Vaginal progesterone is an alternative to cervical cerclage in women with a short cervix and a history of preterm birth

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The problem

Preterm birth continues to be an important and global obstetrical problem. An estimated 15 million preterm births occur throughout the world annually, resulting in approximately 1 million deaths.[1] In addition to the high mortality rate, preterm birth is associated with short- and long-term adverse effects.[2–6] During their early years, infants born prematurely have high rates of cerebral palsy, sensory deficits, learning disabilities, and respiratory illnesses.[7–9] Later in life, these individuals have an increased incidence of diabetes, hypertension, metabolic syndrome, and other adult chronic diseases.[10,11] The problem of preterm birth is not limited to developing countries: for example, the preterm birth rate in the United States has recently increased, from 9.63% in 2015 to 9.85% in 2016.[12]

Treatment of preterm labor with tocolysis—an appealing idea that has not come through

The prevention of preterm birth has eluded obstetricians and reproductive biologists for decades. Initial research focused on the efficacy and safety of several tocolytic agents (eg, intravenous alcohol,[13] beta-adrenergic agents,[14] prostaglandin inhibitors,[15,16] magnesium sulfate,[17,18] oxytocin receptor antagonists,[19] calcium-channel blockers,[20,21] nitroglycerine[22,23]) for the prevention of preterm birth in patients with an episode of preterm labor. It is now accepted that these agents merely delay delivery for a brief period of time, and there is no convincing evidence that they can prevent preterm birth or perinatal morbidity.[24] Tocolysis is currently used to delay delivery, allow maternal transfer to level-3 facilities, and permit corticosteroid administration.[24–27] Whether an ideal tocolytic agent can be identified remains to be proven. Recent evidence suggests that an episode of preterm labor that does not result in preterm delivery is associated with an increased risk of small-for-gestational age,[28] and these infants can have long-term developmental delays.[29,30] The rationale behind tocolytic administration needs to be reexamined, as it now appears to be symptomatic treatment, rather than therapy for the underlying cause of preterm birth.[31,32]

Preterm labor—shifting from acute treatment to prediction and prevention

The emphasis of current research is on decreasing the preterm birth rate in asymptomatic women with known risk factors. Two important risk factors that significantly increase the risk of preterm birth in singleton pregnancies are a history of preterm birth[33,34] and a short cervical length noted in the midtrimester of pregnancy.[35–41] The role of progestogens (synthetic or natural) in parturition has been the subject of recent articles[42–53] as well as the mechanism whereby progesterone may act to prevent cervical ripening and parturition.[54,55] The current practice in the United States is to offer 17-alpha hydroxyprogesterone caproate to patients with a history of preterm birth,[33] and vaginal progesterone to patients with a short cervix.[56]

The patient with a short cervix and a prior preterm birth

Randomized controlled trials (RCTs) and systematic reviews with meta-analyses have shown that either vaginal progesterone administration[57–59] or the placement of a cervical cerclage[60–62] reduce preterm births and improve perinatal outcomes. The availability of these 2 therapies for this group of high-risk patients has raised the question: which strategy is preferable?

Although a small number of RCTs have directly compared the administration of vaginal progesterone vs cerclage to prevent preterm birth in patients with risk factors,[63,64] the majority of published reports have compared one of these modalities with placebo (progesterone) or no treatment (cerclage).[61,65–72] Lack of evidence from direct comparisons between vaginal progesterone and cervical cerclage make it difficult for obstetricians to choose the most effective treatment for patients at risk of preterm birth.

Indirect meta-analysis to compare therapies not tested directly

In the absence of head-to-head clinical trial data directly comparing the efficacy of one therapy vs another, statistical methods have been developed that allow for indirect comparison between therapies.[73–75] A systematic review with meta-analysis indirectly comparing vaginal progesterone and cervical cerclage for the prevention of preterm birth and adverse perinatal outcomes was published in 2013 by

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Received May 7, 2018; accepted May 7, 2018.

The author reports no conflict of interest.

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0002-9378/free

https://doi.org/10.1016/j.ajog.2018.05.010

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Conde-Agudelo et al.[57] Data for vaginal progesterone were obtained from an individual patient data (IPD) meta-analysis performed specifically for the indirect comparison meta-analysis, which included 4 RCTs and a total of 158 patients (75 randomized to vaginal progesterone and 83 randomized to placebo). Summary statistics for the studies assessing the benefit of cervical cerclage were obtained from an IPD meta-analysis published by Berghella et al[62] in 2011 that included 5 RCTs and a total of 504 patients (250 randomized to cerclage placement and 254 to no cerclage). The 2 primary outcomes of the 2013 indirect comparison meta-analysis were birth <32 weeks and composite perinatal morbidity/mortality. For these 2 outcomes, no significant differences were detected between vaginal progesterone and cervical cerclage (relative risk [RR], 0.71; 95% confidence interval [CI], 0.34−1.49; and RR, 0.67; 95% CI, 0.29−1.57, respectively). Likewise, for the secondary outcome of preterm birth <35 weeks, no significant differences were noted (RR, 0.94; 95% CI, 0.56−1.58).

A new indirect meta-analysis comparing vaginal progesterone vs cerclage in patients with a short cervix and a history of preterm birth

Conde-Agudelo et al,[76] in the current issue of this journal, report the results of an updated adjusted indirect comparison meta-analysis employing revised IPD, which included an additional 107 women from a recently published RCT.[77] The new IPD meta-analysis includes data from 5 RCTs for a total of 265 randomized subjects (139 received vaginal progesterone and 126 received placebo) assessing the impact of vaginal progesterone for the prevention of preterm birth in patients with singleton pregnancies, history of preterm birth, and a short cervical length. As in the previous indirect comparison meta-analysis, data for the studies assessing the benefit of cervical cerclage were obtained from the 2011 IPD meta-analysis published by Berghella et al.[62] For the outcomes of preterm birth <35 weeks and perinatal mortality, no significant differences were detected between vaginal progesterone and cervical cerclage placement: RR = 0.97 (95% CI, 0.66−1.44) and RR = 0.97 (95% CI, 0.35−2.69), respectively. Additionally, indirect comparisons showed that there were no significant differences between the efficacy of vaginal progesterone and cerclage for various secondary outcomes including preterm birth <37, <32, <28 weeks and composite perinatal morbidity/mortality.[76]

Vaginal progesterone vs cerclage: are they equivalent?

RCTs and systematic reviews with IPD meta-analyses have shown that vaginal progesterone is associated with a significant reduction in preterm birth in women with singleton pregnancies and a short cervix with or without a history of preterm birth[57,78,79] (similar results have been noted in women with a twin gestation and a short cervix).[80] Data supporting the efficacy of cerclage for the prevention of preterm birth are more limited,[81] with the most supportive evidence coming from the 2011 IPD meta-analysis by Berghella et al,[62] which noted benefits of cerclage in patients with singleton pregnancies, history of preterm birth, and a short cervical length.

The indirect comparison meta-analysis published in the current issue by Conde-Agudelo et al[76] utilized data from 2 separate IPD meta-analyses, one of which was recently updated.[62,76] Each of the IPD meta-analyses found a significant reduction in the primary outcomes (preterm delivery <35 weeks).

Results from previous meta-analyses and systematic reviews

The conclusions and validity of any meta-analysis directly relate to the methodologic thoroughness of the studies identified. The updated IPD meta-analysis conducted by Conde-Agudelo et al[76] as part of the indirect comparison meta-analysis was preceded by a written protocol prospectively registered with the PROSPERO database of systematic reviews and followed the PRISMA Extension for IPD guidelines. Meta-analyses of vaginal progesterone for the prevention of preterm birth in women with a short cervix had been done rigurously.[58,59,78] Whether systematic reviews and meta-analyses of cervical cerclage have similar rigor and quality is less clear. One point to remember is that indirect comparisons could have limited power, and may be subject to greater bias than direct comparisons, therefore, I recommend that a large, well-designed randomized clinical trial directly comparing vaginal progesterone and cervical cerclage be performed. One such trial is currently underway in Egypt and registered at ClinicalTrials.gov (NCT02673359).

Conclusion—vaginal progesterone should be offered as an option to women with a short cervix and a history of preterm birth

Patients with a history of preterm birth and a short cervix determined by ultrasound have a substantial risk for recurrent preterm birth.[33−41] Some professional societies have recommended cerclage for these patients.[82] However, the evidence presented in this issue of the journal by Conde-Agudelo et al[76] suggests that vaginal progesterone is an alternative, given the lack of difference in efficacy. The margin of safety of medical treatment with vaginal progesterone appears superior to that of cervical cerclage, which may lead to cervical lacerations, fever, chorioamnionitis, bleeding, and rupture of membranes.[81,83−85]

The time has come for professional societies to reexamine their recommendations offering only cerclage to patients with a history of preterm birth and a short cervix. Vaginal progesterone does not require anesthesia or surgery and it is as effective as cerclage. ■

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.