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

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We write to inform the Editors and the readership of *Ultrasound in Obstetrics & Gynecology* that the article by El-Refaie et al[1] was retracted on July 27, 2021, by the Editor-in-Chief of *Archives of Gynaecology and Obstetrics*, Professor Olaf Ortmann.[2] This article had been included in a systematic review and meta-analysis of individual patient data (IPD) that we published in *Ultrasound in Obstetrics & Gynecology*.[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 Professor 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] Last year, the authors and the Chair of the Department of Obstetrics and Gynecology, Professor Abdelmageed Mashaly, 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 June 23, 2020, Professor Ortmann indicated that an investigation had been opened at Mansoura University in February 2020 because of allegations of scientific misconduct and that, while the investigation was ongoing, the authors had described the regulatory review and submitted documents. Specifically, Professor Ortmann stated, "*One critical point 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.*

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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). Professor Ortmann and the publisher have since changed their minds about this approval and retracted the paper. The Notice of Retraction[2] states: *"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 we published in *Ultrasound in Obstetrics & Gynecology*[3] was a systematic review and meta-analysis of IPD, addressing the effect of vaginal progesterone in patients with a twin gestation and a short cervix. The study was registered in PROSPERO and identified previous RCTs that had addressed this question. The study of El-Refaie et al[1] was included as it met the inclusion criteria. Our study described the methodology of the IPD meta-analysis, assessment of bias, planned sensitivity analysis, and other details. We planned a sensitivity analysis by excluding studies at high risk of selection bias or performance and detection biases. The study of El-Refaie et al[1] did not have a placebo group; therefore, it was considered to be at high risk for performance and detection biases. The results of what would happen if the information of the El-Refaie et al[1] study was not included is presented in the Results section of our meta-analysis. Moreover, the Abstract and the Discussion informed readers about the contribution of the El-Refaie et al[1] study to the conclusions of the meta-analysis, the limitations of the study, and the implications for practice.

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The following is an itemized description of the relevant statements in our paper. Appendix S1 of this letter contains the original paper, and relevant text described below is highlighted in yellow in the paper published by *Ultrasound in Obstetrics & Gynecology* 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. Such a study was the one by El-Refaie et al[1] (page 303).

2. The Methods section 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). The article stated that sensitivity analyses were only to be performed for the primary outcome of preterm birth <33 weeks of gestation and for the secondary outcome and neonatal death (page 306).

3. The Results section 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 on what would happen if the trial of El-Refaie et al was excluded (page 309):

   "When the sensitivity analysis was restricted to the five trials with adequate blinding of patients, clinical staff and outcome assessors, the effect of vaginal progesterone on the reduction in the risk of preterm birth <33 weeks' gestation and neonatal death was non-

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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 the administration of vaginal progesterone. Composite neonatal morbidity/mortality was significantly lower after the administration of vaginal progesterone assuming independence between twins (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 of El-Refaie et al[1] as described in Table 4. The source of the data for the calculations is provided (references 64-68).

5. The Discussion highlighted the limitations of the IPD meta-analysis and the contribution of the El-Refaie et al[1] study in the following way (page 312):

"Second, 74% of the total sample size of the IPD meta-analysis was provided by one study, which included women with a CL between 20 and 25mm 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

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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, this is what we said (page 312):

"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 the IPD meta-analysis, excluding the trial of El-Refaie et al,[1] and explained, in detail, the reasons for this analysis and its implications. We have requested that *Ultrasound in Obstetrics and Gynecology* link this letter and its supplementary material to our 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].

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Supplementary Material

Appendix S1: IPD meta-analysis published in *Ultrasound in Obstetrics and Gynecology*[3] with relevant material highlighted in yellow. The highlighted sections are reviewed in detail in this Letter to the Editor.