Vaginal progesterone or cerclage to prevent recurrent preterm birth?

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Until recently, prevention of preterm birth (PTB) seemed to be an elusive goal. In the United States, the rate of PTB rose steadily from 9.4% in 1981 to a peak of 12.8% in 2006.[1] Much of our clinical effort during this time involved tocolytic therapy, which proved to be generally ineffective at prolonging pregnancy or reducing the rate of neonatal complications.[2] Until recently, antenatal corticosteroid treatment was practically the only evidence-based weapon in our arsenal to attack the problem of PTB.

Now we have at least 2 new weapons, cervical cerclage and progestational agents. Our much happier current dilemma is not determining whether either of them is effective in certain situations (both are) but deciding which of them is better.

A growing body of recent evidence shows that targeted use of either cerclage or vaginal micronized progesterone can reduce the risk of PTB in a specific group of women at very high risk, those with all 3 of the following:

- A current singleton pregnancy.
- A history of spontaneous PTB in a prior pregnancy.
- A short cervix (<25 mm) before 24 weeks in the current pregnancy.

Untreated, such women have a 15-20% risk of recurrent PTB before 28 weeks of gestation, a 25-30% risk of PTB before 32 weeks, and a 50-60% risk of PTB before 37 weeks.[3] The risks are higher the earlier in the gestation the previous PTB, the shorter the cervical length, and the earlier in pregnancy the short cervix is diagnosed.

Benefits of cerclage or vaginal progesterone

The benefits of cerclage in women with the 3 factors outlined above were shown in a metaanalysis of patient-level data from 5 clinical trials comparing cerclage with no cerclage.[4] Cerclage resulted in significant reductions in the following:

- Recurrent PTB before 35 weeks, relative risk (RR) 0.70.
- Perinatal mortality, RR 0.65.
- Composite neonatal morbidity, RR 0.60.

The benefits of vaginal micronized progesterone in women with the same 3 factors were shown in an individual patient data metaanalysis of 5 high-quality placebo-controlled trials.[5] Vaginal progesterone resulted in significant reductions in the following:

- Recurrent PTB before 33 weeks, RR 0.54.
- Composite neonatal morbidity and mortality, RR 0.41.

Choice of cerclage vs vaginal progesterone

Which treatment is better for these very high-risk women? There have been no clinical trials directly comparing cerclage with vaginal progesterone for such women, and a search of trial registries (clinicaltrials.gov and controlled-trials.com) finds no such trials ongoing. In the absence of direct evidence, it is impossible to give a definitive answer.

In the current issue, Conde-Agudelo et al[3] address this important question with an indirect-comparison metaanalysis. This clever statistical method compares the 2 treatments, cerclage vs vaginal progesterone, which were each tested in clinical trials against a control group but which were never directly tested against each other. The analysis requires the assumption that the control groups were comparable. This assumption appears reasonable, even though the controls were treated differently: those in the cerclage trials received no particular treatment, whereas those in the progesterone trials received the placebo treatment. Despite these differences, the rates of PTB and neonatal morbidity in the control groups (Table 2 of the metaanalysis[3]) were similar.

The indirect-comparison metaanalysis[3] shows trends toward better outcomes with vaginal progesterone compared with cerclage (summary RR <1.0), but these did not reach statistical significance because the 95% confidence intervals (CIs) overlap 1. For the primary outcomes, the following was found:

- Rate of PTB before 32 weeks: RR, 0.71; 95% CI, 0.34–1.49.
- Composite perinatal morbidity/mortality: RR, 0.67; 95% CI, 0.29–1.57.

Conde-Agudelo et al[3] concluded that vaginal progesterone and cerclage are equally efficacious in this setting and suggested that factors other than efficacy should guide the choice of treatment for individual patients. How does this conclusion fit into the context of current existing recommendations for management of women with a prior spontaneous PTB?

Expert recommendations: management of singleton pregnancy with prior PTB

In a comprehensive review, Iams and Berghella[6] recommended serial sonographic cervical length measurement from 16 to 23

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weeks of gestation for women with a history of a prior spontaneous PTB. In addition, prophylactic intramuscular 17-hydroxyprogesterone caproate (17P) is recommended weekly from 16 to 36 weeks of gestation, regardless of cervical length because the large trial of Meis et al[7] showed benefit of this agent without any selection based on cervical length screening.

If the cervical length falls below 25 mm in a woman who is already receiving 17P, Iams and Berghella[6] offer cerclage. A clinical guideline from the Society of Maternal-Fetal Medicine (SMFM) also recommends cerclage, adding that 17P should be continued after the cerclage is placed.[8] A similar recommendation was made in a practice bulletin from the American College of Obstetricians and Gynecologists.[9] In contrast, Conde-Agudelo et al[3] conclude that vaginal progesterone should be offered in this setting, providing equal efficacy and fewer safety concerns than the combination of cerclage and 17P.

If the cervical length falls below 25 mm in a woman with a singleton pregnancy and prior PTB who has not started 17P, the results of Conde-Agudelo et al[3] impy that either vaginal progesterone or cerclage can be considered as the first-line treatment. The choice between them should be based on patient preference after a discussion with her provider of the pros and cons of the 2 options.

Management of other combinations of risk factors

The analysis of Conde-Agudelo et al[3] and the preceding discussion focus on women with a singleton pregnancy, a short cervix, and a history of prior PTB. Current evidence favors different management for women who have different combinations of risk factors including the following:

- Singleton pregnancy, short cervix, no prior PTB: vaginal progesterone is recommended because it reduces the rates of both PTB and neonatal morbidity.[5,8,9] A significant benefit from cerclage[10] or 17P[11] has not been shown.
- Singleton pregnancy, prior PTB, normal cervical length: prophylactic 17P is recommended[6,8,9] along with serial cervical length screening.[6,8]
- Twins, no prior PTB, normal cervical length: both 17P and vaginal progesterone have been shown not to reduce risk of PTB and are not recommended.[8,9]
- Twins, no prior PTB, short cervix: cerclage is not recommended because it may actually increase the rate of PTB.[10] Although the SMFM[8] and ACOG[9] do not recommend treatment with progestins, there is evidence that vaginal progesterone may reduce neonatal morbidity.[5]
- Twins, prior PTB, normal cervical length: there is no evidence of benefit from vaginal progesterone[12] or 17P,[13] but this conclusion is based on very small numbers.

Several relevant ongoing and upcoming clinical trials may yield new evidence that will modify these recommendations. An intriguing new option for treatment of short cervix is a cervical pessary, which was recently shown to substantially reduce early PTB in one trial[14] but not in another.[15] This device is not currently approved for prevention of PTB by the Food and Drug Administration in the United States but is undergoing further evaluation in several randomized clinical trials throughout the world. ■

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