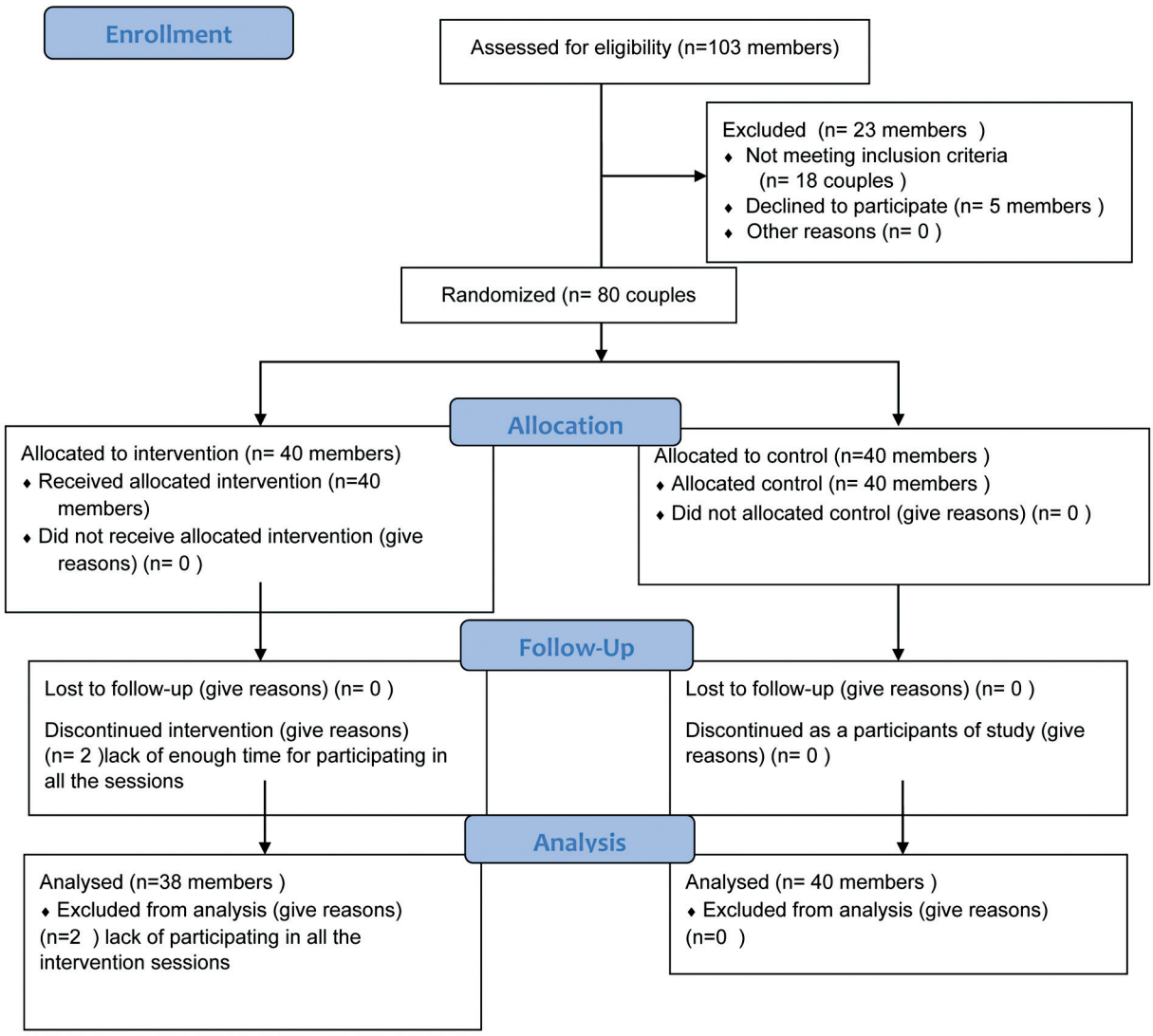

Fig. 1 CONSORT Flow Diagram of participants.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 1 Demographic characteristics of participants

Group Variables		Intervention Mean ± SD	Control Mean ± SD	*p-value*[*]
Age		20.6 ± 84.28	29.03 ± 5.42	0.89
BMI		4.91 ± 52.6 2	26.12 ± 5.38	0.738
Variable		*n* (%)	*n* (%)	*p-value*[**]
Parity	First	13 (34.21)	9 (22.5)	0.317
	Second or more	25 (65.78)	31 (77.5)	
Distance from last pregnancy	0	13 (34.2)	10 (25)	0.428
	≤ 3 years	4 (10.52)	8 (20)	
	3 years≤	21 (55.26)	22 (55)	
Woman education	Diploma and less	22 (57.9)	22 (55)	0.756
	Associate Degree	3 (7.9)	2 (5)	
	Bachelor	12 (31.6)	13 (32.5)	
	Master's degree and higher	1 (2.6)	3 (7.5)	
Woman Job	Housekeeper	34 (89.5)	35 (87.5)	0.894
	Employed	4 (10.5)	5 (12.5)	
Spouse education	Diploma and less	21 (55.3)	22 (55)	0.98
	Associate Degree	3 (7.9)	4 (10)	
	Bachelor	12 (31.6)	12 (30)	
	Master's degree and higher	2 (5.3)	2 (5)	
Spouse Job	Self-employment	15 (39.5)	25 (62.5)	0.069
	Employee	23 (60.5)	15 (375)	

Abbreviations: BMI, body mass index; SD, standard deviation.
[*]T test.
[**]Chi-squared test.

Results

The results showed that the mean age of the patients was 28.84 ± 6.20 in the intervention group and 29.03 ± 5.42 in the control group. In addition, the mean BMI of the patients in the intervention and control groups was 26.52 ± 5.38 and 26.12 ± 5.38, respectively. Two groups were homogeneous in terms of number of pregnancies, interpregnancy interval, own and spouse education level, and own and spouse occupation (►**Table 1**). According to ►**Table 2**, there was a statistically significant difference between the two groups regarding the percentage of relative changes in stress, in a way that the intervention group experienced less perceived stress than the control group after the intervention ($p < 0.001$).

This means that after MBSR sessions, the amount of perceived stress was reduced in the intervention group. The results of the independent *t*-test for parametric data showed that the percentage of relative changes in FBS in the intervention and control groups was significantly different, and the intervention group had a higher decrease in the mean relative changes of FBS ($p = 0.02$). In other words, after MBSR sessions, FBS decreased in the intervention group (►**Table 3**). Moreover, Mann-Whitney test results revealed that there was a significant difference between two groups with respect to the percentage of relative changes in FBS, and the mean FBS was lower in the intervention group than in the control group after the intervention. After the intervention, the mean 2-hour PPBS increased in the control group (20.85 ± 12.35) but decreased in the intervention group (27.35 ± -3.5) ($p < 0.001$). This means that 2-hour PPBS decreased in the intervention group after undergoing MBSR sessions (►**Table 4**).

Table 2 Comparison of relative changes in perceived stress after intervention in two groups

Group	Mean ± SD	Mann-Whitney Statistic	*p-value*[*]
Intervention	27.55 ± −49.19	-7.23	<0.001
Control	120.79 ± 57.35		

Abbreviation: SD, standard deviation.
[*]Mann-Whitney U test.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 3 Comparison of relative changes in FBS after intervention in two groups

Group	Mean ± SD	Mann-Whitney Statistic	*p-value*[*]
Intervention	9.89 ± −11.46	-2.34	0.02
Control	10.65 ± −6.01		

Abbreviation: SD, standard deviation
[*]Independent samples T Test.

Table 4 Comparison of relative changes BS after intervention in two groups

Group	Mean ± SD	Mann-Whitney Statistic	*p-value*[*]
Intervention	27.35 ± −3.5	-3.759	<0.001
Control	20.85 ± 12.35		

Abbreviation: SD, standard deviation
[*]Mann-Whitney U test.

Discussion

According to the findings, MBSR was able to reduce stress in the intervention group. In this regard, Woolhouse et al. also showed that mindfulness-based intervention significantly reduced perceived stress in pregnancy.[8] In line with the present study, Guth et al. and Kiselev et al., showed that mindfulness-based training during pregnancy could effectively reduce pregnancy-related stress and anxiety.[9,10] Similarly, Beattie et al. reported that mindfulness-based training could help manage stressors, fear, and anxiety and regulate attention to be more present.[11] Mindfulness teaches us how to be aware of our thoughts and manage them. Mindfulness is not the cessation of thoughts since thoughts always arise in the mind. We become aware of own thoughts and their consequences through mindfulness, so we can manage them. To deal with physiological effects of stress, methods and programs called stress management have been proposed, including breathing exercises, relaxation techniques, meditation, and guided imagery. In the mindfulness technique, one turns one's mind from the past and the future to the present. When a person focuses on the present time, they see reality with all its internal and external aspects and realizes that the mind is constantly chewing on thoughts, ruminating on ideas, and talking internally because of the judgments and interpretations it makes. Practicing mindfulness gives a person the ability to realize that "thoughts are just thoughts" and when they realize that their thoughts may not be true, they can more easily let go of them, and consequently the perceived stress is reduced. Other findings of the study showed that MBSR could reduce FBS and 2-hour PPBS. Vieten et al. studied the effect of mindfulness-based training on stress and overeating during pregnancy. They found that mindfulness-based group training could help increase the skill in better management of stress and overeating during pregnancy.[12] Epel et al. also examined the effect of mindfulness-based intervention on anxiety, weight gain, and glycemic control in low-income pregnant women. They found that mindfulness-based intervention led to reduction of perceived stress and improvement of glucose tolerance.[13] The results of the present study also showed that MBSR counseling could be effective in reducing 2-hour PPBS in pregnant women with gestational diabetes through reducing stress and training techniques such as mindful eating, mindful seeing, and body scan. Various studies reported the efficacy of mindfulness-based counseling in controlling blood sugar and stress in diabetic patients, which confirms the findings of the present study.[4,14,15] Ni et al. conducted a systematic review and meta-analysis to investigate the effect of mindfulness-based intervention on blood glucose control and psychological outcomes in people with diabetes. In line with the findings of the present study, they concluded that mindfulness-based intervention had a significant effect on the reduction of HbA1c level and, as a result, control of blood glucose level in diabetic patients.[16] Although genetic factors have an important role in the etiology of diabetes, increasing prevalence of diabetes in recent decades is attributed to internal factors such as stress and external factors such as poor diet and low physical activity. In recent years, psychological aspects of diabetes are attended by the researchers. One of the methods for treating psychological problems in diabetic patients is mindfulness counselling. Research results in this field indicated the efficacy of this treatment in reducing stress as well as blood glucose level in people with diabetes. The extent of individual and family characteristics and individual motivations, which may affect the study, were beyond the control of the researcher. Due to holding counseling sessions twice a week, a feeling of tiredness and unwillingness to continue cooperation was observed in some cases. In this regard, a briefing session on the need to continue these sessions with the husbands of these pregnant women was conducted by phone.

Conclusion

According to the results of the present study, stress and blood sugar level can be reduced by early intervention and provision of mindfulness counseling in women under treatment with gestational diabetes diet, especially in the first half of pregnancy. Since pregnant women are a vulnerable group in society and the rate of gestational diabetes is increasing, mental health and increasing the level of awareness on

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

proper diet can be of particular importance in the health system.

Contributions

ZM, KA, AA, MS and MGH contributed to conceiving and designing the research. The data were collected, analyzed, and interpreted by ZM, TD, and KA. ZM, AA, MGH and KA contributed equally to writing and revising the manuscript and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors appreciate all vulnerable pregnant women who kindly participated in the present study. We also appreciate health care centers staff, who cooperated informing about holding counseling sessions.

References

1 Longo Dan ea. Harrison's principles of internal medicine. 18th ed. E DAe, editor. Tehran: Andisheh rafi; 2020
2 Khadivzadeh T, Azhari S, Esmaily H, Akhlaghi F, Sardar MA. Effects of self-care education on perceived stress in women with gestational diabetes under insulin treatment. Evidence Based Care.. 2015;5(03):7–18
3 Zareipour M, Jadgal K, Zare F, Valizadeh R, Ghelichi Ghojogh M. The relationship between perceived stress and blood sugar levels in patients with type 2 diabetes. Rahavard Salamat Magazine. 2017;2(04):1–13
4 Vala M, Razmandeh R, Rambol K, Nasli Esfahani E, Ghodsi Ghasemabadi R. Mindfulness-based stress reduction group training on depression, anxiety, stress, self-confidence and hemoglobin A1C in young women with type 2 diabetes. Majallah-i Ghudad-i Darun/Riz va Mitabulism-i Iran. 2016;17(05):382–390
5 Validi Pak AKS, Moeni Manesh K. Efficacy of mindfulness traning on enhancing optimism in women with pregnancy diabetes quarterly. J Health Psychol. 2015;4(14):62–78
6 Zare H, Zare M, Amirabadi F, Shahriari H. Mindfulness and diabetes: evaluation of effectiveness of Mindfulness Based Stress Reductionon glycemic control in diabetes. Majallah-i Ulum-i Pizishki-i Razi. 2013;20(108):40–52
7 Nejad FK, Shahraki KA, Nejad PS, Moghaddam NK, Jahani Y, Divsalar P. The influence of mindfulness-based stress reduction (MBSR) on stress, anxiety and depression due to unwanted pregnancy: a randomized clinical trial. J Prev Med Hyg. 2021; 62(01):E82–E88
8 Woolhouse H, Mercuri K, Judd F, Brown SJ. Antenatal mindfulness intervention to reduce depression, anxiety and stress: a pilot randomised controlled trial of the MindBabyBody program in an Australian tertiary maternity hospital. BMC Pregnancy Childbirth. 2014;14(01):369
9 Kiselev S, Volik I. Effect of mindfulness training on stress reduction during pregnancy. Psychoneuroendocrinology. 2017;83:45
10 Guth S, Wood S, Ivanova M, Hudziak JJ Eds. Mindfulness Training in Pregnancy, and PostPartum Internalizing Symptoms. 64th Annual Meeting; 2017: AACAP.
11 Beattie J, Hall H, Biro MA, East C, Lau R. Effects of mindfulness on maternal stress, depressive symptoms and awareness of present moment experience: A pilot randomised trial. Midwifery. 2017; 50:174–183
12 Vieten C, Laraia BA, Kristeller J, Adler N, Coleman-Phox K, Bush NR, et al. The mindful moms training: development of a mindfulness-based intervention to reduce stress and overeating during pregnancy. BMC Pregnancy Childbirth. 2018;18(01):201
13 Epel E, Laraia B, Coleman-Phox K, Leung C, Vieten C, Mellin L, et al. Effects of a Mindfulness-Based Intervention on Distress, Weight Gain, and Glucose Control for Pregnant Low-Income Women: A Quasi-Experimental Trial Using the ORBIT Model. Int J Behav Med. 2019;26(05):461–473
14 Kharatzadeh H, Davazdahemami M, Bakh M, Kachuei A, Mahaki B. Effectiveness of mindfulness based stress reduction on glycemic control, stress, anxiety and depression on patients with type 2 diabetes mellitus. Majallah-i Pizishki-i Urumiyyah. 2017;28(03): 207–214
15 Mohammadi Shirmahaleh F, Jomehri F, Keraskian A, Malihi Alzakerini S. The effect of mindfulness-based stress reduction in depression and blood sugar reduction diabetic patients with BIS type of personality. Journal of Research and Health.. 2017;7 (06):1111–1119
16 Ni Y, Ma L, Li J. Effects of Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy in People With Diabetes: A Systematic Review and Meta-Analysis. J Nurs Scholarsh. 2020;52 (04):379–388

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Knowledge, Attitude, and Practice of Brazilian Physicians about Immediate Postpartum and Postabortion Intrauterine Device Insertion

Conhecimento, atitude e prática de médicos brasileiros sobre inserção de dispositivo intrauterino no pós-parto e pós-aborto imediatos

Adalberto Kiochi Aguemi[1,2] Maria Regina Torloni[2] Mirna Namie Okamura[3] Cristina Aparecida Falbo Guazzelli[2]

[1] Women's Health Technical Area, Secretaria Municipal da Saúde de São Paulo, SP, Brazil
[2] Escola Paulista de Medicina, Universidade Federal de São Paulo, SP, Brazil
[3] Coordination of Epidemiology and Information, Secretaria Municipal da Saúde de São Paulo, SP, Brazil

Address for correspondence Adalberto Kiochi Aguemi, Women's Health Technical Area, Secretaria Municipal da Saúde de São Paulo, Rua General Jardim 36, Vila Buarque, 01223-906, São Paulo, SP, Brazil (e-mail: adalbertoaguemi@gmail.com).

Rev Bras Ginecol Obstet 2023;45(9):e524–e534.

Abstract

Objective To assess the knowledge, attitude, and practice of Brazilian physicians about immediate postpartum and postabortion intrauterine device insertion.

Methods Cross-sectional online survey involving physicians on duty in public Brazilian hospitals. Participants answered an anonymous questionnaire with close-ended questions to assess their knowledge, attitude, and experience on the immediate postpartum and postabortion insertion of copper intrauterine devices.

Results One hundred twenty-seven physicians working in 23 hospitals in the 5 geographic regions of Brazil completed the questionnaire. Most were female (68.5%) and worked in teaching hospitals (95.3%). The mean (standard deviation) knowledge score (0–10 scale) was 5.3 (1.3); only 27.6% of the participants had overall scores $\geq$ 7.0. Most physicians (73.2%) would insert a postpartum intrauterine device in themselves/family members. About 42% of respondents stated that they had not received any training on postpartum or postabortion intrauterine device insertion. In the past 12 months, 19.7%, 22.8%, and 53.5% of respondents stated they had not inserted any intrauterine device during a cesarean section, immediately after a vaginal delivery, or after an abortion, respectively.

Conclusion Most study participants have a positive attitude toward the insertion of intrauterine devices in the immediate postpartum period, but they have limited knowledge about the use of this contraceptive method. A large percentage of respondents did not have previous training on postpartum and postabortion

Keywords
- copper intrauterine devices
- postpartum period
- spontaneous abortion
- induced abortion
- health knowledge
- attitudes
- practice

received
April 2, 2023
accepted
April 11, 2023

DOI https://doi.org/10.1055/s-0043-1772187.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

intrauterine device insertion and had not performed any such insertions in the last 12 months. Strategies are needed to improve the knowledge, training, and experience of Brazilian physicians on immediate postpartum and postabortion intrauterine device insertion.

Resumo

Objetivo Avaliar o conhecimento, atitude e prática de médicos brasileiros sobre a inserção de dispositivos intrauterinos no pós-parto e pós-aborto imediatos.

Métodos Estudo transversal com inquérito online envolvendo médicos plantonistas de hospitais públicos brasileiros. Os participantes responderam a um questionário anônimo com perguntas fechadas para avaliar seu conhecimento, atitude e experiência sobre a inserção de dispositivos intrauterinos de cobre no pós-parto e pós-aborto imediatos.

Resultados Cento e vinte sete médicos de 23 hospitais localizados nas 5 regiões do Brasil preencheram o questionário. A maioria era do sexo feminino (68,5%) e trabalhava em hospitais de ensino (95,3%). O escore médio (desvio padrão) de conhecimento (escala 0–10) foi 5,3 (1,3); apenas 27,6% tiveram escore $\geq$ 7,0. A maioria (73,2%) faria inserção de dispositivo intrauterino no pós-parto imediato em si mesma/familiares. Cerca de 42% dos participantes declararam não ter recebido nenhum treinamento sobre inserção de dispositivos intrauterinos no pós-parto ou pós-aborto imediatos. Nos últimos 12 meses, 19,7%, 22,8% e 53,5% declararam não ter inserido nenhum dispositivo intrauterino durante uma cesárea, após um parto vaginal ou um aborto, respectivamente.

Conclusão A maioria dos participantes tem uma atitude positiva em relação à inserção de dispositivos intrauterinos no pós-parto imediato, porém tem um conhecimento limitado sobre esse método. Uma grande porcentagem dos respondentes não teve treinamento sobre inserção de dispositivos intrauterinos no pós-parto ou pós-aborto imediatos e não fez nenhuma inserção desse tipo nos últimos 12 meses. São necessárias estratégias para melhorar o conhecimento, o treinamento e a experiência dos médicos brasileiros sobre a inserção de dispositivos intrauterinos no pós-parto e pós-aborto imediatos.

Palavras-chave

- dispositivos intrauterinos de cobre
- período pós-parto
- aborto espontâneo
- aborto induzido
- conhecimentos
- atitudes e prática em saúde

Introduction

Unplanned (unwanted or untimely) pregnancy is a global public health problem that affects especially low- and middle-income country (LMIC) populations.[1] Between 2015 and 2019, there were ~ 121 million unplanned pregnancies (UPs) annually in the world (64 UPs/1,000 women of reproductive age). Over half of these pregnancies ended in induced abortions, exposing nearly 73 million women per year to the risks associated with this procedure, often performed under inadequate conditions because they are illegal in many countries.[1,2] In Brazil, nearly 55% of pregnancies are unplanned, and the prevalence of induced abortion is estimated to be 15%.[3,4] Besides the physical and mental consequences to women and their families, UPs also have economic impacts.[5] It is estimated that the total annual costs of UPs in Brazil amount to 4.10 billion Brazilian Reais, of which 4.07 billion (99.2%) are pregnancy and childbirth costs, and 32.8 million (0.8%) are costs related to miscarriages or abortions.[6]

Lack of access to effective contraceptive methods, as well as failure in their use, are major contributors to the high rates of UPs. Modern short-acting contraceptives have a smaller impact on reducing UPs than long-acting contraceptives.[7] The copper intrauterine device (IUD) is a safe and inexpensive long-acting reversible contraceptive method with few contraindications. Copper IUDs can be used for up to 10 years and can be inserted in nulliparous women and adolescents.[8] The contraceptive failure rate of copper IUDs (0.8% pregnancy/year in typical use and 0.6% in perfect use) is comparable to the effectiveness of tubal ligation.[9] However, IUDs are still underused, especially in LMICs. In South America, IUDs are used by less than 5% of women, compared with 10 to 35% of women in middle- and high-income countries.[10,11]

Intrauterine device insertion in the immediate postpartum period (IPP-IUD) is safe and could increase the use of this method because this is a period when most women are motivated to avoid a new pregnancy. Intrauterine device insertion immediately after placental extraction does not cause additional discomfort, dispenses pregnancy tests, and precludes the need to schedule a postdischarge visit for device insertion.[12] It is important to encourage the use of

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

an effective contraceptive method in the immediate postpartum period because the risk of UP is high in the first months after giving birth since most women will resume sexual activity within weeks of delivery and many will become fertile soon after, especially if they do not breastfeed.[13,14] However, there are several barriers to expand the use of IPP-IUD, including lack of IUDs, cost or reimbursement issues, physicians' lack of training and their concerns about the risk of expulsion, and women's lack of interest for this contraceptive method.[15] The insertion of an intrauterine device immediately after a spontaneous or induced abortion (IPA-IUD) is another window of opportunity to expand the use of this contraceptive method and prevent UPs.[16] The rapid return of fertility immediately after an abortion, coupled with the fact that most women resume sexual activity within the first 2 weeks after early pregnancy loss, underscore the importance of offering an effective contraceptive method immediately after uterine evacuation.[17,18] Barriers to the use of IPA-IUD include factors related to professionals, such as lack of training on insertion in these patients and fear of complications, as well as women's lack of information and fears regarding this method.[19]

Knowledge attitude and practice (KAP) studies are important to plan effective interventions because they describe the current knowledge of a population, as well as its attitude and practice on a given topic.[20] There are several KAP studies about IPP-IUD and IPA-IUD insertion involving health professionals in other countries, but we did not identify similar studies in Brazil.[15,21–24]

The main objective of this study was to assess the knowledge, attitude, and practice of physicians working in Brazilian public hospitals about IPP-IUD and IPA-IUD use. The secondary objective was to identify possible barriers to the use of this method in these institutions.

Methods

This descriptive cross-sectional study was conducted from February to May 2020. The study design foresaw the inclusion of a representative sample of medium size ($>$ 2,000 deliveries/year) Brazilian public, philanthropic, or mixed (private-public) hospitals. We created a list of all eligible institutions for each of the country's five geographic regions from the Ministry of Health's website.[25] Then, for each region, we used an electronically generated random number list (Microsoft Excel software – Microsoft Corp., Redmond, WA, USA) to identify the institutions that would be invited to participate in the study. The total number of institutions selected in each geographic region was proportional to the number of births in that region in 2019, that is, we included more institutions from the Southeast, Northeast, and South regions, and fewer institutions in the North and Midwest regions. Using this random list of institutions, we contacted (by email and telephone) the directors of the selected institutions and invited them to participate in the study. Hospitals were included in the study after the directors accepted the invitation and the study was approved by the local ethics committees. Study participants were physicians who worked as on-duty professionals in the labor and delivery wards in each of the selected institutions. Physicians who were not fluent in Portuguese or who did not deliver babies were considered ineligible. The directors of the participating institutions sent all eligible physicians a standard e-mail (created by the researchers) explaining the purpose of the study and containing the link to an electronic questionnaire. We included in the study all eligible physicians who accepted the invitation and completed the electronic questionnaire (convenience sample).

The questionnaire was developed by the study authors following the methodological recommendations for knowledge and attitude surveys of the World Health Organization (WHO) and based on similar studies conducted in other countries.[15,20–24] The questionnaire was initially tested in a group of 10 on-duty physicians from maternity hospitals not included in the study, modified and retested on another group of 10 on-duty physicians from these same institutions until all questions and answers were clear to all participants. The final version was converted into an electronic questionnaire (Google forms – Google LLC, Mountain View, CA, USA) to be administered online. The questionnaire was anonymous and divided into two parts. The first part collected participants' characteristic. The second part consisted of nine multiple-choice questions to assess physicians' theoretical knowledge (indications, contraindications, risks, complications) about IPP-IUD and IPA-IUD, three questions to assess participants' attitude toward IUD insertion in women managed in different health settings and sectors, four questions about their personal experience and training in postpartum and postabortion insertions, and three questions about possible barriers to the use of these methods in the public hospital where they worked. We used the best available evidence at the time to create the questions and answers.[8,18,26,27]

We present the characteristics of the participants, and the results of the knowledge, attitude, and practice questions descriptively (number, percentages, mean, and standard deviation). We converted the scores of the nine knowledge questions to a decimal scale (0 to 10).

The study was approved by the research ethics committee of UNIFESP-EPM (CAAEE 06756219.0.0000.5505) and by the ethics committees of the participating institutions. We obtained informed consent from all participants electronically, before they had access to the anonymous online questionnaire.

Results

We contacted the 178 randomly-selected hospitals (50% of the 357 eligible institutions), and 23 agreed to participate. The main reason for refusal, according to the directors of the institutions who responded to our contact, was that their physicians were overloaded due to the first wave of the coronavirus disease 2019 (COVID-19) pandemic that was spreading around the country at that time. Because the situation was getting worse over time, and the public health system was collapsing due to the pandemic, and it was

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

impossible to predict the duration of this situation, we decided to end the study 4 months after it started (May 2020). When we ended the study, 127 physicians working in 23 hospitals located in the 5 geographical regions of Brazil had responded to the questionnaire. Most participants were females (68.5%), had a mean age of 40.6 years, had graduated ~ 15 years earlier, had completed a residency in obstetrics and gynecology (72.4%), and worked in teaching hospitals (95.3%) located in capital cities (84.2%) in the southeast region (51.2%) of Brazil (►**Table 1**).

Table 1 Characteristics of 127 physicians on duty in labor and delivery wards of 23 Brazilian public hospitals

Characteristics	n (%)
Sex	
Female	87 (68.5)
Male	40 (31.5)
Age, years	
Minimum–maximum	24–66
Mean (SD)	40.6 (10.4)
Time since graduation, years	
Minimum–maximum	1–42
Mean (SD)	15.4 (10.7)
Highest degree	
PhD	13 (10.2)
Master's degree	14 (11.0)
OB-GYN residency	92 (72.4)
OB-GYN specialist title	8 (6.3)
Number of hospitals where participants work	
1	93 (73.2)
2	14 (11.0)
3 or more	20 (15.8)
Is the participant's institution a teaching hospital?	
Yes	121 (95.3)
No	6 (4.7)
Weekly workload in participant's institution	
< 24 hours	48 (37.8)
≥ 24 hours	79 (62.2)
Geographic location of participant́s institution	
Southeast (12 institutions)	65 (51.2)
Northeast (5 institutions)	29 (22.8)
South (3 institutions)	16 (12.6)
North (2 institutions)	11 (8.7)
Midwest (1 institution)	6 (4.7)
Location of participant́s institution	
State capital city	107 (84.2)
Other cities	20 (15.8)

Abbreviations: OB-GYN, obstetrics and gynecology; SD, standard deviation.

The mean overall score (standard deviation) of the knowledge questions was 5.3 (1.3), ranging from 2.2 to 8.8 (0–10 scale). Only 27.6% ($n = 35$) of the 127 participants had overall scores ≥ 7. Over ¾ (77.2%) of the physicians overestimated the expulsion rate of IUDs inserted during a cesarean section, most (55.1%) overestimated the risk of expulsion of IUDs inserted immediately after a vaginal birth, and ~ 61% ($n = 77$) overestimated the risk of uterine perforation in IUDs inserted after a vaginal birth. On the other hand, most (50.4%) of the participants underestimated the risk of uterine perforation of IUDs inserted immediately after an abortion. Almost all participants answered correctly the questions about the overall safety of IPP-IUD (100%) and IPA-IUD (98.4%) insertions, and most gave correct answers to the questions about the risks of endometritis in IUD insertions after vaginal births (72.4%), IPA-IUD expulsion rates (63%), and contraindications for IPP-IUD and IPA-IUD use (60.6%) (►**Table 2**).

Most professionals (73.2%, $n = 93$) would probably or certainly insert an IPP-IUD in themselves or family members, and almost 93% ($n = 118$) think it is important or very important to increase postpartum IUD use in Brazil. About 72% ($n = 91$) of the respondents stated that they frequently (i.e., for ≥ 50% of eligible women) recommend IUD use for patients managed in public gynecology outpatient clinics, while 53.5% ($n = 68$) do so for women managed in private outpatient gynecology clinics. The proportion of physicians who frequently recommend IPP-IUD to eligible women was nearly two times higher for women managed in public than in private hospitals (61.4% versus 29.9%, respectively). Less than half of the participants responded that they frequently recommend the use of IPA-IUD for women managed in public or private hospitals (48.0% and 26.8%, respectively) (►**Table 3**).

About 58% ($n = 74$) of the participants reported that they had participated in some type of training about IPP-IUD or IPA-IUD insertion. Most of these physicians (74.3%, $n = 55/74$) informed that the training had occurred more than 12 months before, had been promoted by public authorities (Ministry of Health or local Department of Health), and had taken place at the hospital where they worked (59.5%, $n = 44$). Almost 54% of the participants ($n = 68$) reported that they had not inserted an IPA-IUD in the past 12 months, ~ 23% ($n = 29$) had not inserted an IUD immediately after a vaginal birth, and nearly 20% ($n = 25$) reported that they had not inserted an IUD during a cesarean section in the past year (►**Table 4**).

Over 70% of the participants consider women's resistance to the method as an important or very important barrier to the insertion of IPP-IUD or IPA-IUD in the public hospital where they work. Over 60% of the participants pointed to the unavailability of copper IUDs in the labor and delivery wards and the lack of hospital guidelines as important or very important barriers to IPP-IUD or IPA-IUD insertion. Other important or very important barriers mentioned by most participants were the lack of experience of the doctors and fear of IUD expulsion (in insertions after vaginal or cesarean deliveries), fear of infection or perforation (in insertions after a vaginal birth or an abortion), and lack of support from hospital managers (for IPA-IUD insertion) (►**Table 5**).

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 2 Knowledge of 127 on-duty physicians about immediate postpartum and postabortion intrauterine device insertion

Questions	n (%)
1. Is it safe to insert an IUD in the immediate postpartum period?	
Yes (correct)	127 (100)
No	0
2. Is it safe to insert an IUD in the immediate postabortion period?	
Yes (correct)	125 (98.4)
No	2 (1.6)
3. Usual expulsion rate of IUD inserted immediately after a vaginal birth	
> 27%	19 (15.0)
16–26%	51 (40.2)
5–15% (correct)	45 (35.4)
< 5%	12 (9.4)
4. Usual expulsion rate of IUD inserted immediately after a cesarean section	
> 16%	17 (13.4)
11–16%	30 (23.6)
5–10%	51 (40.2)
< 5% (correct)	29 (22.8)
5. Usual expulsion rate of IUD inserted immediately after an abortion	
< 6% (correct)	80 (63.0)
6–11%	29 (22.8)
12–16%	11 (8.7)
> 17%	7 (5.5)
6. Usual risk of endometritis in IUD insertion immediately after vaginal birth	
< 2% (correct)	92 (72.4)
2–3%	18 (14.2)
4–5%	12 (9.5)
> 6%	5 (3.9)
7. Usual risk of uterine perforation from an IUD inserted immediately after an abortion	
0.1–0.2 per 1,000 insertions	64 (50.4)
1–2 for every 1,000 (correct)	54 (42.5)
3 for every 1,000	4 (3.2)
4 for every 1,000	5 (3.9)
8. Usual risk of uterine perforation from an IUD inserted immediately after vaginal birth	
> 4%	3 (2.4)
2–3%	22 (17.3)
0.5–1%	52 (40.9)
< 0.5% (correct)	50 (39.4)
9. Contraindications to inserting an IUD immediately after childbirth or abortion	
Infected abortion and chorioamnionitis (correct)	77 (60.6)
Rupture of membranes for more than 12 hours	33 (26.0)
Infected abortion	1 (0.8)
Chorioamnionitis	0
Women with diabetes	0

Abbreviation: IUD, intrauterine device

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 3 Attitude of 127 on-duty physicians about immediate postpartum and postabortion intrauterine device insertion

Question	n (%)
Would you have an IUD inserted in yourself or a family member immediately after giving birth?	
certainly not	14 (11.1)
probably not	20 (15.7)
probably yes	31 (24.4)
certainly yes	62 (48.8)
Do you think it is important to increase the use of postpartum IUDs in Brazil?	
Very important	92 (72.4)
Important	26 (20.5)
Slightly important	6 (4.7)
Not at all important	3 (2.4)
Recommends IUD use for eligible women in a public gynecology outpatient clinic	
Never	7 (5.5)
Rarely (to $<$ 10% of eligible women)	6 (4.7)
Sometimes (to 10–49% of eligible women)	23 (18.1)
Frequently (to $\geq$ 50% of eligible women)	91 (71.7)
Recommends IUDs for eligible women in a private gynecology outpatient clinic	
never	14 (11.1)
rarely (to $<$ 10% of eligible women)	12 (9.4)
sometimes (to 10–49% of eligible women)	33 (26.0)
frequently (to $\geq$ 50% of eligible women)	68 (53.5)
Recommends IPP-IUD use in public hospitals	
never	9 (7.1)
rarely (to $<$ 10% of eligible women)	15 (11.8)
sometimes (to 10–49% of eligible women)	25 (19.7)
frequently (to $\geq$ 50% of eligible women)	78 (61.4)
Recommends IPP-IUD use in private hospitals	
never	40 (31.5)
rarely (to $<$ 10% of eligible women)	24 (18.9)
sometimes (to 10–49% of eligible women)	25 (19.7)
frequently (to $\geq$ 50% of eligible women)	38 (29.9)
Recommends IPA-IUD use in public hospitals	
never	17 (13.4)
rarely (to $<$ 10% of eligible women)	24 (18.9)
sometimes (to 10–49% of eligible women)	25 (19.7)
frequently (to $\geq$ 50% of eligible women)	61 (48.0)
Recommends IPA-IUD use in private hospitals	
never	43 (33.9)
rarely (to $<$ 10% of eligible women)	22 (17.3)
sometimes (to 10–49% of eligible women)	28 (22.0)
frequently (to $\geq$ 50% of eligible women)	34 (26.8)

Abbreviations: IPA-IUD, immediate postabortion IUD insertion; IPP-IUD, immediate postpartum IUD insertion; IUD, intrauterine device.

Discussion

The findings of this national survey indicate that on-duty physicians working in Brazilian public hospitals have limited knowledge about IPP-IUD and IPA-IUD insertion. Most participants have a favorable attitude about IPP-IUD but not about IPA-IUD use. A large percentage of respondents did not have any previous training on IPP-IUD and IPA-IUD insertion and have not performed these types of insertions in the past 12 months. The main barriers pointed out as important or

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 4 Training and experience of 127 on-duty physicians about immediate postpartum and postabortion intrauterine device insertion

Questions	n (%)
Received training on IPP-IUD or IPA-IUD insertion	
Yes	74 (58.3)
No	53 (41.7)
How long ago was this training ($n = 74$)	
$<$ 12 months	19 (25.7)
12–24 months	30 (40.5)
$>$ 24 months	25 (33.8)
Where did training take place ($n = 74$)	
At my own hospital, promoted by public health authorities*	44 (59.5)
During medical residency	34 (45.9)
At a congress/conference/symposium	15 (20.3)
Number of IPP-IUD insertions after a vaginal birth the last 12 months ($n = 127$)	
0	29 (22.8)
1–5 per month	63 (49.6)
6–10 per month	19 (15.0)
$>$ 10 per month	16 (12.6)
Number of IPP-IUD insertions in cesarean section in the last 12 months ($n = 127$)	
0	25 (19.7)
1–5 per month	65 (51.2)
6–10 per month	20 (15.7)
$>$ 10 per month	17 (13.4)
Number of IPA-IUD insertions in the last 12 months ($n = 127$)	
0	68 (53.5)
1–5 per month	40 (31.5)
6–10 per month	11 (8.7)
$>$ 10 per month	8 (6.3)

Abbreviations: IPA-IUD, immediate postabortion IUD insertion; IPP-IUD, immediate postpartum IUD insertion.
* Ministry of health or local health department.

very important for IPP-IUD and IPA-IUD insertions were the resistance of women, the unavailability of IUDs in labor and delivery wards, the lack of hospital guidelines for these insertions, and the lack of experience of the on-duty physicians.

The general knowledge of our participants regarding IPP-IUD and IPA-IUD was similar to that reported in comparable studies involving health professionals from developed countries and better than in studies conducted in low- or middle-income countries.[15,21–24] Although most Brazilian physicians were aware of the general safety of IPP-IUD and IPA-IUD insertions and their main contraindications, they had some knowledge gaps about the specific risks associated with this type of insertion. For instance, most Brazilian physicians overestimated the risks of expulsion and perforation in IUDs inserted immediately after a vaginal birth. Similarly, authors of a survey involving 58 American physicians working in teaching hospitals reported that less than half gave correct answers to questions about expulsion rates of IUDs inserted immediately after a vaginal birth and perforation rates of IUDs inserted immediately after an abortion.[24] Healthcare providers' overestimation of the risks associated with IPP-IUD use may contribute to the underutilization of the method.[21]

The attitude of most of our participants toward IPP-IUD and IPA-IUD insertion was heterogeneous. While most respondents seem to have a positive attitude about IPP-IUD insertion for themselves/family members and in women giving birth in public hospitals, most physicians have less favorable attitudes about IPA-IUD for women managed in the public and private sectors. This could be due participants' lack of knowledge, training, and confidence about IPA-IUD insertion. In agreement with our findings, an American study involving 97 health professionals (32% physicians) working in family-planning clinics reported that 30% of the participants did not believe that IPA-IUD was appropriate and safe.[28] We observed a difference in the attitude of Brazilian physicians when recommending IUD use for women managed in public versus private sectors. In all scenarios (gynecology clinic, immediate postpartum or postabortion),

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 5 Barriers to immediate postpartum and postabortion intrauterine device insertion in Brazilian public hospitals

Possible barriers	Postvaginal birth IUD insertion	Postcesarean section IUD insertion	Postabortion IUD insertion
	n (%)	n (%)	n (%)
IUDs are not available in labor/delivery ward			
Not at all important	28 (22.0)	31 (24.4)	34 (26.8)
Somewhat important	18 (14.2)	12 (9.5)	9 (7.0)
Important	32 (25.2)	30 (23.6)	26 (20.5)
Very important	49 (38.6)	54 (42.5)	58 (45.7)
Women's resistance			
Not at all important	9 (7.1)	10 (7.9)	8 (6.3)
Somewhat important	23 (18.1)	25 (19.7)	25 (19.7)
Important	48 (37.8)	53 (41.7)	51 (40.2)
Very important	47 (37.0)	39 (30.7)	43 (33.8)
Hospital does not have guideline for insertion			
Not at all important	27 (21.2)	30 (23.6)	17 (13.4)
Somewhat important	18 (14.2)	17 (13.4)	15 (11.8)
Important	41 (32.3)	42 (33.1)	39 (30.7)
Very important	41 (32.3)	38 (29.9)	56 (44.1)
On-duty physicians lack experience in these insertions			
Not at all important	18 (14.2)	32 (25.2)	14 (11.0)
Somewhat important	24 (18.9)	24 (18.9)	27 (21.3)
Important	48 (37.8)	40 (31.5)	46 (36.2)
Very important	37 (29.1)	31 (24.4)	40 (31.5)
Lack of support from hospital managers			
Not at all important	42 (33.1)	42 (33.1)	36 (28.3)
Somewhat important	25 (19.7)	23 (18.1)	26 (20.5)
Important	26 (20.5)	33 (26.0)	35 (27.6)
Very important	34 (26.7)	29 (22.8)	30 (23.6)
Fear of risk of IUD expulsion			
Not at all important	17 (13.4)	23 (18.1)	23 (18.1)
Somewhat important	29 (22.8)	38 (29.9)	43 (33.8)
Important	50 (39.4)	48 (37.8)	43 (33.8)
Very important	31 (24.4)	18 (14.2)	18 (14.2)
Fear of risk of postinsertion infection			
Not at all important	17 (13.4)	23 (18.1)	13 (10.2)
Somewhat important	34 (26.8)	42 (33.1)	37 (29.1)
Important	53 (41.7)	44 (34.6)	50 (39.4)
Very important	23 (18.1)	18 (14.2)	27 (21.3)
Fear of risk of uterine perforation			
Not at all important	19 (15.0)	43 (33.9)	18 (14.2)
Somewhat important	44 (34.6)	46 (36.2)	45 (35.4)
Important	45 (35.4)	28 (22.0)	42 (33.1)
Very important	19 (15.0)	10 (7.9)	22 (17.3)

Abbreviation: IUD, intrauterine device.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Brazilian physicians recommended IUD insertion to fewer eligible women managed in the private sector than in the public sector. We found no other studies that evaluated the attitude of health providers about IPP-IUD and IPA-IUD use for women managed in different health sectors. It is possible that this attitude may reflect the popular, albeit anecdotal, perception of Brazilian OB-GYNs that the copper IUD is a less sophisticated or modern contraceptive method than the levonorgestrel IUD, a contraceptive method with similar efficacy to that of the copper IUD but that is much more expensive and not available in the public sector.[9]

The limited practice of many study participants in IPP-IUD and IPA-IUD insertions may be due to several factors. These include personal issues (lack of confidence, training, or negative attitude toward the method), institutional deficiencies (unavailability of IUDs, lack of hospital support and guidelines), and patient-related factors (lack of knowledge or rejection of the method) identified in the questions about barriers to device use. Women's resistance to the method, one of the main barriers to IPP-IUD and IPA-IUD use according to our respondents, is also reported in the literature and could be due to women's lack of information about the availability of IUDs in delivery wards and lack of knowledge about the contraceptive efficacy of IUDs inserted immediately after birth or abortion.[29] According to a Brazilian study conducted in a public hospital in Campinas, 42% of 242 women refused the offer for free IPP-IUD insertion, and the most important reason was misinformation related to fear of pain, method failure, increased menstrual bleeding, and effects of IUDs on future fertility.[30] Education about the method during prenatal care can significantly increase women's decision to insert IPP-IUD.[31] On the other hand, research indicates that physicians are the greatest source of influence on women's attitude about and choice of contraceptive methods.[32] Considering the impact that physicians have on women's contraceptive decisions, it is important to improve the knowledge, attitude, and practical experience of Brazilian physicians about IPP-IUD and IPA-IUD use to overcome their own resistance to this method. The other three major barriers to IPP-IUD and IPA-IUD insertion in this survey (unavailability of IUDs in the labor and delivery wards, lack of experience of on-duty physicians, and lack of hospital guidelines) are organizational issues that could be solved with relatively simple institutional interventions. The lack of IUDs in labor and delivery wards should not be a barrier to IPP-IUD and IPA-IUD insertions in Brazilian public hospitals because the Ministry of Health has made copper IUDs available to all maternity hospitals in the Unified Health System since 2017.[33] This suggests possible administrative problems, or lack of knowledge of hospital managers, to ensure the continuous and uninterrupted supply of copper IUDs in the labor and delivery wards of all public Brazilian hospitals.

This study has several strengths, including its originality, the use of the best available evidence to design the survey questions and answers, and the pilot testing phase of the questionnaire in a group of volunteers before it was sent to the final participants. This survey is unique in its inclusion of questions to detect possible differences in participants' attitudes toward IPP-IUD and IPA-IUD insertion in patients managed in the public and private sectors, and questions to gather participants' views on the main barriers to the use of this contraceptive method in their own hospitals. The main limitation of this study was that most of the hospitals contacted did not respond to or declined the invitation to participate in the survey. This probably occurred because the study coincided with the first wave of the COVID-19 pandemic in Brazil, when the attention of hospital directors was totally focused on reorganizing their infrastructure and staff to manage this public health emergency. Despite the low adherence of hospitals, we were able to include institutions located in the five Brazilian geographic regions, and the distribution of participating hospitals was proportional to the total number of births in the country. Another limitation of the study was its exclusively quantitative design, involving only close-ended questions. Ideally, the online survey could have included open-ended questions, and we could have complemented the study with individual online interviews or focus groups with a sample of the participants (mixed methods quantitative-qualitative study). This could have allowed a more in-depth analysis of physicians' attitudes about IPP-IUD and IPA-IUD use, and the identification of additional barriers to the use of this contraceptive method. Finally, the findings of this study cannot be generalized to all Brazilian public hospitals, because almost all participating institutions were teaching hospitals and over 20% of the physicians had postgraduate degrees.

The results of this study have several implications for practice. The limited knowledge of the participants about IPP-IUD was surprising since most of them report having received specific training about this type of insertion promoted by public health authorities. This finding indicates the need to reevaluate and improve the quality of the theoretical training currently offered by these authorities or offer refresher courses. To overcome the lack of experience detected in this study, authorities could consider the creation of a practical training module, including hands-on clinical demonstrations and supervision by a tutor in the labor and delivery wards, after the theoretical module. This could increase the experience as well as the confidence of on-duty physicians about IPP-IUD and especially about IPA-IUD insertion in public Brazilian hospitals. The involvement and support of clinical directors and hospital managers are essential to overcome the main organizational barriers to IPP-IUD and IPA-IUD insertion reported by study participants.

This study can serve as a model for similar surveys involving other types of participants (e.g., residents) and institutions (non-teaching, smaller or private hospitals) in Brazil. New studies could also include a qualitative component to further investigate participants' attitudes and identify additional barriers to IPP-IUD and IPA-IUD use. Finally, results suggest the need for studies involving pregnant and postpartum women, as well as women who have just gone through an early pregnancy loss, to investigate their knowledge and attitude about IPP-IUD and IPA-IUD insertion. The

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

results of these new studies will be useful to help develop effective strategies to expand the use of this contraceptive method in Brazil.

Conclusion

On-duty physicians working in public Brazilian hospitals have a limited knowledge about IPP-IUD and IPA-IUD insertion. Most physicians have a positive attitude toward IPP-IUD insertion, especially for women managed in the public sector, but their attitude is less favorable toward IPA-IUD insertion. A large percentage of participants reported lack of training and experience in IPP-IUD and especially in IPA-IUD insertions. The main barriers to the use of this method in public hospitals are the resistance of women, unavailability of IUDs in the labor and delivery wards, lack of institutional guidelines, and physicians' lack of experience.

Contributions

AKA was responsible for the conception and design of the study, data collection, analyses, and interpretation of data, writing of the article, and approved the final version of the manuscript. MNO contributed to data analyses and interpretation, reviewed critically the intellectual content of the article, and approved the final version of the manuscript. MRT contributed substantially to the conception and design of the study, analyses, and interpretation of data, was co-responsible for writing of the article, and approved the final version of the manuscript. CAFG contributed to data analyses, reviewed critically the content of the article, and approved the final version of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

AKA received a 2-year postgraduate scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

References

1 Santelli J, Rochat R, Hatfield-Timajchy K, Gilbert BC, Curtis K, Cabral R, et al; Unintended Pregnancy Working Group. The measurement and meaning of unintended pregnancy. Perspect Sex Reprod Health. 2003;35(02):94–101. Doi: 10.1363/3509403
2 Bearak J, Popinchalk A, Ganatra B, Moller AB, Tunçalp O, Beavin C, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990-2019. Lancet Glob Health. 2020;8(09):e1152–e1161
3 Leal MDC, Gama SGND. 2014Being born in Brazil. Cad S Pública. 30 (suppl.1): S5–S7. https://doi.org/10.1590/0102-311XED01S114
4 Domingues RMSM, Fonseca SC, Leal MC, Aquino EML, Menezes GMS. 2020Unsafe abortion in Brazil: systematic review of scientific production, 2008–2018. Cad. S Pública 36(Suppl 1). https://doi.org/10.1590/0102-311X00190418
5 Maxson P, Miranda ML. Pregnancy intention, demographic differences, and psychosocial health. J Womens Health (Larchmt). 2011;20(08):1215–1223. Doi: 10.1089/jwh.2010.2379
6 Le HH, Connolly MP, Bahamondes L, Cecatti JG, Yu J, Hu HX. The burden of unintended pregnancies in Brazil: a social and public health system cost analysis. Int J Womens Health. 2014; 6:663–670. Doi: 10.2147/IJWH.S61543
7 Bradley SEK, Polis CB, Bankole A, Croft T. Global Contraceptive Failure Rates: Who Is Most at Risk? Stud Fam Plann. 2019;50(01): 3–24. Doi: 10.1111/sifp.12085
8 WHO - World Health Organization. 2015Reproductive Health and Research. Medical eligibility criteria for contraceptive use. 268p. https://apps.who.int/iris/bitstream/handle/10665/181468/9789241549158_ eng.pdf
9 Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(05):397–404. Doi: 10.1016/j.contraception.2011.01.021
10 Ponce de Leon RG, Ewerling F, Serruya SJ, Silveira MF, Sanhueza A, Moazzam A, et al. Contraceptive use in Latin America and the Caribbean with a focus on long-acting reversible contraceptives: prevalence and inequalities in 23 countries. Lancet Glob Health. 2019;7(02):e227–e235. Doi: 10.1016/S2214-109X(18)30481-9
11 United Nations. Department of Economic and Social Affairs. Population Division. 2019) Contraceptive use by method. data booklet. 25 p. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un_2019_contraceptiveusebymethod_databooklet.pdf
12 Whitaker AK, Chen BA. Society of Family Planning Guidelines: Postplacental insertion of intrauterine devices. Contraception. 2018;97(01):2–13. Doi: 10.1016/j.contraception.2017.09.014
13 Sok C, Sanders JN, Saltzman HM, Turok DK. Sexual Behavior, Satisfaction, and Contraceptive Use Among Postpartum Women. J Midwifery Womens Health. 2016;61(02):158–165. Doi: 10.1111/jmwh.12409
14 Jackson E, Glasier A. Return of ovulation and menses in postpartum nonlactating women: a systematic review. Obstet Gynecol. 2011;117(03):657–662. Doi: 10.1097/AOG.0b013e31820ce18c
15 Holden EC, Lai E, Morelli SS, Alderson D, Schulkin J, Castleberry NM, McGovern PG. Ongoing barriers to immediate postpartum long-acting reversible contraception: a physician survey. Contracept Reprod Med. 2018;3:23. Doi: 10.1186/s40834-018-0078-5
16 Roe AH, Bartz D. Society of Family Planning clinical recommendations: contraception after surgical abortion. Contraception. 2019;99(01):2–9. Doi: 10.1016/j.contraception.2018.08.016
17 Sääv I, Stephansson O, Gemzell-Danielsson K. Early versus delayed insertion of intrauterine contraception after medical abortion - a randomized controlled trial. PLoS One. 2012;7(11):e48948. Doi: 10.1371/journal.pone.0048948
18 Okusanya BO, Oduwole O, Effa EE. Immediate postabortal insertion of intrauterine devices. Cochrane Database Syst Rev. 2014; 2014(07):CD001777. Doi: 10.1002/14651858.CD001777.pub4
19 Luo Z, Gao L, Anguzu R, Zhao J. Long-acting reversible contraceptive use in the post-abortion period among women seeking abortion in mainland China: intentions and barriers. Reprod Health. 2018;15(01):85. Doi: 10.1186/s12978-018-0543-2
20 World Health Organization & Stop TB Partnership. 2008Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys. https://apps.who.int/iris/bitstream/handle/10665/43790/9789241596176_eng.pdf
21 Thompson EL, Vamos CA, Logan RG, Bronson EA, Detman LA, Piepenbrink R, Daley EM, Sappenfield WM. Patients and providers' knowledge, attitudes, and beliefs regarding immediate postpartum long-acting reversible contraception: a systematic review. Women Health. 2020;60(02):179–196. Doi: 10.1080/03630242.2019.1616042
22 Stone L, Puri MC, Guo M, Shah IH. Assessing knowledge, attitudes, and practice of health providers towards the provision of postpartum intrauterine devices in Nepal: a two-year follow-up. Reprod Health. 2021;18(01):43

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

23 Rupley DM, Morhe ES, Moyer CA, Dalton VK. Maternity care provider knowledge, attitudes, and practices regarding provision of postpartum intrauterine contraceptive devices at a tertiary center in Ghana. Int J Gynaecol Obstet. 2015;128(02):137–140. Doi: 10.1016/j.ijgo.2014.09.010
24 Holland E, Michelis LD, Sonalkar S, Curry CL. Barriers to Immediate Post-placental Intrauterine Devices among Attending Level Educators. Womens Health Issues. 2015;25(04):355–358. Doi: 10.1016/j.whi.2015.03.013 1
25 Brazil, Ministry of Health, DATASUS (2020). Data from the Information System on Live Births - SINASC. Brasília. http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinasc/cnv/nvuf.def
26 Jatlaoui TC, Whiteman MK, Jeng G, Naomi KTepper, Erin Berry-Bibee, Denise J Jamieson, et al. Intrauterine Device Expulsion After Postpartum Placement: A Systematic Review and Meta-analysis. Obstet Gynecol. 2018;132(04):895–905. Doi: 10.1097/AOG.0000000000002822
27 Makins A, Taghinejadi N, Sethi M, Machiyama K, Munganyizi P, Odongo E, et al. FIGO postpartum intrauterine device initiative: Complication rates across six countries. Int J Gynaecol Obstet. 2018;143(Suppl 1):20–27. Doi: 10.1002/ijgo.12600
28 Philliber AE, Hirsch H, Brindis CD, Turner R, Philliber S. The Use of ACOG Guidelines: Perceived Contraindications to IUD and Implant Use Among Family Planning Providers. Matern Child Health J. 2017;21(09):1706–1712. Doi: 10.1007/s10995-017-2320-1
29 Cleland J, Conde-Agudelo A, Peterson H, Ross J, Tsui A. Contraception and health. Lancet. 2012;380(9837):149–156
30 Kraft MBPL, Miadaira M, Marangoni M, Juliato CRT, Surita FG, Surita FG. Postplacental placement of intrauterine devices: acceptability, reasons for refusal and proposals to increase its use. Rev Bras Ginecol Obstet. 2021;43(03):172–177. Doi: 10.1055/s-0041-1725053
31 Dev R, Kohler P, Feder M, Unger JA, Woods NF, Drake AL. A systematic review and meta-analysis of postpartum contraceptive use among women in low- and middle-income countries. Reprod Health. 2019;16(01):154. Doi: 10.1186/s12978-019-0824-4
32 Johnson S, Pion C, Jennings V. Current methods and attitudes of women towards contraception in Europe and America. Reprod Health. 2013;10:7. Doi: 10.1186/1742-4755-10-7
33 Brazil, Ministry of Health Ordinance No. 3265, December 1, 2017. Provides for the expansion of access to the Tcu 380 Intrauterine Device (copper IUD) within the Unified Health System (SUS). Brasília DF. https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prt3265_07_12_2017.htmll

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Core Needle Biopsy Accuracy for Androgen Receptor Expression in Invasive Breast Cancer

Precisão da biópsia com agulha de grande calibre para expressão de receptores androgênicos no câncer de mama invasivo

Marcelle Morais dos Santos[1] Antonio Luiz Frasson[1] Vinicius Duval da Silva[2] Aluísio de Castro Antunes Maciel[3] Guilherme Watte[4] Gustavo Werutsky[5] Tomás Reinert[5,6] André Poisl Fay[5,6]

[1] Department of Breast Surgery, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[2] Department of Pathology, Hospital do Câncer de Barretos, Barretos, SP, Brazil
[3] Department of Pathology, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[4] Department of Medical Oncology, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[5] School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[6] Oncoclínicas, Porto Alegre, RS, Brazil

Address for correspondence Marcelle Morais dos Santos, MD, Department of Breast Surgery, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga 6690/709, Jardim Botânico, 90610-000, Porto Alegre, RS, Brazil (e-mail: marcellems.mastologia@gmail.com).

Rev Bras Ginecol Obstet 2023;45(9):e535–e541.

Abstract

Objective Breast cancer (BC) biomarkers, such as hormone receptors expression, are crucial to guide therapy in BC patients. Antiandrogens have been studied in BC; however, limited data are available on androgen receptor (AR) expression test methodology. We aim to report the core needle biopsy (CNB) accuracy for AR expression in BC.

Methods Patients diagnosed with stage I-III invasive BC from a single institution were included. Androgen receptor expression was evaluated by immunohistochemistry (IHC) using 1 and 10% cutoff and the AR expression in surgical specimens (SS) was the gold standard. Kappa coefficients were used to evaluate the intraprocedural agreement.

Results A total of 72 patients were included, with a mean age of 61 years old and 84% were Luminal A or B tumors. The prevalence of AR expression in all BC samples was 87.5% using a cutoff $\geq$ 10% in SS. With a cutoff value $\geq$ 1%, CNB had an accuracy of 95.8% (Kappa value = 0.645; 95% confidence interval [CI]: 0.272–1.000; $p < 0.001$) and 86.1% (Kappa value = 0.365; 95% CI: 0.052–0.679; $p < 0.001$) when $\geq$ 10% cutoff was

Keywords
- breast cancer
- androgen receptor
- core needle biopsy
- immunohistochemistry
- biomarkers

received
August 16, 2022
accepted
May 4, 2023

DOI https://doi.org/10.1055/s-0043-1772486.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

used for AR positivity. Androgen receptor expression in CNB (cutoff $\geq$ 1%) had a sensitivity of 98.5%, specificity of 60%, positive predictive value of 97.0%, and a negative predictive value of 76.9% in the detection of AR expression in SS.
Conclusion Core needle biopsy has good accuracy in evaluating AR expression in BC. The accuracy of CNB decreases with higher cutoff values for AR positivity.

Resumo

Objetivo Biomarcadores, como a expressão de receptores hormonais, são cruciais para guiar a terapia de pacientes com câncer de mama. Apesar de ter sido estudado, poucos dados estão disponíveis sobre o método de testagem. Buscamos avaliar a precisão da biópsia com agulha de grande calibre (CNB, na sigla em inglês) para a expressão de receptores androgênicos (AR, na sigla em inglês) no câncer de mama.
Métodos Foram incluídos pacientes de uma única instituição diagnosticados com câncer de mama invasivo estágio I-III. A expressão de AR foi avaliada por imunohistoquímica, com valores de cutoff de 1 e 10%. A expressão de AR em espécimes cirúrgicos foi o padrão ouro. O coeficiente Kappa foi usado para avaliar a concordância entre procedimentos.
Resultados Foi incluído um total de 72 pacientes, com idade média de 61 anos; 84% eram tumores luminais A ou B. A prevalência da expressão de AR em todas as amostras foi de 87.5%, com cutoff $\geq$ 10%. Com um valor de cutoff $\geq$ 1%, a CNB teve precisão de 95.8% (Kappa = 0.64; intervalo de confiança [IC] 95%: 0.272–1.000; $p < 0.001$) e 86.1% (Kappa = 0.365; CI95%: 0.052–0.679]; $p < 0.001$) quando um cutoff $\geq$ 10% foi usado para AR positivo. A expressão de AR na CNB (cutoff $\geq$ 1%) teve a sensibilidade de 98.5%, especificidade de 60%, valor preditivo positivo de 97.0% e valor preditivo negativo de 76.9% na detecção.
Conclusão | Biópsia com agulha de grande calibre tem uma boa precisão em avaliar a expressão de AR no câncer de mama. A precisão do método cai com valores elevados de cutoff para AR positivo.

Palavras-chave
- câncer de mama
- receptores androgênicos
- biópsia com agulha de grande calibre
- imuno-histoquímica
- biomarcadores

Introduction

Breast cancer (BC) is a heterogeneous disease. Immunohistochemistry (IHC) is the routine pathological technique used to evaluate hormone receptor (HR) status, HER2 expression, among other markers to better stratify BC subtypes.[1,2] Immunohistochemistry performed in the diagnostic preoperative core needle biopsy (CNB) samples is critical to define whether neoadjuvant therapy is necessary and the type of drug regimen to be used.[3,4] In case of pathologic complete response, which is common in more aggressive BC subtypes after neoadjuvant treatment, the CNB specimen can be the only biological material left for further biomarkers analysis. However, IHC assessment in CNB samples may be less reliable than in surgical specimens (SS) due to a variety of factors, including the relatively smaller sample size and tumor heterogeneity.[5]

Androgen receptor (AR) expression in breast cancer is often associated with better prognostic tumors, was identified as a subtype of triple negative breast cancer (TNBC) and as a potential therapeutic target, especially in TNBC.[6–14] Androgen receptor-targeted agents such as bicalutamide, enzalutamide and abiraterone acetate have shown promising preliminary results in advanced BC[15–18] and there are currently ongoing trials evaluating the role of antiandrogens in HR-positive and TNBC,[19–21] although CNB accuracy for AR expression in invasive BC has not been evaluated in previous studies.

The primary goal of the present study is to describe the CNB accuracy for the evaluation of AR expression in BC in a Brazilian population.

Methods

We conducted a cross-sectional study to evaluate biomarkers expression in BC specimens. Clinical data from consecutive patients diagnosed with invasive BC treated in the Surgical Breast Unit of Hospital São Lucas of the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS) in Brazil, from March 2017 to March 2018, were retrospectively collected. All patients underwent CNB and subsequently had surgical procedure in our institution. Women $\geq$18 years old who have agreed to participate in our study and have signed a written informed consent were included in the analysis. Patients who received neoadjuvant treatment and for whom material from surgical specimens was sufficient for AR, estrogen receptor (ER) and progesterone receptor (PR) status evaluation were also included. Neoadjuvant treatment may impair the biomarker analysis once intratumoral heterogeneity and different responses of cellular clones may result in discordant

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

IHC. The exclusion criteria were in situ or microinvasive BC, because this subgroup of carcinomas was not included in the trials that evaluated the role of anti-androgens as a potential therapeutic target. We also excluded multicentric or multifocal tumors to make sure that we analyzed the same tumor by core biopsy and surgical specimen, to evaluate the accuracy properly. The Local Ethics Committee approved the study under the Certificate of Ethical Assessment (CAAE) registration number 60989316.0.0000.5336. Clinical data such as patient age, menopausal status, surgical treatment type, neoadjuvant treatment history, number of fragments obtained from CNB and main pathological findings from both CNB and SS, which included tumor size, tumor grade, and tumor biomarkers expression, were collected through retrospective review of medical records and pathologic reports.

Percutaneous CNB was performed under local anesthesia with a semiautomated biopsy gun with a 14 Gauge (14-G), 10 cm long needle. A mean of 6 core samples per lesion (range 2–11) were obtained. In 58 cases, ultrasound guidance was performed and in 14 cases the guidance was performed by the assistant physician, because the tumor was easily palpable. Fragments of CNB were placed immediately into an adequate volume of 10% buffered formaldehyde. A minimum fixation time of 6 hours and a maximum of 72 hours were ensured, according to the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines[22] prior to tissue processing and paraffin embedding.

The tumor was incised after painting of the surgical margins to facilitate fixation of breast conserving surgery specimens and the mastectomy specimens were inked and cut into 1-cm-thickness slices before fixation. Sampled tissue blocks were fixed in an adequate volume of 10% buffered formaldehyde for between 12 and 24 hours, processed in a Shandon Excelsior ES (ThermoFischer Scientific, Waltham, MA, USA) and then embedded in paraffin. Three-µm-thickness paraffin sections were cut for hematoxylin-eosin staining and IHC analysis.

The evaluation of AR, PR, and ER by IHC was performed using the following validated primary antibodies: anti-AR, clone AR441, dilution 1:100 (Biocare, Monoclonal Mouse Anti-Human Androgen Receptor); anti-ER, clone EP1, ready-to-use (Dako, Monoclonal Rabbit Anti-Human Estrogen Receptor α) and anti-PR, clone 636, ready-to-use (Dako, Monoclonal Mouse Anti-Human Progesterone Receptor). Material was processed in an automated system for immunohistochemical reactions (EnVision Flex/ HRP, Agilent, USA) and IHC analysis was done by a trained pathologist with qualitative and semiquantitative image analysis. The IHC uses labeled antibodies to localize specific activations of antigen proteins in the tissue sections. The qualitative image analysis consists in simple observation of the presence and darkness of specific stains within the tissue, while the semiquantitative method estimates the quantity of proteins on chromogen-labeled immunohistochemical (IHC) tissue sections via computer-aided methods. Material from both CNB and SS were processed and analyzed in the same institution.

The ASCO/CAP guideline[22] was used to define dichotomy – define the cutoff for positivity and negativity, which recommends that ER and PR assays be considered positive if there are at least 1% positive tumor nuclei in the testing sample, in the presence of expected reactivity of internal (normal epithelial elements) and external controls. For AR expression, we used two cutoff values to consider positivity. First: $\geq$ 1% and second: $\geq$ 10%, due to different cutoffs used in previous studies.[23,24]

Breast surgery was categorized as breast conserving surgery or mastectomy. The later includes simple mastectomy (without immediate reconstruction procedure), nipple sparing mastectomy, and skin-sparing mastectomy (both with immediate reconstruction procedure).

Surgical specimens were classified into molecular subtypes according to the 12th St. Gallen International Breast Cancer Conference [4] as: luminal A, luminal B (HER2 negative or HER2 positive), HER2 positive nonluminal (also known as HER2-enriched), and triple negative.

The primary endpoint was to describe the CNB accuracy for the evaluation of AR expression in BC by IHC. The secondary endpoint was to perform the same evaluation for ER and PR expression. Definitive histological diagnosis and biomarkers on SS served as the gold standard in subsequent analyzes.

Sample size calculation was performed with R/R Studio software. It was estimated that, in different Kappa coefficients, 80 patients would provide a margin of error between 0.10 and 0.11 for agreement evaluation. We also took into consideration the consecutive sample available with AR analysis in our institution, a limited sample. Data were presented as mean $\pm$ standard deviation (SD) or frequency and percentage. Kappa coefficients were used to evaluate the intraprocedural agreement. Its interpretation was conducted based on the following parameters: Kappa of 0.01 indicates "poor" agreement; Kappa ranges from 0.01 to 0.20 indicate "slight" agreement; Kappa from 0.21 to 0.40 indicate "fair" agreement; Kappa from 0.41 to 0.60 indicate "moderate" agreement; Kappa from 0.61 to 0.80 indicate "substantial" agreement, and Kappa ranging from 0.81 to 1.00 indicate "almost perfect" agreement.[25] Using SS as the gold standard, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for CNB were calculated for each of the IHC analysis: AR, ER, and PR expression. In all cases, p-values < 0.05 were considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics for Windows version18 (IBM Corp., Armonk, NY, USA).

Results

The study included 72 patients with a mean age of 61 years old; 78% were postmenopausal. The mean number of samples in each CNB was 6 ± 2; 51 (71%) patients underwent breast conserving surgery and 21 (29%) underwent mastectomy. The majority had Luminal A (44%) and Luminal B HER2 negative (40%) tumors. There were no HER-enriched breast carcinomas in our sample. For all patients included

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

independent of BC subtype, the frequency of AR expression was 87.5% using a cutoff point of $\geq$ 10% and 94.4% when the cutoff point was $\geq$ 1%. Patient characteristics are summarized on ►**Table 1**.

The AR expression accuracy was 95.8% using a cutoff $\geq$ 1% (Kappa = 0.645; 95% confidence interval [CI]: 0.272–1.000; $p < 0.001$). A lower accuracy of 86.1% for AR expression was found when using a cutoff $\geq$ 10% (Kappa = 0.365; 95%CI: 0.052–0.679; $p < 0.001$). For hormone receptor status, the accuracy of ER expression was 943% (Kappa = 0.636; 95%CI: 0.309–0.964; $p < 0.001$), and 88.5% for PR expression (Kappa = 0.643; 95%CI: 0.417–0.869; $p < 0.001$), which were similar to AR. ►**Table 2** shows results for the diagnostic capability of CNB to evaluate AR, ER, and PR expression. With a cutoff value $\geq$ 1%, the AR expression in CNB samples had a sensitivity of 98.5%, specificity of 60%, PPV of 97.0%, and NPV of 76.9% in the detection of AR expression in SS. With a cutoff value $\geq$ 10%, the AR expression in CNB samples had a sensitivity of 92%, specificity of 44.4%, PPV of 92% and NPV of 44.4% in the detection of AR expression in SS.

The prevalence of ER expression was 91.3% with the cutoff point $\geq$ 1%. The ER in CNB samples had a sensitivity of 98.4%, specificity of 57.1%, PPV of 95.3% and NPV of 80% in the detection of ER expression in SS. The prevalence of PR expression was 78,5% with the cutoff point $\geq$ 1%. The PR expression in CNB samples had a sensitivity of 94.5%, specificity of 66.6%, PPV of 91.2%, and NPV of 76.9% in the detection of PR expression in SS. ►**Table 3** shows the distribution of AR positivity in CNB and in SS by BC subtypes.

Table 1 Patient characteristics

Parameter	*n* = 72
Age (years old)	61 ± 12
Menopausal status	
Pre- or peri-	16 (22)
Post-	56 (78)
Mean number of core biopsies	6 ± 2
Surgical treatment	
Axillary surgery	
No	1 (1)
Axillary dissection	15 (21)
Sentinel lymph node biopsy	56 (78)
Breast surgery	
Breast conserving surgery	51 (71)
Mastectomy	21 (29)
Histologic type	
Invasive carcinoma NST	62 (86)
Invasive lobular carcinoma	6 (8)
Mucinous carcinoma	3 (4)
Papillary carcinoma	1 (1)
Tumor size in mm	16 [10–24]
Tumor grade	
I	21 (30)
II	35 (49)
III	15 (21)
Molecular subtype	
Luminal A	32 (44)
Luminal B HER2 negative	29 (40)
Triple negative	07 (10)
Luminal B HER2 positive	4 (6)
Pathologic N stage	
N0	46 (69)
N1	13 (19)
N2	2 (3)
N3	6 (9)
Neoadjuvant chemotherapy	17 (23)
Neoadjuvant hormonal therapy	2 (3)

Abbreviations: HER2, human epithelial growth factor receptor 2; NST, no special type.
Data were presented as mean ± standard deviation, median (IQR – interquartile range) or No. (%).

Discussion

In our analysis, we demonstrate that CNB accuracy for AR expression is high, but it decreases when a higher cutoff value ($\geq$ 10%) is used. Five (6.9%) of the 72 patients had AR negative in CNB and positive in SS (2 received neoadjuvant chemotherapy). On the other hand, 5 (6.9%) patients who had positive AR in CNB turned out to have a negative result in the SS (1 received neoadjuvant chemotherapy). Therefore, it is expected that a small number of patients will have discordant results possibly due to intratumoral heterogeneity and exposure to neoadjuvant chemotherapy.[26]

Estrogen receptor and PR expression remain the most important biomarkers in breast cancer over the last decades, even though the definition of the optimal threshold to define HR positivity remain controversial. Recently, the ASCO/CAP guideline for estrogen and progesterone receptor testing in breast cancer was updated [1]. Results with 1 to 10% of cells staining positive should be reported using a new category ("low positive"). The limited data on endocrine therapy benefit in this subgroup tailored the new reporting recommendation, but it should not change the patient eligibility for endocrine therapies. The same issue is important regarding the evaluation of the AR expression.

The AR is a steroid-hormone activated transcription factor belonging to the nuclear receptor superfamily, which also includes the ER and PR. The AR pathway is associated with regulation of normal breast development, as it appears to balance the estrogen-induced cell proliferation, and also with breast tumor carcinogenesis.[27–30] The precise mechanism and clinical implications of AR action in BC remains poorly understood. Several studies support the prognostic role of AR, with different mechanisms dependent on coexpression of HR or HER2 amplification.[31–33] A subset of TNBC (the luminal androgen receptor [LAR]) is dependent upon androgen signaling for growth and therapies that inhibit

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 2 Diagnostic capability of core biopsy using surgical specimens as the gold standard

Core biopsy	Surgical specimen		Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive	Negative					
Estrogen receptor			98.41%	57.14%	95.38%	80.00%	94.29%
$\geq$ 1%	62	02					
$<$ 1%	01	04					
Progesterone receptor			94.55%	66.67%	91.23%	76.92%	88.57%
$\geq$ 1%	52	05					
$<$ 1%	03	10					
Androgen receptor			98.51%	60.00%	97.06%	76.92%	95.83%
$\geq$ 1%	66	02					
$<$ 1%	01	03					
Androgen receptor			92.06%	44.44%	92.06%	44.44%	86.11%
$\geq$ 10%	58	05					
$<$ 10%	05	04					

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 3 Distribution of AR positivity in core biopsy and surgical specimens by molecular subtypes

Molecular subtype	AR core biopsy		AR surgical specimens	
	$\geq$1%	$\geq$10%	$\geq$1%	$\geq$10%
Luminal A ($n = 32$)	32	31	32	31
Luminal B HER2 negative ($n = 29$)	28	25	28	25
Triple negative ($n = 7$)	03	03	04	03
Luminal B HER2 positive ($n = 4$)	04	04	04	04

Abbreviation: HER2, human epithelial growth factor receptor-type 2.

androgen signaling have been tested with promising results.[34–36]

Neoadjuvant therapies have been increasingly used in breast oncology not only as a clinical tool to allow tumor downstaging and less extensive surgeries, but also as a scientific tool to the evaluation of biomarkers and development of targeted therapies. In this case, the systemic therapy that will be offered will depend on disease staging and tumor biomarkers, such as HR evaluated on CNB.

Androgen receptor expression was associated with chemoresistance in TNBC and endocrine therapy resistance in Luminal tumors.[37–41] Mohammed et al. have shown that TNBC AR+ had a lower rate of pathological complete response (pCR, defined as no invasive residual disease in the breast or nodes after neoadjuvant chemotherapy) compared with TNBC AR- (24.1 versus 60%, respectively; $p < 0.01$).[42]

In our study, the prevalence of AR expression was 87.5% in SS using a cutoff $\geq$ 10% and 94.4% with a cut-off $\geq$1%, which are similar to previous data.[28,43] The distribution of AR expression according to BC subtypes using a cutoff $\geq$ 10% were: 96.8% in Luminal A, 86.2% in Luminal B HER2 negative, 42.8% in TNBC, and 100% in Luminal B HER2 positive. A previous study identified AR expression in a range of 50 to 90% in Luminal A and B, 50 to 60% in HER2-positive, and between 20 and 40% in TNBC.[43]

Nonetheless, the AR expression in BC has no standard procedure and evaluation and results are variable depending on the cutoff levels for positivity ($\geq$ 1%, $\geq$ 5% or $\geq$ 10% in IHC),[23] the antibody used in staining, and the methodology (if it was automated qualitative, semiquantitative, or quantitative image analysis. The papers available in the literature are very heterogeneous in this analysis). A recent study presented at ASCO 2020 corroborated the inconsistency in AR evaluation.[20] For example, a cutoff point $\geq$ 30% for AR IHC had the best concordance with LAR subtype ($r = 0.6$; $p < 0.001$).

Two ongoing studies [20,21] evaluating the role of antiandrogen drugs in a neoadjuvant setting selected patients to receive therapy with enzalutamide using AR positivity based on CNB IHC, each study using a different cutoff for AR positivity (1 and 10%), which clearly highlight the lack of consensus in methodology and the potential implications of trial results in practice.

Several studies have shown a high concordance between ER and PR status evaluated on CNB and SS. The concordance found in these studies ranged from 92 to 96% for ER and from 88 to 94% for PR.[44–47] Our analysis of CNB accuracy for ER and PR expression was similar to those of previous reports, 94.2% for ER and 88.5% for PR, which reinforces the quality of IHC methodology applied in our study.

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

The AR expression is usually not evaluated in current clinical practice but the increasing interest in this biomarker as a predictive and therapeutic target corroborates the need of an accurate evaluation and consensus regarding the threshold to define positivity as it may be used for BC classification subtype and therapeutic decision. It is also important to address the potential harm of indicating the use of antiandrogen drugs in false-positive cases. It includes adverse effects (AE) like headache, muscular weakness, and anxiety, mostly grade 1 or 2 (slight to mild), which are usually tolerable for the patients.

The present study has some limitations. We evaluated a relatively small sample size, which impair a sub-analysis in different BC subtypes, and there was a higher proportion of Luminal A and B tumors, which may impact the results of AR expression prevalence. Furthermore, we have included a subgroup of patients who have received neoadjuvant treatment (chemotherapy or endocrine therapy), which may impact biomarker analysis. Nevertheless, our study contributes to the very limited data regarding AR expression accuracy in terms of CNB and SS, also to add validity to our methodology, we performed analysis of ER and PR expression, which showed consistent accuracy results.

Conclusion

Our study shows that evaluation of AR expression by IHC using CNB samples is feasible and has a high accuracy. Using a cutoff $\geq$ 10% for AR expression decreases the agreement between CNB and SS. This finding has implications for the pathological analysis of AR especially in clinical trials evaluating antiandrogen agents.[48]

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

We thank Juliana dos Santos Silva for all support in the Department of Pathology, especially in photography edition.

References

1 Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020; 38(12):1346–1366
2 Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105–2122
3 Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869–10874
4 Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJPanel members. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(08):1736–1747
5 You K, Park S, Ryu JM, Kim I, Lee SK, Yu J, et al. Comparison of Core Needle Biopsy and Surgical Specimens in Determining Intrinsic Biological Subtypes of Breast Cancer with Immunohistochemistry. J Breast Cancer. 2017;20(03):297–303
6 Vera-Badillo FE, Templeton AJ, de Gouveia P, Diaz-Padilla I, Bedard PL, Al-Mubarak M, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(01):djt319
7 Wang C, Pan B, Zhu H, Zhou Y, Mao F, Lin Y, et al. Prognostic value of androgen receptor in triple negative breast cancer: A meta-analysis. Oncotarget. 2016;7(29):46482–46491
8 McGhan LJ, McCullough AE, Protheroe CA, Dueck AC, Lee JJ, Nunez-Nateras R, et al. Androgen receptor-positive triple negative breast cancer: a unique breast cancer subtype. Ann Surg Oncol. 2014;21(02):361–367
9 Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(07):2750–2767
10 Kono M, Fujii T, Lim B, Karuturi MS, Tripathy D, Ueno NT. Androgen Receptor Function and Androgen Receptor-Targeted Therapies in Breast Cancer: A Review. JAMA Oncol. 2017;3(09): 1266–1273
11 Barton VN, D'Amato NC, Gordon MA, Christenson JL, Elias A, Richer JK. Androgen Receptor Biology in Triple Negative Breast Cancer: a Case for Classification as AR+ or Quadruple Negative Disease. Horm Cancer. 2015;6(5-6):206–213
12 Chia K, O'Brien M, Brown M, Lim E. Targeting the androgen receptor in breast cancer. Curr Oncol Rep. 2015;17(02):4
13 Choi JE, Kang SH, Lee SJ, Bae YK. Androgen receptor expression predicts decreased survival in early stage triple-negative breast cancer. Ann Surg Oncol. 2015;22(01):82–89
14 Niméus E, Folkesson E, Nodin B, Hartman L, Klintman M. Androgen Receptor in Stage I-II Primary Breast Cancer -Prognostic Value and Distribution in Subgroups. Anticancer Res. 2017;37(12): 6845–6853
15 Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, et al; Translational Breast Cancer Research Consortium (TBCRC 011) Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. Clin Cancer Res. 2013;19(19):5505–5512
16 Arce-Salinas C, Riesco-Martinez MC, Hanna W, Bedard P, Warner E. Complete Response of Metastatic Androgen Receptor-Positive Breast Cancer to Bicalutamide: Case Report and Review of the Literature. J Clin Oncol. 2016;34(04):e21–e24
17 Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, et al. Enzalutamide for the Treatment of Androgen Receptor-Expressing Triple-Negative Breast Cancer. J Clin Oncol. 2018;36(09):884–890
18 Bonnefoi H, Grellety T, Tredan O, Saghatchian M, Dalenc F, Mailliez A, et al. A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1). Ann Oncol. 2016;27(05):812–818
19 National Institutes of Health (NIH)/U.S. National Library of Medicine. Preoperatice Fulvestrant With or Without Enzalutamide in ER+/Her2- Breast Cancer. NCT02955394. Available online: https://clinicaltrials.gov/ct2/show/NCT02955394 (acessed on 12 june 2020)
20 National Institutes of Health (NIH)/U.S. National Library of Medicine. Enzalutamide and Paclitaxel Before Surgery in Treating

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Patients With Stage I–III Androgen Receptor- Positive Triple-Negative Breast Cancer. NTC02689427. Available online: https://clinicaltrials.gov/ct2/show/NTC02689427 (acessed on 12 june 2020)
21 National Institutes of Health (NIH)/U.S. National Library of Medicine
22 Short-term Preoperative Treatment With Enzalutamide, Alone or in Combination With Exemestane in Primary Breast Cancer (ARB). NTC02676986. Available online: https://clinicaltrials.gov/ct2/show/NTC02676986 (acessed on 12 june 2020)
23 Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28(16):2784–2795
24 Safarpour D, Pakneshan S, Tavassoli FA. Androgen receptor (AR) expression in 400 breast carcinomas: is routine AR assessment justified? Am J Cancer Res. 2014;4(04):353–368
25 Ricciardelli C, Bianco-Miotto T, Jindal S, Butler LM, Leung S, McNeil CM, et al. The Magnitude of Androgen Receptor Positivity in Breast Cancer Is Critical for Reliable Prediction of Disease Outcome. Clin Cancer Res. 2018;24(10):2328–2341
26 Rahim B, O'Regan R. AR Signaling in Breast Cancer. Cancers (Basel). 2017;9(03):21
27 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(01):159–174
28 McNamara KM, Moore NL, Hickey TE, Sasano H, Tilley WD. Complexities of androgen receptor signalling in breast cancer. Endocr Relat Cancer. 2014;21(04):T161–T181
29 Park S, Koo J, Park HS, Kim J-H, Choi S-Y, Lee JH, et al. Expression of androgen receptors in primary breast cancer. Ann Oncol. 2010;21(03):488–492
30 Giovannelli P, Di Donato M, Galasso G, Di Zazzo E, Bilancio A, Migliaccio A. The Androgen Receptor in Breast Cancer. Front Endocrinol (Lausanne). 2018;9(09):492
31 Fioretti FM, Sita-Lumsden A, Bevan CL, Brooke GN. Revising the role of the androgen receptor in breast cancer. J Mol Endocrinol. 2014;52(03):R257–R265
32 Tsang JY, Ni YB, Chan SK, Shao MM, Law BKB, Tan PH, et al. Androgen receptor expression shows distinctive significance in ER positive and negative breast cancers. Ann Surg Oncol. 2014;21(07):2218–2228
33 Jiang HS, Kuang XY, Sun WL, XU Y, Zheng YZ, Liu YR, et al. Androgen receptor expression predicts different clinical outcomes for breast cancer patients stratified by hormone receptor status. Oncotarget. 2016;7(27):41285–41293
34 García X, Elía A, Galizzi L, May M, Spengler E, Vázquez PM, et al. Increased androgen receptor expression in estrogen receptor-positive/progesterone receptor-negative breast cancer. Breast Cancer Res Treat. 2020;180(01):257–263
35 Gucalp A, Traina TA. Targeting the androgen receptor in triple-negative breast cancer. Curr Probl Cancer. 2016;40(2-4):141–150
36 Gerratana L, Basile D, Buono G, De Placido S, Giuliano M, Minichillo S, et al. Androgen receptor in triple negative breast cancer: A potential target for the targetless subtype. Cancer Treat Rev. 2018;68:102–110
37 Dieci MV, Tsvetkova V, Griguolo G, Miglietta F, Mantiero M, Tasca G, et al. Androgen Receptor Expression and Association With Distant Disease-Free Survival in Triple Negative Breast Cancer: Analysis of 263 Patients Treated With Standard Therapy for Stage I-III Disease. Front Oncol. 2019;9:452
38 Asano Y, Kashiwagi S, Onoda N, Kurata K, Morisaki T, Noda Satory, et al. Clinical verification of sensitivity to preoperative chemotherapy in cases of androgen receptor-expressing positive breast cancer. Br J Cancer. 2016;114(01):14–20
39 Santonja A, Sánchez-Muñoz A, Lluch A, Chica-Parrado MR, Albanell J, Chacón JI, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. Oncotarget. 2018;9(41):26406–26416
40 Jongen L, Floris G, Wildiers H, Claessens F, Richard F, Laenen A, et al. Tumor characteristics and outcome by androgen receptor expression in triple-negative breast cancer patients treated with neo-adjuvant chemotherapy. Breast Cancer Res Treat. 2019;176(03):699–708
41 Witzel I, Loibl S, Wirtz R, Fasching PA, Denkert C, Weber K, et al. Androgen receptor expression and response to chemotherapy in breast cancer patients treated in the neoadjuvant TECHNO and PREPARE trial. Br J Cancer. 2019;121(12):1009–1015
42 Rechoum Y, Rovito D, Iacopetta D, Barone I, Andò S, Weigel NL, et al. AR collaborates with ERα in aromatase inhibitor-resistant breast cancer. Breast Cancer Res Treat. 2014;147(03):473–485
43 Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: Correlation between Androgen Receptor Expression and Pathological Response. Asian Pac J Cancer Prev. 2020;21(02):563–568
44 Niikura N, Tomotaki A, Miyata H, Iwamoto T, Kawai M, Anan K, et al. Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21,755 patients from the Japanese breast cancer registry. Ann Oncol. 2016;27(03):480–487
45 Loubeyre P, Bodmer A, Tille JC, Egger J-F, Diebold-Berger S, Copercini M, et al. Concordance between core needle biopsy and surgical excision specimens for tumour hormone receptor profiling according to the 2011 St. Gallen Classification, in clinical practice. Breast J. 2013;19(06):605–610
46 Park SY, Kim KS, Lee TG, Park SS, Kim SM, Han W, et al. The accuracy of preoperative core biopsy in determining histologic grade, hormone receptors, and human epidermal growth factor receptor 2 status in invasive breast cancer. Am J Surg. 2009;197(02):266–269
47 Meattini I, Bicchierai G, Saieva C, De Benedetto D, Desideri I, Becherini C, et al. Impact of molecular subtypes classification concordance between preoperative core needle biopsy and surgical specimen on early breast cancer management: Single-institution experience and review of published literature. Eur J Surg Oncol. 2017;43(04):642–648
48 Tamaki K, Sasano H, Ishida T, Miyashita M, Takeda M, Amari M, et al. Comparison of core needle biopsy (CNB) and surgical specimens for accurate preoperative evaluation of ER, PgR and HER2 status of breast cancer patients. Cancer Sci. 2010;101(09):2074–2079

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Relationship Involving Sexual Function, Distress Symptoms of Pelvic Floor Dysfunction, and Female Genital Self-Image

Relação entre função sexual, incômodo dos sintomas de disfunção do assoalho pélvico e autoimagem genital feminina

Guilherme Tavares de Arruda[1] Gabrielle Peres Paines[2] Bianca Rangel da Silva[2] Lauren Xavier Pairé[2] Hedioneia Maria Foletto Pivetta[2] Melissa Medeiros Braz[2] Janeisa Franck Virtuoso[3]

[1] Departamento de Fisioterapia, Universidade Federal de São Carlos, São Carlos, SP, Brazil
[2] Departamento de Fisioterapia e Reabilitação, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil
[3] Departamento de Fisioterapia, Universidade Federal de Santa Catarina, Araranguá, SC, Brazil

Address for correspondence Guilherme Tavares de Arruda, Universidade Federal de São Carlos, São Carlos, SP, Brazil (e-mail: gui_tavares007@hotmail.com).

Rev Bras Ginecol Obstet 2023;45(9):e542–e548.

Abstract

Objective To assess the relationship involving sexual function (SF), the distress symptoms caused by pelvic floor dysfunction (PFD), and female genital self-image (GSI).

Materials and Methods We assessed the GSI, SF and PFD distress symptoms by the Female Genital Self-Image Scale (FGSIS), the Female Sexual Function Index (FSFI), and the Pelvic Floor Distress Inventory (PFDI-20) respectively. Data were analyzed by multiple linear regression.

Results Among the 216 women (age: 50.92 ± 16.31 years) who participated in the study, 114 were sexually active in the previous 4 weeks. In the total sample ($p < 0.001$; adjusted $R^2 = 0.097$) and among sexually active women ($p = 0.010$; adjusted $R^2 = 0.162$), the distress symptoms caused by pelvic organ prolapse (POP) were related to the GSI. Among sexually active women, sexual desire also was related to the GSI ($p < 0.001$; adjusted $R^2 = 0.126$).

Conclusion The findings of the present study provide additional knowledge about female GSI and suggest that SF and POP distress symptoms should be investigated together with the GSI in the clinical practice.

Keywords
- women
- sexual function
- pelvic floor dysfunction
- genital self-image

received
October 21, 2022
accepted after revision
June 12, 2023

DOI https://doi.org/10.1055/s-0043-1772474.
ISSN 0100-7203.

© 2023. Federação Brasileira 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 relação entre a função sexual (FS), o incômodo provocado pelos sintomas de disfunção do assoalho pélvico (DAP) e a autoimagem genital (AIG) feminina.

Materiais e Métodos A AIG, a FS e incômodo causado pelos sintomas de DAP foram avaliados pela Genital Self-Image Scale (FGSIS), pelo Female Sexual Function Index (FSFI) e pelo Pelvic Floor Distress Inventory (PFDI-20), respectivamente. Os dados foram analisados por regressão linear múltipla.

Resultados Das 216 mulheres (idade: $50{,}92 \pm 16{,}31$ anos) que participaram do estudo, 114 eram sexualmente ativas nas últimas 4 semanas. Na amostra total ($p < 0{,}001$; R^2 ajustado $= 0{,}097$) e entre as mulheres sexualmente ativas ($p = 0{,}010$; R^2 ajustado $= 0{,}162$), o incômodo provocado pelos sintomas de prolapso de órgãos pélvicos (POP) relacionou-se à AIG. Entre as mulheres sexualmente ativas, o desejo sexual também se relacionou à AIG ($p < 0{,}001$; R^2 ajustado $= 0{,}126$).

Conclusão Os achados deste estudo fornecem conhecimento adicional sobre a AIG feminina e sugerem que a FS e o incômodo causado pelos sintomas de POP devem ser investigados juntamente com a AIG na prática clínica.

Palavras-chave

- mulheres
- função sexual
- disfunção do assoalho pélvico
- autoimagem genital

Introduction

Genital self-image (GSI) is defined as the feelings and opinions of an individual about their own genitals,[1] and it is an important component of body image.[2] In women who are dissatisfied with their genitals, the level of anxiety increases when exposing them during sexual activity,[1] which can decrease the sensation of pleasure and generate pain during penetration.[3,4] Therefore, studies indicate the relationship between GSI and sexual function (SF), including its six domains: sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and pain.[1–5] Thus, a worse GSI can interfere with quality of life, generating cases of sexual dysfunction and reducing the frequency of gynecological exams.[4,6]

In women with pelvic floor dysfunction (PFD), including urinary incontinence (UI), pelvic organ prolapse (POP), and anorectal disorders, the SF and GSI can be negatively influenced. This can lead to cases of depression, decreased sexual activity, social isolation, and decreased quality of life.[3,7–9] It seems that distress symptoms, including those caused by PFD, as well as anxiety, and depression, negatively affect female GSI.[8] Among women with POP, there is a relationship involving the SF, the GSI and the severity of the POP, as the concern about showing the prolapsed genitalia to the sexual partner during sexual activity involving penetration and oral sex generates fear and insecurity in the woman, which contributes to a worse SF, especially in terms of sexual desire and satisfaction.[7]

Although studies on the relationship involving the SF, female GSI and PFD is scarce in the literature,[7,8] understanding the impact of the SF and the distress symptoms caused by PFD on female GSI is necessary, because the PFD distress symptoms affect the quality of sex life.[9] Once health professionals have a better understanding of this relationship, they can promote care and treatment strategies aimed at this population. Thus, the aim of the present study was to assess the relationship involving the SF, the PFD distress symptoms, s and female GSI. Therefore, we have hypothesized that the best SF would be related to the best GSI,[2] and that the greater the PFD distress symptoms, the worse the GSI.[7]

Materials and Methods

The present is a cross-sectional and observational study approved by the institutional Ethics Committee (CAAE: 13189919,0,0000,0121; n° 3,437,754) and carried out with a sample of women from three cities in the states of Rio Grande do Sul and Santa Catarina, Southern Brazil. Women were intentionally invited to participate in the study between November 2019 and March 2020. Data collection was interrupted due to the coronavirus disease 2019 (COVID-19) pandemic. We invited women to participate while they waited for a medical appointment at the General Medicine Ward, which were selected due to convenience and because it receives the largest number of people. Trained researchers interviewed the participants face-to-face in a private room. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[10]

Women aged over 18 years who could read and write in Brazilian Portuguese were included. We excluded women who reported symptoms of urinary tract infection in the previous week (pain and burning sensation when urinating), pregnant women, those with ≤ 6 months of puerperium, and wheelchair users.

To characterize the sample, a questionnaire developed by the authors was applied, and it included questions about age, level of schooling, skin color, smoking, alcohol intake, physical activity, number of pregnancies, vaginal deliveries, cesarean sections, abortions, gynecological surgery, and

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

episiotomy. A digital scale and a stadiometer were used to measure weight and height respectively, to calculate the body mass index (BMI).

To evaluate female GSI, we used the Female Genital Self-Image Scale (FGSIS) validated for Brazilian Portuguese, which showed excellent values in terms of internal consistency ($\alpha = 0.81$), intra- (intraclass correlation coefficient [ICC] $= 0.89$) and interobserver (ICC $= 0.83$) reliability in its validation in Brazil. The FGSIS contains 7 items whose scores range from 1 (strongly disagree) to 4 (strongly agree). The total FGSIS score ranges from 7 to 28 points, and the higher the score, the better the GSI.[12]

Sexual function was assessed by the Female Sexual Function Index (FSFI) regarding the previous 4 weeks through 19 items divided into 6 SF domains: sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and pain. This instrument was validated among Brazilian women, with excellent values for internal consistency for the total score ($\alpha = 0.96$) and for test-retest reliability (ICC $= 1.00$). The total FSFI score ranges from 2 to 36 points, and it is the sum of the scores On each domain multiplied by a factor that equalizes the influence of each weighted score on the total score; the higher the score, the better the SF. With the exception of the sexual desire domain, all other domains can only be assessed in women who have been sexually active in the previous four weeks.[13]

To assess the PFD distress symptoms, we used the Pelvic Floor Distress Inventory (PFDI-20) which was validated among Brazilian women with adequate values for internal consistency ($\alpha \geq 0.70$) and test-retest reliability (ICC ≥ 0.70). This instrument contains twenty items divided into three subscales to assess the POP (through the Pelvic Organ Prolapse Distress Inventory, POPDI-6), anorectal (through the Colorectal-Anal Distress Inventory – CRADI-8) and urinary (Urinary Distress Inventory – UDI-6) distress symptoms. The calculation of the score on each subscale is made by the average of the 6 or 8 items multiplied by 25, and the higher the score, the worse the distress symptoms. The total PFDI-20 score is the sum of the scores on each subscale.[14]

Initially, the data were considered to have a non-parametric distribution by the Kolmogorov-Smirnov test. Thus, we used the Spearman correlation coefficient (rho) to assess the correlation regarding the GSI, the SF domains, and the PFD distress symptoms. The strength of the correlation was determined by the Cohen criteria:[15] $r \leq 0.29$–weak correlation; r ranging from 0.30 to 0.49–moderate correlation; and $r \geq 0.50$–a strong correlation. The coefficient of determination (R^2) was used to measure the effect of the correlation; it is presented as a percentage, and it expresses the proportion of variation in one measure that is explained by the variation in another measure. Multiple linear regression with the orward insertion method was used to determine the variable that best predicts the GSI. We presented the regression with the F values (degrees of freedom), *p*-value and adjusted R^2. Variables with $p < 0.05$ in the correlation analysis entered the regression model. In all tests, we adopted $p < 0.05$. All analyzes were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 22.0.

The calculation of the sample power was performed after we obtained the results based on the R^2 of the correlation between the GSI and the POP distress symptoms in the total sample. For this calculation, we used $R^2 = 0.097$, $\alpha = 0.05$, and $n = 216$ in a multiple linear regression model in G*Power 3.1.9.7. Thus, the power of the sample was of 99%.

Results

In total, 262 women participated in the study; however, 35 were excluded due to reports of symptoms or a diagnosis of lower urinary tract infection in the previous week, 10, for not completing the interview, and 1, for being pregnant. Thus, data from 216 women were analyzed. Of these, 114 (52.78%; age: 43.91 ± 14.60 years) were sexually active in the previous 4 weeks. ►**Table 1** shows the characteristics of the total sample (age: 50.92 ± 16.31 years) and of the sexually active subgroup (age: 43.91 ± 14.60 years); their respective GSI values were of 22.37 ± 4.25 and 22.95 ± 3.81 points. Most women in the total sample and in the sexually active subgroup were white (68.98% and 69.30% respectively), non-smokers (90.74% and 89.47% respectively), had not had an episiotomy (55.09% and 59.65% respectively), and did not practice physical activity (58.33% and 56.14% respectively). As for the distress symptoms among the total sample and the sexually active subgroup respectively, the mean values are as follows: POP -10.82 ± 17.17 and 9.10 ± 12.84 points; anorectal -16.07 ± 19.00 and 13.92 ± 16.09 points; urinary $- 19.79 \pm 25.16$ and 16.04 ± 21.08 points; and PFD $- 46.69 \pm 52.44$ and 39.07 ± 39.21 points (►**Table 1**).

►**Table 2** shows the correlations regarding the GSI, the SF and the PFD distress symptoms for the total sample and for the subgroup of sexually active women. Among the sexually active women, except for the lubrication domain, all other domains and the overall SF were significantly correlated with GSI. These correlations were moderate for sexual desire (rho $= 0.338$), arousal (rho $= 0.374$), orgasm (rho $= 0.303$), and overall SF (rho $= 0.377$), and weak for sexual satisfaction (rho $= 0.264$) and pain (rho $= 0.275$). In both samples, the worse the POP (rho $= -0.284$), urinary (rho $= -0.287$) and PFD (rho $= -0.293$) distress symptoms, the worse the GSI, and these correlations are weak. The anorectal distress symptoms had a significant and negative correlation only in the total sample (rho $= -0.202$). The variable that best explained the variation in GSI in the total sample was the PFD distress symptoms (8.6%). Among the sexually active women, overall SF was the variable that best explained the variation in GSI (14.2%).

The POP distress symptoms significantly influenced the GSI in the total sample ($F[1, 214] = 23.898$; $p < 0.001$; adjusted $R^2 = 0.097$). According to **table 3**, in the total sample, for each increase of 1 point in the GSI, there was a decrease of 0.079 points in the POP distress symptoms, a variable that explained 9.7% of the GSI variation. For sexually active women, a significant influence of the POP distress symptoms on the GSI was also observed ($F[2, 111] = 11.918$; $p = 0.010$; adjusted $R^2 = 0.162$). For every one-point increase in the GSI, 1.059 points were increased in sexual desire and 0.067 points were decreased in the POP distress symptoms distress. The

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 1 Characteristics of the study participants

Characteristics	Total sample (n = 216): mean ± SD or n (%)	Sexually active women (n = 114): mean ± SD or n (%)
Age (years)	50.92 ± 16.31	43.91 ± 14.60
Schooling (years)	10.86 ± 5.83	12.02 ± 5.21
Skin color		
White	149 (68.98)	79 (69.30)
Black	17 (7.87)	12 (10.53)
Brown	43 (19.91)	19 (16.67)
Other	07 (3.24)	04 (3.50)
Body mass index (kg/m^2)	27.49 ± 7.04	26.60 ± 6.75
Smoker		
No	196 (90.74)	102 (89.47)
Yes	20 (9.26)	12 (10.53)
Number of pregnancies	2.44 ± 1.84	1.89 ± 1.52
Number of vaginal deliveries	1.40 ± 1.69	0.97 ± 1.39
Number of cesarean sections	0.70 ± 1.00	0.68 ± 0.98
Number of abortions	0.35 ± 0.68	0.26 ± 0.58
Episiotomy		
No	119 (55.09)	68 (59.65)
Yes	95 (43.98)	46 (40.35)
Do not remember	02 (0.93)	0
Physical activity		
No	126 (58.33)	64 (56.14)
Yes	90 (41.67)	50 (43.86)
Genital self-image	22.37 ± 4.25	22.95 ± 3.81
Sexual desire	–	3.55 ± 1.23
Arousal	–	4.21 ± 1.28
Lubrication	–	4.97 ± 1.30
Orgasm	–	4.71 ± 1.40
Sexual satisfaction	–	5.11 ± 1.23
Pain	–	5.09 ± 1.30
Overall sexual function	–	27.65 ± 6.41
Distress symptoms		
Pelvic organ prolapse	10.82 ± 17.17	9.10 ± 12.84
Anorectal	16.07 ± 19.00	13.92 ± 16.09
Urinary	19.79 ± 25.16	16.04 ± 21.08
Pelvic floor dysfunction	46.69 ± 52.44	39.07 ± 39.21

Abbreviation: SD, standard deviation.

variable that most explained the variation in GSI (16.2%) was the POP distress symptoms. The other domains of SF and the PFD distress symptoms did not show a significant relationship ($p > 0.05$) with the GSI in both groups.

Discussion

The study investigated the relationship involving SF, PFD distress symptoms, and GSI. In the multivariate analysis, our findings showed that the POP distress symptoms influenced the GSI of the total sample and of the subgroup of sexually active women, and that sexual desire influenced the GSI among sexually active women. In the bivariate analysis, better scores on the domains of sexual desire, arousal, orgasm, sexual satisfaction, and overall SF were related to better GSI among sexually active women. On the other hand, better GSI was related to worse urinary, POP and PFD distress symptoms in this subgroup of women. In the total sample,

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Table 2 Correlation regarding genital self-image, sexual function, and the distress symptoms of pelvic floor dysfunction

	Genital self-image			
	Total sample (n = 216)		Sexually active women (n = 114)	
	rho	R^2	rho	R^2
Sexual desire	–	–	0.338**	0.114
Arousal	–	–	0.374**	0.140
Lubrication	–	–	0.089	0.008
Orgasm	–	–	0.303*	0.092
Sexual satisfaction	–	–	0.264*	0.070
Pain	–	–	0.275*	0.076
Overall sexual function	–	–	0.377**	0.142
Distress symptoms				
Pelvic organ prolapse	-0.284**	0.081	-0.239*	0.057
Anorectal	-0.202*	0.041	-0.131	0.017
Urinary	-0.287**	0.082	-0.232*	0.054
Pelvic floor dysfunction	-0.293**	0.086	-0.241*	0.058

Notes: R^2, coefficient of determination; rho, spearman correlation coefficient; * $p < 0.05$; ** $p < 0.001$.

Table 3 Multiple linear regression of the predictors of genital self-image of

		Total sample (n = 216)				
Variables	**Non-standardized beta**	**Standardized beta**	**t**	***p***	**R^2**	**ΔR^2**
Distress symptoms						
Pelvic organ prolapse	-0.079	-0.317	-4.898	< 0.001	0.097	0.101
Anorectal	-0.001	–	-0.012	0.991	0.001	–
Urinary	-0.109	–	-1.318	0.189	0.090	–
Pelvic floor dysfunction	-0.125	–	-0.976	0.330	0.67	–
		Sexually active women (n = 114)				
Variables	**Non-standardized beta**	**Standardized beta**	**t**	**p**	**R^2**	**ΔR^2**
Sexual desire	1.059	0.343	3.976	< 0.001	0.126	–
Arousal	0.198	–	1.545	0.125	0.145	–
Orgasm	0.138	–	1.257	0.211	0.118	–
Sexual satisfaction	0.148	–	1.322	0.189	0.125	–
Pain	0.143	–	1.492	0.138	0.140	–
Overall sexual function	0.182	–	1.270	0.207	0.120	–
Distress symptoms						
Pelvic organ prolapse	-0.067	-0.226	-2.617	0.010	0.162	0.051
Urinary	-0.099	–	-1.098	0.275	-0.104	–
Pelvic floor dysfunction	-0.162	–	-1.818	0.072	-0.170	–

Notes: R^2, coefficient of determination; ΔR^2, variation of the coefficient of determination; t, t-test.

better GSI was related to worse urinary, anorectal, POP, and PFD distress symptoms.

The relationship between POP and female GSI has been discussed previously, especially given the severity of the POP.[7] The more severe the POP, the worse the GSI, as the image of an organ coming out of the vagina can be strange for the woman and the sexual partner. This can also interfere with their intimate relationship on the female SF in all domains.[7,8,16] In addition, maintaining a satisfying sex life contributes to physical and mental well-being, which is essential for a positive GSI. Although the GSI can directly influence intimacy, attention, and trust during sexual intercourse,[17] women with negative GSI can maintain an active sex life to avoid personal insecurities, negative emotions, and partner conflicts.[18]

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Although in the present study we did not assess POP severity, its distress symptoms were assessed through a subjective questionnaire, and they influenced the GSI among the subgroup of sexually active women. It is possible that feelings of shame and concern about the genital image are also related to the women's concern that the POP may worsen during sexual activity.[7] Also, in the current study the better the scores on the domains of desire, arousal, orgasm, sexual satisfaction, pain, and overall SF, the better the GSI among sexually active women. Similar results were found in a study[7] conducted in Indonesia, in which a low GSI was related to cases of sexual dysfunction in women with POP. In a study[8] with Israeli women with PFD, the GSI predicted total SF and sexual desire. In the same study,[8] when the SF increased, the GSI also increased.

While female GSI encompasses a woman's feelings about her genitals, the genitalia reflects a person's sexual experience, and it can influence SF. Due to the complexity of the PFD and its negative relationship with GSI, the SF also suffers a negative impact. The aforementioned Israeli study[8] showed that infrequent orgasm, decreased arousal, and increased dyspareunia are present in women with all types of PFD.[8]

The present study is on issues scarcely addressed in the literature regarding female GSI. We separately examined GSI behavior in the subset of sexually active women in different analysis. However, there were some limitations. First, we assessed PFD distress symptoms subjectively by the PFDI-20, which also made it impossible to assess POP severity for the analysis of the relationship with GSI and the inclusion of women diagnosed with PFD. Second, the convenience sample of women waiting for a medical appointment makes it difficult to generalize the results of the present study. Third, we did not investigate the diagnosis of depression or the use of antidepressants, as they may influence women's perception of their body/genital image.[1] Finally, the cross-sectional design does not enable the determination of the cause and effect of the variables investigated. Thus, future studies with longitudinal design should consider the objective assessment of PFD distress symptoms to assess the causes and effects regarding GSI, SF and PFD distress symptoms.

Conclusion

In the present study, female GSI was negatively influenced by the POP distress symptoms and positively influenced by sexual desire. These findings provide additional knowledge about female GSI and suggest that SF and POP distress symptoms should be investigated alongside GSI in the clinical practice. Thus, it will be possible to collect precious information about female GSI and plan the appropriate treatment aimed at sexual dysfunction, since SF is a component of quality of life.

Contributions

GTA: project development, data collection and analysis, and writing of the manuscript. GPP, BRS, and LXP: data collection and writing of the manuscript. HMFP and MMB: project development and writing of the manuscript. JFV: project development, data analysis, and writing of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgements

We would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the grant to conduct the present study (grant code 001).

References

1 Berman LA, Berman J, Miles M, Pollets DAN, Powell JA. Genital self-image as a component of sexual health: Relationship between genital self-image, female sexual function, and quality of life measures. J Sex Marital Ther.. 2003;29(sup1):11–21. Doi: 10.1080/713847124
2 Komarnicky T, Skakoon-Sparling S, Milhausen RR, Breuer R. Genital self-image: associations with other domains of body image and sexual response. J Sex Marital Ther. 2019;45(06): 524–537. Doi: 10.1080/0092623X.2019.1586018
3 Zielinski R, Miller J, Low LK, Sampselle C, DeLancey JO. The relationship between pelvic organ prolapse, genital body image, and sexual health. Neurourol Urodyn. 2012;31(07):1145–1148. Doi: 10.1002/nau.22205
4 Schick VR, Calabrese SK, Rima BN, Zucker AN. Genital appearance dissatisfaction: Implications for women's genital image self-consciousness, sexual esteem, sexual satisfaction, and sexual risk. Psychol Women Q. 2010;34(03):394–404. Doi: 10.1111/j.1471-6402.2010.01584.x
5 Amos N, McCabe M. Positive perceptions of genital appearance and feeling sexually attractive: is it a matter of sexual esteem? Arch Sex Behav. 2016;45(05):1249–1258. Doi: 10.1007/s10508-015-0680-4
6 DeMaria AL, Hollub AV, Herbenick D. Using genital self-image, body image, and sexual behaviors to predict gynecological exam behaviors of college women. J Sex Med. 2011;8(09):2484–2492. Doi: 10.1111/j.1743-6109.2011.02379.x
7 Djusad S, Meutia AP, Tunggadewi SA, Sari YM, Hakim S, Priyatini T, , et al. Genital self-image as predictor of sexual dysfunction in women with pelvic organ prolapse in Indonesia. Womens Health (Lond Engl). 2021;17:17455065211066019. Doi: 10.1177/17455065211066019
8 Handelzalts JE, Yaakobi T, Levy S, Peled Y, Wiznitzer A, Krissi H. The impact of genital self-image on sexual function in women with pelvic floor disorders. Eur J Obstet Gynecol Reprod Biol. 2017;211:164–168. Doi: 10.1016/j.ejogrb.2017.02.028
9 Verbeek M, Hayward L. Pelvic floor dysfunction and its effect on quality of sexual life. Sex Med Rev. 2019;7(04):559–564. Doi: 10.1016/j.sxmr.2019.05.007
10 Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFPD. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. Rev Saude Publica. 2010;44:559–565. Doi: 10.1590/S0034-89102010000300021
11 Felix GAA, Nahas FX, Marcondes GB, Dos Santos AG, de Brito MJA, Ferreira LM. Brazilian Portuguese version of the Female Genital Self Image Scale (FGSIS) for women seeking abdominoplasty. J Plast Reconstr Aesthet Surg. 2017;70(12):1786–1787. Doi: 10.1016/j.bjps.2017.07.007
12 Arruda GT, Silva EV, Somavilla P, Oliveira MCR, Braz MM. Female Genital Self-image Scale (FGSIS): cut-off point, reliability, and validation of measurement properties in Brazilian women. Fisioter Pesqui. 2023;30(e22015823en):1–10. Doi: 10.1590/1809-2950/e22015823en

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

13 Thiel RdoR, Dambros M, Palma PCR, Thiel M, Riccetto CLZ, Ramos MdeF. Tradução para português, adaptação cultural e validação do Female Sexual Function Index. Rev Bras Ginecol Obstet. 2008;30(10):504–510. Doi: 10.1590/S0100-72032008001000005
14 de Arruda GT, Dos Santos Henrique T, Virtuoso JF. Pelvic floor distress inventory (PFDI)-systematic review of measurement properties. Int Urogynecol J. 2021;32(10):2657–2669. Doi: 10.1007/s00192-021-04748-4
15 Cohen J. Statistical power analysis forthe behavioral. Sciences. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988:18–74. Doi: 10.1234/12345678
16 Shah FI, Ramage K, Scime NV, Brennand EA, Walker LM. Pelvic Organ Prolapse Takes Up Space in the Bedroom: A Mixed Method Exploration of the Circular Sexual Response Cycle in Women With Pelvic Organ Prolapse. Female Pelvic Med Reconstr Surg. 2022;28(05):315–320. Doi: 10.1097/SPV.0000000000001123
17 Leavitt CE, Lefkowitz ES, Waterman EA. The role of sexual mindfulness in sexual wellbeing, Relational wellbeing, and self-esteem. J Sex Marital Ther. 2019;45(06):497–509. Doi: 10.1080/0092623X.2019.1572680
18 Poovey K, de Jong DC, Morey K. The Roles of Body Image, Sexual Motives, and Distraction in Women's Sexual Pleasure. Arch Sex Behav. 2022;51(03):1577–1589. Doi: 10.1007/s10508-021-02210-6

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Commentary on "Nonpharmacological Methods to Reduce Pain During Active Labor in a Real-life Setting"

Comentário sobre "Métodos não farmacológicos para reduzir a dor durante o trabalho de parto ativo em um ambiente da vida real"

Roxana Knobel[1] Mariane de Oliveira Menezes[2] Carla Betina Andreucci[3]

[1] Department of Obstetrics and Gynecology, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
[2] Department of Gynecology and Obstetrics, Universidade Estadual Paulista "Júlio de Mesquita Filho," Botucatu, SP, Brazil
[3] Department of Medicine, Universidade Federal de São Carlos, São Carlos, SP, Brazil

Address for correspondence Roxana Knobel, PhD, Department of Obstetrics and Gynecology, Universidade Federal de Santa Catarina, (e-mail: rknobel@gmail.com).

Rev Bras Ginecol Obstet 2023;45(9):e549–e550.

Dear Editor,

We have read with interest the article by Silva et al.[1] The study concluded that in a real-life setting there was no difference in the intensity of labor pain between patients who used nonpharmacological methods during the active phase of labor and those who did not. We appreciate the efforts of the research team, as their study undoubtedly contributes to enhance knowledge about labor and childbirth care. We find it crucial to highlight the widespread use of non-pharmacological methods for pain control in the institution in which the study was conducted, a highly recommended practice[2] that is not frequently available in Brazilian settings.[3]

While we acknowledge the importance of their results, we would like to raise some concerns we believe are relevant for a more accurate understanding of their findings.

Measuring pain is challenging because pain is a personal, subjective, and multifaceted experience. Labor pain presents additional difficulties because of all the emotions and concerns involved in the process, the duration of the painful sensations (which can last several hours), and the increasing intensity of the pain during the progression of dilation and fetus descent through the maternal pelvis.[4,5]

We have considered that one single evaluation using the Visual Analog Scale (VAS) after the delivery would not suffice to measure all multifaceted, variable, and usually long-lasting aspects of labor pain. In most of the studies using VAS included in the Cochrane Systematic Reviews, the tool was applied several times throughout the course of labor and/or before and after the intervention.[6,7] Additionally, although the VAS is widely used, more comprehensive instruments that enable multidimensional assessments of pain and the experience of the parturient are necessary.[5] Furthermore, regarding the interpretation of results, it would be important to consider not only pain, but also satisfaction, the perception of a safe environment, personal achievement, and situation control.[8,9]

Moreover, there is a comparative issue that needs to be taken into consideration. The study compares groups that are not analogous in terms of the time of exposure to non-pharmacological methods. It is important to note that one group had little to no time to become familiar with the resources, and even use them, while the other group had a more extensive opportunity to become familiar with the pain control methods, and a longer active phase period.

Moreover, the abstract and conclusions of the aforementioned study may lead readers to believe that non-pharmacological methods are ineffective, when the measurement of pain was imprecise, and the groups were not comparable. We

received
May 26, 2023
accepted
May 31, 2023

DOI https://doi.org/10.1055/s-0043-1772470.
ISSN 0100-7203.

© 2023. Federação Brasileira 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

believe the misconceptions the conclusion produces might restrict women's access to non-pharmacological methods.

Overall, we believe the collected data depict an interesting quantitative analysis of non-pharmacological methods and factors associated with their use. In the abstract, we suggest the authors clarify that the method chosen to measure pain has limitations, and that the use of non-pharmacological methods to cope with pain should be encouraged.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Silva CBO, Rodrigues KMD, Zoldan C, Nomura RMY, Araujo Júnior E, Peixoto AB. Nonpharmacological Methods to Reduce Pain During Active Labor in A Real-life Setting. Rev Bras Ginecol Obstet. 2023;45(01):3–10

2 World Health Organization Intrapartum care for a positive childbirth experience [Internet]. 2018. 200 p. Available from: http://www.who.int/reproductivehealth/publications/intrapartum-care-guidelines/en/

3 Leal M do C, Pereira APE, Domingues RMSM, Theme Filha MM, Dias MAB, Nakamura-Pereira M, et al. Intervenções Obstétricas durante o trabalho de parto e parto em mulheres brasileiras de risco habitual. Cad Saude Publica. 2014;30(x):S17–S47

4 Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, et al. Pain management for women in labor: an overview of systematic reviews. Cochrane Database Syst Rev Online. 2012;3:9234

5 Blumenstock AK, Mauter D. [Pain assessment during birth: Which assessment tools comprehensibly depict the labor pains during physiological birth?] Schmerz. 2023;x:x

6 Smith CA, Levett KM, Collins CT, Armour M, Dahlen HG, Suganuma M. Relaxation techniques for pain management in labour. Cochrane Database Syst Rev. 2018;3(03):CD009514. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6494625/ cited 2023 May 18 [Internet]

7 Smith CA, Levett KM, Collins CT, Dahlen HG, Ee CC, Suganuma M. Massage, reflexology and other manual methods for pain management in labor. Cochrane Database Syst Rev. 2018;x(03):CD009290

8 Downe S, Finlayson K, Oladapo OT, Bonet M, Gülmezoglu AM. What matters to women during childbirth: A systematic qualitative review. PLoS One. 2018;13(04):e0194906. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194906 cited 2023 May 18 [Internet]

9 Chaillet N, Belaid L, Crochetière C, Roy L, Gagné G-P, Moutquin JM, et al. Nonpharmacologic approaches for pain management during labor compared with usual care: a meta-analysis. Birth. 2014;41(02):122–137. https://onlinelibrary.wiley.com/doi/abs/10.1111/birt.12103 cited 2023 May 18 [Internet]

 © 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

febrasgo
Federação Brasileira das Associações de Ginecologia e Obstetrícia

CC BY

FEBRASGO POSITION STATEMENT

Challenges of breast cancer screening

DOI: https://doi.org/10.1055/s-0043-1775931

Number 9 – September 2023

The National Specialized Commission on Breast Imaging of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. Content production is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- Mammography is the method of choice for breast cancer screening and the only one that demonstrates a reduction in mortality in the population at usual risk.
- The frequency of performing and the age at which mammogram screening begins are a controversial topic in the literature. Data in our country point to a significant portion of breast cancer in women under 50 years of age.
- The Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo), the Brazilian Society of Mastology (SBM) and the Brazilian College of Radiology and Diagnostic Imaging (CBR) agree that mammogram screening should be performed annually by all women from 40 years old.
- In Brazil, there is an unequal distribution of mammography devices in different regions. Screening policies must consider this inequality.
- The vast majority of services in Brazil perform opportunistic screening for breast cancer. The implementation of screening organized by age group and risk stratification can optimize the costs of the public health system.
- High-risk patients need to be screened differently from usual-risk patients. These patients need to have access to breast magnetic resonance imaging (MRI) and start screening at an earlier age.
- The abbreviated MRI protocol for breast cancer screening of high-risk patients may improve their adherence and access to the screening program.
- Breast ultrasound is not a screening method in isolation. However, it plays a role as a complementary method to mammography and MRI in specific scenarios, and replaces MRI in patients with contraindications to the use of this method.
- Dense breasts have low sensitivity for screening mammography.

Recommendations

- Mammography should be performed as the preferred method of breast cancer screening for women at usual risk.
- The subgroup of women between 40 and 50 years of age at usual risk should preferably be evaluated with annual mammography, given the prevalence of breast cancer in this age group in Brazil.
- Ultrasonound should not be used as an isolated method in the screening scenario, but always complementary to mammography or MRI of the breasts. Ultrasound can also be used in patients with contraindications to MRI (allergy to contrast, incompatibility with the device, claustrophobia, presence of a pacemaker or other implanted device).
- Screening of high-risk patients should be done with annual MRI and mammography. When it is not possible to access the MRI exam, ultrasound can be used with reservations related to the examiner's experience in the breast ultrasound exam.
- The abbreviated protocol for breast cancer screening of high-risk patients should be considered in services that perform breast MRI, as it saves time and has shown to be equally effective in published series. Furthermore, this protocol can increase patients' adherence to an annual screening program.
- The implementation of organized screening should be encouraged in breast cancer screening services, since this measure optimizes program costs.

© 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

- The subgroup of patients with dense breasts should be evaluated with caution, considering the low sensitivity of mammography. In these patients, complementary ultrasound can be performed, as well as MRI screening for patients at normal risk and dense breasts (considering the availability of this resource in the various regions of the country).
- Patients at intermediate risk for breast cancer should be evaluated individually for the proposed screening. Some of these patients, especially those with dense breasts or lesions that increase the risk, may be candidates for annual MRI in addition to mammography.

Background

Breast cancer is the most prevalent in Brazil and the leading cause of cancer death among women. As the chance of cure is higher than 95% if diagnosed early, breast cancer screening measures are fundamental. Technological advances in diagnostic methods, such as digital mammography, tomosynthesis and MRI associated with the evolution in drug treatment for breast cancer are identified as the cause of the drop in breast cancer mortality in developed countries. However, breast cancer mortality curves continue to rise in most regions in Brazil, as a reflection of the lack of access to diagnosis and treatment. These data should make us reflect on the challenges of screening, which go beyond the correct use of available methods and include health policies and public management, allowing the early detection of a lesion, its diagnosis and treatment, so that the screening results in reducing mortality from breast cancer. At least 70% of the target population must be involved for an effective cancer screening program, and these numbers reach a maximum of 35% of women in Brazil. Several factors contribute to this scenario, such as: difficult access to the exam (although the number of mammography devices in Brazil is sufficient, they are very unevenly distributed); fear of performing the exam (even with several awareness campaigns, especially the Pink October, information is often not clear, simple and direct as it should be); and, above all, the fact that screening is done opportunistically in Brazil, depending on whether the patient seeks the physician, without active tracking of patients. There are many challenges to the success of a screening program. The first step is to ensure the quality of the image and the mammogram report, which can be achieved through mammogram quality programs. The second step is to ensure quick access to the diagnosis of the suspicious mammographic finding through biopsy. And, finally, provide adequate treatment, avoiding delays and providing access to the most effective drugs. Investments in a more effective screening program to address these issues are high, but are also cost-effective. The diagnosis of initial lesions allows treatment to be de-escalated, whether surgical (more conservative surgeries) or adjuvant (less use of chemotherapy and radiotherapy), consequently increasing the chances of cure for patients.[1-2]

What is the starting age for mammogram for breast cancer screening and how often should mammography be performed for women at usual risk?

According to CBR, SBM and Febrasgo recommendations published in 2012 and updated in 2017, breast cancer imaging screening by age group should occur as follows:

- Women under 40 years old – usual risk; in general, mammography is not recommended in this age group;
- Women between 40 and 74 years old – all women in this age group should have a mammogram on an annual basis, preferably using the digital technique (category A); in places where breast tomosynthesis is available, it should preferably be used;
- Women over 75 years old – screening, preferably with the digital technique, is recommended on an individual basis in this age group; women with a life expectancy greater than seven years and who may undergo cancer treatment, considering their comorbidities, should continue mammographic screening (category D).

What is the starting age for mammogram for breast cancer screening and how often should mammography be performed in high-risk women?

According to the CBR, SBM and Febrasgo recommendations published in 2012 and updated in 2017, guidelines for the subgroup of high-risk patients are:

- Women with a mutation in BRCA1 or BRCA2 genes or first-degree relatives with a proven mutation should undergo annual mammogram screening from the age of 30 (category B);
- Women with a lifetime risk ≥ 20% calculated by one of the mathematical models based on family history should start 10 years before the age of diagnosis of the youngest relative (not earlier than 30 years of age) (category B);
- Women with a history of having undergone chest irradiation between ages of 10 and 30 years should undergo annual mammogram screening from the eighth year after radiotherapy treatment (not earlier than 30 years of age) (category C);

© 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

- Women diagnosed with genetic syndromes that increase the risk of breast cancer (such as Li-Fraumeni, Cowden and others) or affected first-degree relatives should undergo annual mammogram screening after diagnosis (not earlier than 30 years of age) (category D).

Note that personalized mammogram screening is being discussed more and more nowadays. Before starting this screening, it is important that the patient has her risk assessment carried out by the professional assisting her. If it is a high-risk patient, the screening program should be intensified. Clearly, the future is to adjust screening for these populations.[1-2]

Categories

- Category A – Recommendation based on strong scientific evidence, with uniform consensus between CBR, SBM and Febrasgo in strong support of this recommendation.
- Category B – Recommendation based on reasonable scientific evidence, with uniform consensus between the CBR, SBM and Febrasgo in strong support of this recommendation.
- Category C – Recommendation based on little scientific evidence, but with consensus between the CBR, SBM and Febrasgo in strong support of this recommendation.
- Category D – Recommendation based on consensus of experts from CBR, SBM and Febrasgo in support of this recommendation.

What is the role of ultrasound in breast cancer screening?

Breast echography or ultrasound has the challenges of its quality and the expertise of the examiner. This method is not used alone in breast cancer screening neither for usual-risk nor high-risk patients. It can be used in addition to mammography and MRI and to guide biopsies in case of suspicious lesions.[2] In the scenario of screening high-risk patients, ultrasound can be used in places without access to breast MRI, and/or if there is any contraindication to this exam (allergy to contrast, incompatibility with the device, claustrophobia, presence of a pacemaker or other implanted device). The major limitation of ultrasonography is its high false-positive rate and consequently, the need to perform biopsies. This is a highly operator-dependent method with increased effectiveness if performed by a professional experienced in the method and knowledgeable about breast imaging and its nuances in various imaging methods.[2] The cost-effectiveness of performing ultrasound should be analyzed before proposing the use of this method. High breast density can decrease the sensitivity of mammography by 30-48%, as breast cancer is normally radiodense. Furthermore, breast density itself is an independent risk factor for breast cancer. Even though advances were obtained with digital mammography and tomosynthesis, increasing sensitivity from 55% to 70% (digital x conventional), some cancers may still not be detectable in the midst of dense breast parenchyma. In these cases, a complementary exam is recommended for patients with dense breasts at usual risk, and ultrasound is considered the complementary modality of choice. Supplemental screening with ultrasound is an option to increase cancer detection in women with dense breasts at intermediate risk.[2]

What is the role of MRI in screening high-risk populations?

High-risk patients are usually a group of younger patients and consequently, with denser breasts. In this specific subgroup, the use of mammography alone has low sensitivity. Since breast MRI is a functional method and not purely morphological, it does not depend on breast density for its effectiveness. Therefore, the use of MRI in high-risk patients is more effective, alone or in combination with mammography.[3-5] Breast MRI in high-risk women has shown greater sensitivity than mammography as a screening method. The combination of mammography and MRI in this population has greater sensitivity (92%) than MRI alone. Furthermore, combined MRI and mammography are more sensitive (92.7%) than combined ultrasound and mammography (52%). Therefore, MRI is recommended annually in high-risk women. Screening high-risk women with breast MRI is cost-effective and the cost-effectiveness of MRI screening increases with increasing risk of breast cancer, i.e., the greater the risk of the studied population the greater the positive predictive value and specificity of the method.[5]

Final considerations

An optimized screening program is essential to reduce breast cancer mortality in Brazil, plus it is cost-effective. All women should have their breast cancer risk assessment at age 30 to ensure they do not belong to a minority classified as high risk. Every asymptomatic woman at usual risk should undergo annual mammography/tomosynthesis starting at 40 years of age, as studies indicate a reduction in mortality from breast cancer due to early diagnosis, which also offers better surgical treatment options and more effective systemic treatment. Regarding the age to stop screening, the patient's clinical conditions, comorbidities and life expectancy should be considered. Particularly in patients aged 75 years or older who will undergo breast cancer screening. We should discuss the possibility of recall for repeat exams or even to perform additional exams, the risk of undergoing unnecessary (benign) biopsies,

© 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

the risk of an overdiagnosis (diagnosis of a cancer that might never manifest itself clinically), and finally, the anxiety generated by screening. The risks and benefits of screening for each woman should not be discussed in general, but on an individual basis. For high-risk patients and in some special conditions, another complementary diagnostic method (MRI or ultrasound) should be considered.

References

1. Urban LA, Schaefer MB, Duarte DL, Santos RP, Maranhão NM, Kefalas AL, et al. Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para rastreamento do câncer de mama por métodos de imagem. Radiol Bras. 2012;45(6):334-9. doi: 10.1590/S0100-39842012000600009
2. Urban LA, Chala LF, Bauab SP, Schaefer MB, Santos RP, Maranhão NM, et al. Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama. Radiol Bras. 2017;50(4):244-9. doi: 10.1590/0100-3984.2017-0069
3. Kuhl CK, Baltzer P. You get what you pay for: breast MRI screening of women with dense breasts is cost-effective. J Natl Cancer Inst. 2021;113(11):1439-41. doi: 10.1093/jnci/djab120
4. Kuhl CK. Abbreviated breast MRI for screening women with dense breast: the EA1141 trial. Br J Radiol. 2018;91(1090):20170441. doi: 10.1259/bjr.20170441
5. Kuhl CK. Abbreviated Magnetic Resonance Imaging (MRI) for breast cancer screening: rationale, concept, and transfer to clinical practice. Annu Rev Med. 2019;70:501-19. doi: 10.1146/annurev-med-121417-100403

Alexandre Vicente de Andrade[1]
1-Pontifícia Universidade Católica de São Paulo, São Paulo, SP, Brazil.

Clécio Ênio Murta de Lucena[2]
2-Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

Danielle Chambô dos Santos[3]
3-Faculdade de Medicina da Santa Casa de Misericórdia de Vitoria, Vitória, ES, Brazil.

Eduardo Carvalho Pessoa[4]
4-Universidade Estadual Paulista, Botucatu, SP, Brazil.

Fabio Postiglione Mansani[5]
5-Universidade Estadual de Ponta Grossa, Ponta Grossa - PR, Brazil.

Felipe Eduardo Martins de Andrade[6]
6-Hospital Sírio-Libanês, São Paulo, SP, Brazil.

Giuliano Tavares Tosello[7]
7-Universidade do Oeste Paulista, Presidente Paulista, SP, Brazil.

Henrique Alberto Portella Pasqualette[8]
8-Centro de Pesquisas da Mulher Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Henrique Lima Couto[9]
9-Clínica Redimama-Redimasto de Belo Horizonte, Belo Horizonte, MG, Brazil.

Jose Luis Esteves Francisco[10]
10-Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP, Brazil.

Rodrigo Pepe Costa[11]
11-Hospital de Base do Distrito Federal, Brasília, DF, Brazil.

Sandra Regina Campos Teixeira[12]
12-Pontifícia Universidade Católica de São Paulo, Campinas, SP, Brazil.

Thaís Paiva Moraes[13]
13-Rede Mater Dei de Saúde, Belo Horizonte, MG, Brazil.

Agnaldo Lopes da Silva Filho[14]
14-Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

Conflicts of interest: none to declare.

National Specialized Commission on Breast Imaging of the Brazilian Federation of Gynecology and Obstetrics Associations

President:
Eduardo Carvalho Pessoa

Vice-President:
Henrique Lima Couto

Secretary:
Clecio Enio Murta de Lucena

Members:
Alexandre Vicente de Andrade
Danielle Chambô
Fabio Postiglione Mansani
Felipe Eduardo Martins de Andrade
Giuliano Tavares Tosello
Hélio Sebastião Amâncio de Camargo Júnior
Henrique Alberto Portella Pasqualette
Jorge Villanova Biazús
José Luis Esteves Francisco
Rodrigo Pepe Costa
Sandra Regina Campos Teixeira
Thais Paiva Moraes

© 2023. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

BRAZILIAN FEDERATION OF GYNECOLOGY AND OBSTETRICS ASSOCIATIONS
Affiliated to the Brazilian Medical Association

PRESIDENCY
Av. Brigadeiro Luiz Antônio, 3.421, sala 903, São Paulo, SP,
Brasil – 01401-001 – Telefone: 55 (11) 5573-4919

EXECUTIVE SECRETARIAT
Av. das Américas, 8.445, sala 711, Rio de Janeiro, RJ,
Brasil – 22793-081 – Telefone: 55 (21) 2487-6336
www.FEBRASGO.org.br

Instructions to Authors

About the journal

Basic information

The *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO - Revista Brasileira de Ginecologia e Obstetrícia – ISSN 1806-9339) is a monthly scientific publication of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo). It is aimed at obstetricians, gynecologists and professionals in related areas with the purpose to publish research results on relevant topics in the field of Gynecology, Obstetrics and related areas. The journal is open to national and international contributions and accepts submissions in English only.

As a **Vision**, the *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO) intends to become an internationally recognized reference as a journal for research in Gynecology and Obstetrics (GO), becoming one of the world's leading journals in the specialty. The RBGO will be an essential vehicle to disseminate Brazilian and international scientific production and it can become a support reference in the training of undergraduate and postgraduate students and residents and in the scientific improvement of preceptors and researchers in GO.

The RBGO's **Mission** is to contribute to the development of Brazilian research in GO and become a facilitating instrument for the dissemination of research results that can contribute to the improvement of women's care and their quality of life.

The **Values** cultivated by the RBGO in its editions will always be innovation and commitment to quality and respect for **Ethics** in research.

Subareas of knowledge of interest GO:

1. Basic and translational science in ObGyn;
2. Bioethics
3. Contraception;
4. Epidemiology and Statistics in ObGyn;
5. Fetal Medicine;
6. General Gynecology;
7. Gynecological Endocrinology;
8. Gestational Trophoblastic Neoplasia
9. Gynecological Endoscopy;
10. Gynecological Oncology;
11. Gynecological Surgery and Urogynecology;
12. High Risk Pregnancy;
13. Human Reproduction and Assisted Fertilization;
14. Image in ObGyn;
15. Lower Genital Tract Diseases;
16. Mastology;
17. Menopause;
18. Multidisciplinarity and ObGyn;
19. Obstetrics;
20. Pediatric and Adolescent Gynecology;
21. Physiology in ObGyn;
22. Primary care in ObGyn;
23. Quality of Life and ObGyn;
24. Sexually Transmitted Infection;
25. Sexuality;
26. Teaching and Training in ObGyn;
27. Technology;
28. Transgender.

Indexing sources:

- PubMed/Medline;
- Isi – Web of Science (*Emerging Sources Citation Index*);
- Scopus;
- SciELO – *Scientific Electronic Library on-line*;
- Lilacs –Latin American and Caribbean Health Sciences Literature

Intellectual property

(cc) BY All content in the journal, except where otherwise noted, is licensed under a Creative Commons Attribution BY license. **This is a free and open access online journal.**

Sponsors

RBGO does not receive any type of support from funding sources. It is fully maintained by the Brazilian Federation of Gynecology and Obstetrics Associations and receives sponsorships.

Responsibilities of the Editorial Board

Responsibilities of the Editor-in-Chief

- Ensure that the journal is published within the established deadlines.
- Ensure the quality of selected texts and their appropriateness to the interests of readers.
- Establish the policy for manuscript submission, peer review, reviews and resubmission.
- Ensure that articles are reviewed and accepted only on the basis of scientific merit and not on the basis of any influence, whether commercial or personal.
- Maintain transparency throughout the manuscript review and editing process.
- Investigate all complaints and/or doubts related to submissions to the journal, whether accepted or not, and give authors the opportunity to respond whenever necessary.
- Provide support for the selection process of members of the journal's editorial board to define the types of publication and selection criteria for manuscripts accepted by the journal.
- Develop policies and procedures to attract scientific quality manuscripts.
- Examine the digital proofs of the journal, ensuring their quality.
- Adopt procedures protecting ethical issues, conflicts of interest and compliance with the policies adopted by the Brazilian Federation of Gynecology and Obstetrics Associations to which it is affiliated.
- Treat all individuals with respect, impartiality and without discrimination based on gender identity, race, sexual orientation, religion or political beliefs and geographic region.

- Maintain impartiality and clarity in the publication of sponsored supplements and/or with any other type of sponsorship/funding.
- Ensure open access and describe in all articles the Creative Commons license modality adopted by the journal.
- Ensure the organization of all documents related to the journal submission process.

Associate Editor responsibilities

- Read and evaluate the scientific quality of manuscripts received from the Editor-in-Chief.
- Appropriately choose the reviewers of manuscripts under their responsibility.
- Expedite the progress of evaluations made by reviewers and keep the review process within the schedule established by the Editor-in-Chief.
- Analyze the opinions issued by reviewers and assist them in preparing recommendations to authors.

Responsibilities of Reviewers

- Reviewers have the responsibility to review the manuscript objectively and fairly.
- Critically analyze manuscripts by offering suggestions to improve quality and contribute to the decision-making process.
- Maintain the confidentiality of any information provided by the editor.
- Maintain strict confidentiality during the review process. The reviewer must not share information from a manuscript prior to completion of the review and prior to acceptance and publication.
- Inform the editor about any similarity of articles under review to be published or ongoing studies that may be considered plagiarism.
- Disclose any potential conflicts of interest (financial, institutional, collaborative, or other relationships between reviewer and author). If there is a conflict of interest or if the reviewer does not have the necessary expertise, the manuscript must be immediately returned to the editor for the selection of another reviewer.

Responsibilities of the Author(s)

- Attest to the originality of the submitted study and confirm the article is not being considered elsewhere, nor accepted for publication in another journal.
- Ensure approval by the Research Ethics Committee of the institution where the study was developed.
- Participate sufficiently in the work to take public responsibility for its content. Authors' contributions can be made in different ways: conceptual, intellectual, experimental and analytical, and by participating in the writing and review of the manuscript. The final approval of the version to be submitted must be approved and signed by all authors responsible for all aspects of the work (typed or printed name is not acceptable).
- Ensure that studies including humans or animals comply with national and international requirements and guidelines (Declaration of Helsinki [2013], Declaration of Human and Animal Rights [Unesco, 1978]). This information must be stated in the manuscript, and the protocol number or exemption status of approved protocols must be stated in the manuscript at the time of submission for review.
- Inform the registration number referring to the research approval report at the National Council for the Control of Animal Experimentation (Concea). Studies involving animal experiments must comply with Law No. 11.794, of October 8, 2008, which establishes procedural rules for the scientific use of animals in Brazil. International manuscripts must submit local ethical documentation to proceed with the submission process. Any manuscript involving animal or human experiments submitted without proof of approval by institutional or local research committees will not be reviewed and will be returned to authors.
- Inform potential conflicts of interest in a written statement signed by all authors.
- Inform the journal editor when a major error is found in the study and provide all necessary information for publication correction, errata and retraction.
- Provide data records associated with the study when requested by the editor.
- Provide the definitive list of authors and their order at the time of original submission, containing the author registration with the respective Open Researcher and Contributor Identifier (ORCID) at https://orcid.org/signin. Any addition, removal or rearrangement of authors' names in the authorship list should be done only before the manuscript is accepted and only if approved by the journal editor. If that is the case, the corresponding author must obtain agreement of the other authors in writing, justifying the reason for alteration (addition, removal or rearrangement), and send the request by letter or e-mail. The editor will consider adding, deleting or rearranging authors after acceptance of the manuscript only in exceptional circumstances. If the manuscript has already been published in an online edition, any requests approved by the editor will result in rectification.
- Meet the deadlines for corrections and clarifying answers to questions made by reviewers.
- Use language that promotes social inclusion. The manuscript content must respect readers and not contain anything that could imply that an individual is superior to another because of age, sex, race, ethnicity, culture, sexual orientation, disability or health condition. Writing must be free from prejudice, stereotypes, slang, references to the dominant culture and/or cultural assumptions. The recognition of diversity is sensitive to differences, promotes equal opportunities and expresses respect for all people.

Scientific misconduct

Presenting results of animal or clinical research conducted without proper approval and written informed consent, as set out above, is considered unethical scientific behavior. Duplicate publication or when results are falsified, fabricated or plagiarized is also considered unethical. The RBGO allows the partial presentation of data from a manuscript in another means of dissemination, although in these cases, the author must acknowledge the previous presentation and identify the source. The citation of the original publication is essential in the disclosure. Splitting data, analysis and presentation of the same study into smaller units (practice called "salami slicing") should be avoided. Thus, the author must acknowledge in his or her cover letter any similar publications or manuscripts that have been submitted for publication based on the same material.

Investigation of scientific misconduct

Submission of an article implies that the work described has not been previously published, except in the form of an abstract, published lecture or academic thesis. Scientific misconduct may be suspected during the manuscript review process by reviewers. Thus, the RBGO may use additional resources to investigate the author's unethical conduct in order to certify the originality or plagiarism of the article (examples: Crossref Similarity Check, iThenticate and others). All suspected cases will be investigated initially by the Editor-in-Chief and by the Ethics and Professional Defense Committee of the Brazilian Federation of Gynecology and Obstetrics Associations. The author will be notified in writing of the allegations and asked to provide useful information to the investigation, including access to all original data, notes and copies of previous publications. The author's affiliation may also be contacted.

Retraction policy

The retraction policy of the RBGO is based on COPE's Retraction guidelines for advice and guidance for editors (DOI: https://doi.org/10.24318/cope.2019.1.4).

Editors will consider a publication retractable in case:

- It is plagiarism;
- It reports unethical research;
- It contains material or data without authorization for use;

- The copyright has been infringed or there is any other serious legal issue (e.g. defamation, privacy);
- There is clear evidence that results are unreliable, either as a result of a major error (e.g. miscalculation or experimental error) or as a result of fabrication or falsification of data and/or images, for example;
- Findings have been previously published elsewhere without proper attribution to prior sources or disclosure to the Editor, permission for republication or justification (i.e. cases of redundant publication);
- It has been published solely based on a compromised or manipulated peer review process;
- The author(s) have not disclosed a major conflict of interest which, in the Editor's opinion, may have unduly affected the interpretations of the work or the editors' and reviewers' recommendations.

Retraction notices must:

- Be linked to the retracted article in all versions printed or online;
- Clearly identify the retracted article (e.g. including the title and authors in the retraction header or citing the retracted article);
- Be clearly identified as a retraction (i.e. distinct from other types of correction or comment);
- Be published promptly to minimize harmful effects;
- Be freely available to all readers (i.e. open access or available only to subscribers);
- Inform who is removing the article;
- Indicate the reason(s) for the retraction;
- Be objective and factual and avoid aggressive language.

Retractions are generally inappropriate if:

- Authorship is disputed, even though there is no reason to doubt the validity of findings;
- The main conclusions of the work are still reliable and the correction can sufficiently address the errors or concerns;
- An editor has inconclusive evidence to support the retraction or is awaiting additional information, such as from an institutional investigation;
- Authors' conflicts of interest were reported to the journal after publication, but in the editor's opinion, they likely did not exert influence in interpretations, recommendations or conclusions of the article;

The RBGO will follow the flowchart suggested by COPE (DOI:**https://doi.org/10.24318/cope.2019.2.7**) to track an undisclosed conflict of interest in a published article.

Receipt of articles deposited in preprint repositories

Manuscripts submitted and coming from preprint repositories will necessarily be peer-reviewed and receive the definitive DOI issued by the RBGO if approved. Manuscripts submitted for analysis by the RBGO editorial board cannot contain references to articles that have not been published in scientific journals and that have fully complied with the peer review process.

Instructions to authors for manuscript submission

The material sent for analysis must not have been submitted simultaneously for publication in other journals or previously published. The selection of manuscripts for publication involves evaluation of originality, relevance of the topic, quality of the methodology used, its updating and whether it is appropriate and interesting to readers, in addition to adequacy to the editorial standards adopted by the journal.

Evaluation of manuscripts

Manuscripts in English submitted to the journal are received by the editorial office that checks the mandatory documentation and analyzes if the editorial rules contained in instructions to authors have been complied with. If the process is in accordance, the manuscript is sent to the editor-in-chief, who will make an initial merit assessment of the submitted manuscript. If the editor-in-chief concludes the work is in favorable scientific and technical conditions, the manuscript will be forwarded to associate editors, who, in turn, will appoint reviewers (double mind process) to evaluate the work. The reviewers' opinions and the editor's instructions will be sent to authors so they are aware of the editor's decision, criticism and eventual changes to be introduced. Authors must resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections must be highlighted in the text (marked in yellow). In cases of disagreement with the suggestions, the authors must include the justifications and observations in comment balloons. Authors must be assertive and punctual with the inquiry, supporting the hypothesis with references. **IMPORTANT!** Authors must comply with the deadlines. Failure to do so will result in a delay in their publication or even in the shelving of the process. Authors can request the suspension of the process and withdrawal of the work at any point in the process of analyzing and editing the text, except when the manuscript is accepted for publication. The concepts and statements contained in the articles are the responsibility of the authors.

Preparing a manuscript for submission

Mandatory documents for submission

When submitting a manuscript to the RBGO, documents listed below must be attached to the ScholarOne submission platform. Note that failure to submit or incomplete documentation will result in cancellation of the submission process. Mandatory documentation for online submission:

- Authorization for copyright transfer signed by all authors (scanned and attached) – **Template**;
- In accordance with chapter XII.2 of CNS Resolution No. 466/2012, in Brazil, research involving human beings needs to inform the registration number referring to the Certificate of Presentation for Ethical Assessment (CAAE) or the number of the research approval report (CEP/Conep) in the Research Ethics Committee. In the case of manuscripts involving animal experimentation, it must be indicated if it complies with Law No. 11.794 of 8 October, 2008, which establishes procedures for the scientific use of animals in Brazil, informing the registration number referring to approval of the research at the National Council for the Control of Animal Experimentation (Concea). International manuscripts must submit local ethical documentation to proceed with the submission process;
- The cover letter must be written with the purpose of justifying the publication. Authors must be identified with the respective Open Researcher and Contributor Identifier (ORCID), the authors' affiliation institution and the intention of publication. The qualification/title of the corresponding author must be included.

Title page:

- Title of the manuscript in English with a maximum of 18 words;
- Full name of authors without abbreviations (include a maximum of 8 authors per article, except in the case of multicenter studies, consensus, guidelines and position statements of societies or research groups);
- Corresponding author (full name, qualification/title and contact e-mail);
- Institutional affiliation of each author. Example: Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil (Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil);
- Conflicts of interest: authors must inform any potential conflict of interest, whether of resources, political, economic for developing the study or of intellectual property;
- Acknowledgments: acknowledgments are restricted to people and institutions that contributed in a relevant way to the development of the study. Any financial support, whether from funding agencies or private companies, must be mentioned in the **Acknowledgments** section. For Brazilian authors, RBGO requests that funding

from the agencies Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes), or any other state research support agency (eg. Fapesp), should be mentioned with the number of the research process or grants awarded;

- Contributions: according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on three conditions that must be fully met: (1) substantial contributions to conception and design, data collection or analysis and interpretation of data; (2) article writing or relevant critical review of intellectual content; and (3) final approval of the version to be published.

Manuscript

The Revista Brasileira de Ginecologia e Obstetrícia(RBGO) publishes the following categories of manuscripts:

- **Original articles:** full prospective, experimental or retrospective works.
- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
- **Letters to the Editor:** Must address editorial matters or not, but present relevant information to readers. The letters may be summarized by the editorial board, always keeping the main points. In the case of criticism or comments on published works, the letter is sent to the authors of the cited article so their response can be published simultaneously. All data presented in the letter must be fully citable and cited in the supporting reference list (unpublished data should not be described in the letter).
- **Editorial:** By invitation of the editor only.

OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

When writing a scientific article, the researcher must pay attention to the title of the manuscript. The title is the business card of any publication. It should be prepared with great care and preferably be written only after the article is finished. A good title adequately describes the content of the manuscript. It is usually not a sentence, as it does not contain the subject or arranged verbs and objects. **Abbreviations, chemical formulas, excess of adjectives, names of cities and institutions, among others, should be avoided in titles.** The titles of manuscripts submitted to the RBGO must contain a maximum of 18 words.

Abstract

The abstract must provide the context or basis for the study, establish the objectives, basic procedures of the methodology used, main results and main conclusions. It should emphasize new and important aspects of the study or observations. As abstracts are the only substantive part of the article that is indexed in many electronic databases, authors must ensure they accurately reflect the content of the article and highlight the research contribution/innovation to the topic. Abbreviations, symbols and references should not be used in the abstract. In case of original articles from clinical trials, the authors must inform the registration number at the end of the abstract.

1. Abstract: for original articles

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

Objective: Retrospective on the topic and the question posed by researchers.

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

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

Conclusion: What was the conclusion; the answer to the question asked.

2. Abstract: for systematic review articles

Abstracts of systematic review articles submitted to the RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: State the main objective of the article.

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

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

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

Data synthesis: Present the main results of the review and the methods employed to obtain them.

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

It must contain the essence of the article, covering the purpose, method, results and conclusions or recommendations. Expose enough detail so readers can decide on the convenience of reading the entire text (word limit: 150).

NOTE: An abstract in Portuguese may be optionally added by the authors.

Keywords

The keywords of a scientific work indicate the thematic content of the text they represent. The identification of thematic content, the indexing of the work in databases and the quick location and retrieval of the content are considered the main objectives of the mentioned terms. The keyword systems used by the RBGO are DeCS (Health Sciences Descriptors – Lilacs Indexer) and MeSH (Medical Subject Headings – MEDLINE-PubMed Indexer). Five descriptors that represent the work must be chosen on these platforms.

Manuscript body

Manuscripts submitted to the RBGO should have a maximum of 4,000 words. Tables, charts and figures in the **Results** section, as well as references, are not counted.

Introduction

This part of the article prepares the reader to understand the investigation and the justification for its development. It should include the current state of knowledge on the subject, offering only strictly relevant and up-to-date references. The content to be reported in this section should provide context or background for the study, that is, the nature of the problem and its importance, and state the specific purpose, research objective, or hypothesis tested in the study or observation. The research objective is the final part of the introduction and both the main and secondary objectives must be clear and any analyzes in a pre-specified subgroup must be described. The introduction should not include data or conclusions from the work being reported.

Methods

The **Methods** section of a scientific work aims to present the study in a clear and concise way so that it is understandable and can be replicated. It should state how, when and where the study was developed. The

method comprises the material and procedures adopted in the study in order to be able to answer the main question of investigation. The **Methods** section should be structured starting with the type of study design, to show if it is appropriate to achieve the research objective; the research setting (the place and time in which it was developed); the data collection; the intervention to be performed and evaluated (if any) and also the alternative intervention; the statistical methods used and the ethical aspects of research.

NOTE: the RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, aimed at improving the presentation of research results. Check related interactive guides:

Randomized clinical trial:

http://www.equator-network.org/reporting-guidelines/consort/

Systematic reviews and meta-analyses:

http://www.equator-network.org/reporting-guidelines/prisma/

Observational studies in epidemiology:

http://www.equator-network.org/reporting-guidelines/strobe/

Qualitative studies:

http://www.equator-network.org/reporting-guidelines/srqr/

Results

The purpose of the **Results** section is to show the findings of the research. These are original data obtained and synthesized by the author in order to provide an answer to the question that motivated the investigation. Results should be presented in a logical sequence in the text, tables and illustrations, mentioning the most important findings first. Whenever appropriate, the statistical significance of results should be indicated. All information in tables or illustrations should not be repeated in the text, and only important observations should be emphasized or summarized. Additional or supplementary materials and technical details may be placed in an appendix, accessible via a link, that will not interrupt the flow of the text. When data are summarized in the **Results** section, numerical results must be presented not only in derived values (e.g. percentages) but also in absolute values from which the derived values were calculated, and specify the statistical methods used to analyze them. Only the tables and figures necessary to explain the argument of the work and to assess its basis should be used. When scientifically appropriate, analyzes of data with variables such as age and sex should be included. The limit of a maximum of five tables, five charts or five figures must not be exceeded. Tables, charts and/or figures must be included in the body of the manuscript and do not account for the requested limit of 4,000 words. For clarification on the resolution of figures, please check https://www.ncbi.nlm.nih.gov/pmc/pub/filespec-images/.

Discussion

In the **Discussion** section, new and important aspects of the study and the conclusions derived from them should be emphasized. Data or other information presented in the **Introduction** or **Results** sections should not be repeated in detail. In experimental studies, it is useful to start the discussion with a brief summary of the main findings, compare and contrast the results with those of other relevant studies, state the limitations of the study and explore the implications of the findings for future research and clinical practice. Claiming precedence and alluding to incomplete works should be avoided, as well as discussing data not directly related to the results of the research presented. New hypotheses may be proposed when justified, but they must be clearly qualified as such. The last paragraph of the **Discussion** section should include the information of the study that relatively contributes to new knowledge.

Conclusion

The **Conclusion** section is intended to relate the conclusions to the objectives of the study. Authors should avoid unsubstantiated statements and conclusions not appropriately supported by their data. In particular, authors should avoid making claims about economic benefits and costs unless their manuscript includes economic analysis and appropriate data.

References

In manuscripts submitted to the RBGO, authors must number references in order of entry in the work and use these numbers for citations in the text. An excessive number of references should be avoided, selecting the most relevant for each statement and giving preference to more recent works. Do not use citations of difficult to access, such as abstracts of works presented at conferences, theses or publications with restricted circulation (not indexed). Cite primary and conventional references (articles in scientific journals and textbooks). References such as "unpublished observations" and "personal communication" should not be used. Authors' publications (self-citation) should only be used if there is a clear need and they are related to the topic. In this case, include only original works published in regular journals (do not cite chapters or reviews) among the bibliographic references. The number of references should be limited to 35, except for review articles. Citations of references must be placed after the period in superscript, without space after the last word (sequential and numerical citations). Authors are responsible for the accuracy of data contained in the references. To format your references, check **Vancouver:** https://www.ncbi.nlm.nih.gov/books/NBK7256/.

Submission of manuscripts

Articles must be submitted electronically, according to instructions available on the website: http://mc04.manuscriptcentral.com/rbgo-scielo.

Brazilian Journal of Gynecology and Obstetrics

Address: Av. Brigadeiro Luís Antônio, 3.421, sala 903, Jardim Paulista – 01401-001 – São Paulo, SP, Brazil
Telephone: + 55 (11) 5573-4919
E-mail: editorial.office@febrasgo.org.br

Thieme homepage

https://www.thieme-connect.com/products/ejournals/issue/10.1055/s-006-33175

SciELO homepage

https://www.scielo.br/j/rbgo/

Febrasgo homepage

https://www.febrasgo.org.br/pt/revista-rbgo