

Maternal Fetal Medicine (San Diego, CA; 2015), we showed that, in Switzerland, as compared with placebo, progesterone use increased the risk for spontaneous delivery within 14 days and preterm birth at <37 weeks of gestation.³

Suhag et al¹ might argue that the 4P trial was not included in their review because progesterone was given within 24 hours of the start of acute tocolysis and therefore could not be considered as “maintenance” tocolysis. The study medication was initiated after stabilization of the patient (diminution/arrest of uterine contractions with acute tocolysis) and continued until 36 weeks of gestation or delivery, if it happened before. There were only 9 women who delivered within the first 48 hours. Analysis that included only women who were stabilized for at least 48 hours showed the same result (ie, progesterone did not decrease the risk of preterm delivery).^{2,4}

Regarding the studies included in the review of Suhag et al,¹ they were all small (between 52 and 183 cases), and only 2 were compared with placebo. Metaanalysis is of great help in clinical practice, especially when large studies are not available. The decision to exclude trials should be based on strict inclusion criteria. We do not understand why Suhag et al decided not to include the largest randomized trial on vaginal progesterone in women with preterm labor to be published until now.

On the basis of existing literature, progesterone should not be given as maintenance tocolysis in women with preterm labor. Benefits have not been found, and harms have not been excluded. New large, randomized, and placebo-controlled studies will be soon published and will help in drawing conclusions. ■

Begoña Martínez de Tejada, MD, PhD
Department of Gynecology and Obstetrics
University of Geneva Hospitals and Faculty of Medicine
University of Geneva
Geneva, Switzerland
Begona.martinezdetejada@hcuge.ch

Ariel Karolinski, MD, MSc
Centro de Investigación en Salud Poblacional-CISAP-(Population Health Research Centre)
Hospital GA Carlos G Durand
Buenos Aires, Argentina

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REPLY

Thank you for the interest in our metaanalysis.¹ We congratulate Dr Martínez de Tejada et al² on their recent publication on vaginal progesterone for prevention of preterm birth (4P trial).

One of the most important aspects of a metaanalysis is the inclusion criteria. Strict inclusion criteria are needed to reduce both clinical and statistical heterogeneity. Moreover, the protocol of every metaanalysis should be decided a priori before the data extraction and should not be modified. These are key elements that are needed to evaluate the reliability of a metaanalysis. In 2011, the first international prospective register of systematic reviews (PROSPERO) was launched by the Centre for Reviews and Dissemination, University of York, UK. All journals should encourage prospective registration of all planned systematic review protocols because it helps to promote transparency and safeguards against publication bias and duplication of reviews. Recently, preferred reporting items for systematic review and meta-analysis guidelines for protocols have also been published.³ In our protocol, which is registered with PROSPERO (CRD42014013706), we a priori decided to include all published randomized controlled trials (RCTs) of singleton gestations that had arrested preterm labor (PTL) and were randomized to maintenance tocolysis treatment with either vaginal progesterone or control.¹

As Martínez de Tejada et al² knows well, we tried our best to include their trial in our metaanalysis, as we can confirm by the several emails that we exchanged directly with her early in 2015. In their RCT,² vaginal progesterone was given within 48 hours of the start of acute tocolysis and was used as an additional agent with primary tocolysis, not as maintenance tocolysis,⁴ which was also pointed out by the Commentary to their study.⁵ Indeed, in their RCT, vaginal progesterone appears to be used for women both who had (perhaps) arrested PTL and those who did not.² Maintenance tocolysis means that preterm contractions have resolved, at least 48 hours have elapsed from presentation, and steroids have been given; now the patient is being considered for discharge. This is not at all what happened in the 4P RCT. The 4P authors did not mention whether the study subjects were assessed for arrested PTL before randomization and allocation of vaginal progesterone vs placebo. For these reasons, including their RCT would have been methodologically incorrect, which would have compromised the reliability of our metaanalysis on maintenance tocolysis. We had already explained this well in several emails to Martínez de Tejada, who was aware. There are indeed other RCTs that use progesterone as an additional

agent to primary tocolysis.⁶ The RCT by Martinez de Tejada et al² can, if desired, possibly be combined with this RCT and other future similar trials.

After carefully reviewing the 4P trial, we agree with Dr Norwitz's commentary⁵ to this trial and then his reply again to Martinez de Tejada et al that the 4P study is underpowered to conclude that there is no benefit of vaginal progesterone as a tocolytic, given, among other reasons, the fact that they did not reach their own precalculated sample size. Unlike these authors, we did not make any absolute and definitive clinical recommendations in our study. In our metaanalysis, we concluded that "Maintenance tocolysis with vaginal progesterone is associated with prevention of PTB, significant prolongation of pregnancy, and lower neonatal sepsis. However, given the frequent lack of blinding and the generally poor quality of the trials, we do not currently suggest a change in clinical care of women with arrested PTL. We suggest instead well-designed placebo-controlled randomized trials to confirm the findings of our meta-analysis."¹

Once again, congratulations to Martinez de Tejada et al for their 4P trial. We look forward to more excellent work and publications from their group. ■

Gabriele Saccone, MD
Department of Neuroscience
Reproductive Sciences and Dentistry
School of Medicine
University of Naples Federico II
Naples, Italy

Anju Suhag, MD
Vincenzo Berghella, MD
Department of Obstetrics and Gynecology
Division of Maternal-Fetal Medicine
Thomas Jefferson University Hospital
Philadelphia, PA
Vincenzo.berghella@jefferson.edu

The authors report no conflict of interest.

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Skin incision for cesarean delivery in morbidly obese women

TO THE EDITORS: In reference to the recent dialogue generated by Marrs et al¹ in the article associated with complications found on cesarean deliveries on obese parturients and the letter by Gordon and Welch.² We would like to bring to the attention of the authors that Joel-Cohen³ in 1954 proposed a detailed manner to enter the abdominal cavity in obese women with the use of a transverse incision 3 cm below the level of the anterior superior iliac spines. This detailed and elegant description is convincing. Krebs and Helmkamp⁴ further described transverse incisions below and above the umbilicus in obese female patients with marked advantages for the supraumbilical incision. These techniques must be reviewed thoroughly by the teams who are planning randomized trials that will involve cesarean deliveries in morbidly or extremely obese patients. ■

Karen Plymel, MD
Department of Obstetrics and Gynecology
Beaumont Health System
Michigan Perinatal Associates
Dearborn, MI
plymelk@oakwood.org

Federico G. Mariona, MD
Division of Maternal Fetal Medicine
Beaumont Health System
Michigan Perinatal Associates
Dearborn, MI
The authors report no conflict of interest.

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