High dose progesterone for prevention of preterm birth in twins

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TO THE EDITORS: We read with interest the recent randomized clinical trial comparing vaginal progesterone with placebo in women with twin pregnancies for the prevention of spontaneous preterm birth.[1] We want to congratulate the authors on this large study that answers the question as to whether high dose vaginal progesterone reduces preterm birth in unselected women with a twin pregnancy: it does not. However, we have concerns regarding the study design, which downplays the potential of progesterone in women with short cervix.

Our concern is the primary outcome: spontaneous preterm birth between 24+0 and 33+6 weeks' gestation, reported as a relative risk (RR) of 1.35 with a 95% confidence interval (CI) of 0.88 to 2.05. The choice not to include women who deliver before 24 weeks makes the groups on the primary endpoint less comparable, specifically because 2.6% of the progesterone group delivered before 24 weeks compared with 4.4% in the placebo group. In our opinion, the primary outcome should have been any delivery before 34 weeks, which occurred in 16.7% and 15.8% respectively in this study, with RR of 1.10 (95% CI, 0.80−1.51). It is not surprising that delivery between 24 and 34 weeks occurs more in women with compliance above 80% (RR, 1.73; 95% CI, 1.04−2.91), which is not a sign of harm, but probably owing to the fact that with good compliance progesterone prevents preterm birth before 24 weeks (we cannot extract these data from the paper).

This becomes even more important when the authors report the treatment effect in women with a cervical length below 30 mm. Of the massive number of comparisons in the paper, the most relevant one is shown in Supplemental Table 7. Although in women with a cervical length of 30 mm or more the endpoint of delivery at <34 weeks is not influenced by progesterone (RR, 1.1; 95% CI, 0.82−1.5), there is a clear benefit from progesterone (RR, 0.44; 95% CI, 0.17−0.91) in women with a cervix of <30 mm. ■

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We thank McGannon et al[1] for their letter. In the EVENTS trial, we found that in women with twin pregnancies universal administration of progesterone at a dose of 300 mg twice per day from 11 to 14 to 34 weeks' gestation did not reduce the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation.[2] However, post hoc time-to-event analysis led to the suggestion that progesterone may reduce the risk of spontaneous birth at <32 weeks in women with first-trimester cervical length measurement of <30 mm. In the prespecified primary outcome, we selected spontaneous rather than all early preterm births, because there is no reason to believe that progesterone would reduce indicated preterm births. We excluded births before 24 weeks to allow comparison with the results of previous trials

that recruited patients at midgestation. However, as we wrote in the discussion, this exclusion could mask an effect of progesterone of converting late miscarriages to early preterm births. Birth between randomization and 24 weeks occurred in 2.6% of pregnancies in the progesterone group and in 4.4% in the placebo group (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.30−1.10), but the rate of all births between randomization and 34 weeks was 16.7% for the progesterone group and 15.8% for the placebo group. Among those with compliance of ≥80%, births before 24 weeks occurred in 11 of 474 (2.3%) in the progesterone group and 17 of 478 (3.6%) in the placebo group (OR, 0.63; 95% CI, 0.29−1.35).

Regarding the effect of progesterone in women with first-trimester cervical length measurement of <30 mm, the results presented in Supplemental Table 7 are not relative risks, as McGannon et al[1] have wrongly assumed, but hazard ratios (HR). More importantly, there seems to be some confusion in the way these authors have extracted figures from Table 7. The HR (progesterone to placebo) for all deliveries before 34 weeks was 0.74 (95% CI, 0.37−1.49) which cannot be interpreted as evidence of clear benefit. In contrast, as shown in Figure 4 of our paper and in Table 7, in the group with cervical length of <30 mm, there is a suggestion of benefit for spontaneous preterm birth before 34 weeks (HR, 0.40; 95% CI, 0.17−0.91) and more so for birth before 32 weeks (HR, 0.23; 95% CI, 0.079−0.69).

We would like to reiterate the point made in our paper that the results of the post hoc analyses should be considered as exploratory. This is the first phase III study to suggest that first-trimester cervical length may be used to discriminate treatment response to vaginal progesterone, and further study is required to validate this observation. We are planning such a trial in which the primary outcome will be births between randomization and 32 weeks' gestation. ■

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Enhanced Recovery After Surgery Society recommendations for scheduled cesarean deliveries: is the developing world ready?

TO THE EDITORS: The recently released Enhanced Recovery After Surgery (ERAS) guidelines for antenatal, preoperative, intraoperative, and postoperative care in cesarean delivery (CD) have aroused interest in healthcare providers both in developed and developing world.[1−3] These guidelines emphasized that ERAS is a comprehensive, interdisciplinary, protocol-based approach expected to benefit both the patient and health system.

The application of bundles of ERAS would prove to be of paramount benefit in tertiary care centers of low-resource countries with a high incidence of CD. However, barriers to application in the developing world need to be addressed before implementing them in daily practice.

Owing to the unpredictable nature of mode of delivery, the exact percentage of planned CD is minimal (only 30% of all CDs). Even fewer are planned since early pregnancy to allow the application of optimal pathway of ERAS which should begin in the antenatal period. Data in an Indian scenario showed that only 58% of women visited antenatal clinics in the first trimester and only half of the total pregnancies had at least 4 antenatal care visits.[4] Another aspect obscuring the pathway of ERAS protocol is resource crunch. Lack of dedicated theater facilities and the need to triage CD per the indications of CD may contribute adversely to the application of ERAS protocol.

From surgical aspects, there is a need to consider unexpected surgical issues like bladder adhesions requiring prolonged catheterization, gut adhesions requiring prolonged postoperative fasting, longer surgery, or unanticipated neonatal complications needing resuscitation which impair the application of intraoperative pathway of ERAS even in the best of settings.

In addition, it needs to be considered that surgical site infections may take >48 hours to present and subtle signs of