Ultrasound Obstet Gynecol 2021; **58**: 943–953
Published online in Wiley Online Library (wileyonlinelibrary.com).

Letters to the Editor

Vaginal progesterone in twin gestation with a short cervix: revisiting an individual patient data systematic review and meta-analysis

We write to inform the Editors and the readership of *Ultrasound in Obstetrics & Gynecology* (UOG) that the article by El-Refaie *et al.*[1], assessing the value of vaginal progesterone for the prevention of preterm birth in asymptomatic women with a twin gestation and a sonographic short cervix, was retracted on 27 July 2021 by the Editor-in-Chief of *Archives of Gynecology and Obstetrics*, Prof. Olaf Ortmann[2]. This article had been included in a systematic review and meta-analysis of individual patient data (IPD) that we published in UOG in 2017[3]. Herein, we describe what has occurred and the implications to the conclusions of our article.

The matter emerged after allegations of scientific misconduct were filed with Prof. Ortmann. The published paper stated that the study was conducted at the Mansoura University Hospital and in private practice settings in Mansoura, Egypt, and that the study protocol had been reviewed and approved by the Institutional Review Board (IRB)[1]. In May 2020, in response to a communication from some of the authors of the IPD meta-analysis, the authors of the trial and Prof. Abdelmageed Mashaly, the Chair of the Department of Obstetrics and Gynecology at Mansoura University Hospital at the time the protocol was approved and the study was conducted, represented that the study had been approved and endorsed by the Department and reviewed and approved by the IRB of the Mansoura Faculty of Medicine (copy of email communication and IRB approval document are available from the corresponding author on request).

On 23 June 2020, Prof. Ortmann indicated that an investigation had been opened at Mansoura University in February 2020 given the allegations of scientific misconduct and that, during the ongoing investigation, the authors had described the regulatory review process and had submitted documents that met the requirements of the publisher. Specifically, Prof. Ortmann stated: '*One critical point [raised in the allegation] was that ethical approval for the study did not exist. The investigators at Mansoura University describe[d] the regulatory process and provided documents. These are in accordance with the requirements of Springer [N]ature. We have followed the e-mail communication, which in the meanwhile is highly complex. Myself and the Research Integrity Team at Springer [N]ature treat this matter with high priority. We decided to wait for the final result of the investigation at Mansoura University*.' (copy of email communication is available from the corresponding author on request).

Prof. Ortmann and the publisher have since changed their minds about the ethical approval and retracted the paper. The Notice of Retraction[2] states that '*Contrary to the statement in the article, the authors did not obtain approval from a research ethics committee before conducting the randomized control trial . . .* '. The authors did not agree with the retraction. The investigation at Mansoura University is still in progress.

The paper published by our group in UOG is a systematic review and meta-analysis of IPD addressing the effect of vaginal progesterone in patients with a twin gestation and a short cervix[3]. The study was registered in PROSPERO (The International Prospective Register of Systematic Reviews) and identified previous randomized controlled trials (RCTs) that had addressed this question. The study by El-Refaie *et al.*[1] met the eligibility criteria and was included. Our study described the methodology of the IPD meta-analysis, assessment of bias, planned sensitivity analysis and other details. We planned and carried out a sensitivity analysis by excluding studies at high risk of selection bias or performance and detection biases[3]. The study by El-Refaie *et al.*[1] did not have a placebo group and, therefore, it was considered to be at high risk for performance and detection biases. The results of a sensitivity analysis excluding the trial of El-Refaie *et al.*[1] were reported in the results section of our meta-analysis[3]. Moreover, the contribution of the trial by El-Refaie *et al.*[1] to the conclusions of the meta-analysis, the limitations of the study and the implications for practice were described in the abstract and in the Discussion of our study[3].

An itemized description of the relevant statements in our paper is presented below. In addition, the original paper, as published in UOG, is provided in Appendix S1, and the relevant text is highlighted in yellow for the convenience of the interested reader.

(1) The Abstract indicated that one study provided 74% of the total sample size in the IPD meta-analysis. This was the study by El-Refaie *et al.*[1] (page 303).
(2) In the Methods section, we described the plan to carry out sensitivity analyses to explore the effect of trial quality assessed by allocation concealment, random sequence generation (considering selection biases) and blinding (considering performance and detection biases). In the Methods section, we stated that sensitivity analyses would be performed only for the primary outcome of preterm birth < 33 weeks of gestation and for the secondary outcome of neonatal death (page 306).
(3) In the Results section, we described that the study by El-Refaie *et al.*[1] was considered at high risk of performance and detection biases (page 307), and we reported the results based on the entire dataset and after excluding the trial of El-Refaie *et al.*[1] (page 309): '*When the sensitivity analysis was restricted to the five trials with adequate blinding of patients, clinical*

staff and outcome assessors[64–68], the effect of vaginal progesterone on the reduction in the risk of preterm birth < 33 weeks' gestation and neonatal death was non-significant (RR, 0.77 (95% CI, 0.48–1.24) and 0.56 (95% CI, 0.21–1.48), respectively). However, it should be noted that the sensitivity analyses did not substantially change the magnitude and direction of effect sizes obtained in the overall analyses. Sensitivity analyses based on allocation concealment and random sequence generation were not performed because there were no trials at unclear or high risk of bias for these domains.'

(4) Table 4 (page 310) described the risk of adverse perinatal outcomes after administration of vaginal progesterone. Composite neonatal morbidity/mortality was significantly lower after the administration of vaginal progesterone, assuming independence between twins (relative risk (RR), 0.57 (95% CI, 0.36–0.93)) and after adjustment for non-independence between twins (adjusted RR, 0.61 (95% CI, 0.34–0.98)). These calculations were based on five trials and did not include data from the study by El-Refaie *et al.*[1], as noted in the table. The source of the data for the calculations is provided in the table (references 64–68).

(5) The Discussion highlighted the limitations of our IPD meta-analysis and the contribution of the trial by El-Refaie *et al.*[1] as follows (page 312): '*Second, 74% of the total sample size of the IPD meta-analysis was provided by one study[69], which included women with a CL [cervical length] between 20 and 25 mm and was not placebo-controlled. However, it should be highlighted that assessment and measurement of most outcomes included in our review are considered objective in nature, and therefore not likely to be influenced by lack of blinding[49]. It is noteworthy that estimates of pooled RRs obtained after excluding this study were not significantly different from those obtained in the overall analyses. Moreover, the significant 39% reduction in the risk of composite neonatal morbidity and mortality associated with vaginal progesterone administration was obtained without including data from the study by El-Refaie et al.[69] in the meta-analysis.*'

(6) When discussing the implications for practice and research (page 312), we stated the following: '*Although the results of our meta-analysis appear promising, further research is required before conclusive advice can be provided with regard to the benefits of using vaginal progesterone in women with a twin gestation and a short cervix. Evidence from this updated IPD meta-analysis and three ongoing RCTs comparing vaginal progesterone with placebo (NCT02697331 and NCT02518594) or no treatment (NCT02329535) in ~750 women with a twin gestation and a sonographic short cervix will help to determine whether vaginal progesterone can be recommended to these patients with the aim of preventing preterm birth and improving perinatal outcomes.*'

In conclusion, we have already reported a sensitivity analysis of the results of our IPD meta-analysis excluding the trial by El-Refaie *et al.*[1] and explained, in detail, the reasons for this analysis and its implications. UOG has linked this Letter to the Editor and its supplementary material to the article[3]. We will provide an update of our IPD meta-analysis on the effects of vaginal progesterone in twin gestations with a short cervix excluding the study of El-Refaie *et al.*[1].

R. Romero[1,2,3,4,5]*, A. Conde-Agudelo[1], L. Rode[6,7], M. L. Brizot[8], E. Cetingoz[9], V. Serra[10,11], E. Da Fonseca[12], A. Tabor[6,13], A. Perales[11,14], S. S. Hassan[15,16,17] and K. H. Nicolaides[18]

[1]*Perinatology Research Branch,* Eunice Kennedy Shriver *National Institute for Child Health and Human Development, National Institutes of Health, United States Department of Health and Human Services, Bethesda, MD, and Detroit, MI, USA;*
[2]*Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA;*
[3]*Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA;*
[4]*Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA;*
[5]*Detroit Medical Center, Detroit, MI, USA;*
[6]*Center of Fetal Medicine and Pregnancy, Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark;*
[7]*Juliane Marie Centre, Department of Obstetrics, Copenhagen, Denmark;*
[8]*Department of Obstetrics and Gynecology, Pontifical Catholic University of São Paulo School of Medical and Health Sciences, São Paulo, Brazil;*
[9]*Department of Obstetrics and Gynecology, Zeynep Kamil Women and Children Diseases Education and Research Hospital, Uskudar, Istanbul, Turkey;*
[10]*Maternal–Fetal Medicine Unit, Instituto Valenciano de Infertilidad, University of Valencia, Valencia, Spain;*
[11]*Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia, Spain;*
[12]*Departamento de Obstetrícia e Ginecologia, Hospital do Servidor Publico Estadual 'Francisco Morato de Oliveira' and School of Medicine, University of São Paulo, São Paulo, Brazil;*
[13]*University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark;*
[14]*Department of Obstetrics, University Hospital La Fe, Valencia, Spain;*
[15]*Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA;*
[16]*Office of Women's Health, Integrative Biosciences Center, Wayne State University, Detroit, MI, USA;*
[17]*Department of Physiology, Wayne State University School of Medicine, Detroit, MI, USA;*

[18]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK*
**Correspondence.*
(e-mail: prbchiefstaff@med.wayne.edu)
DOI: 10.1002/uog.24765

Acknowledgments

This article was supported, in part, by the Perinatology Research Branch, Division of Obstetrics and Maternal–Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services (NICHD/NIH/DHHS) and, in part, with federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C. R.R. has contributed to this work as part of his official duties as an employee of the United States Federal Government.

References

1. El-Refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet* 2016; **293**: 61–67.
2. El-Refaie W, Abdelhafez MS, Badawy A. Retraction Note: Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet* 2021; **304**: 1113.
3. Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, Serra V, Da Fonseca E, Abdelhafez MS, Tabor A, Perales A, Hassan SS, Nicolaides KH. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol* 2017; **49**: 303–314.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Individual patient data meta-analysis published in *Ultrasound in Obstetrics & Gynecology*[3], with relevant sections reviewed in detail in this Letter to the Editor highlighted in yellow

