The Vexing Problem of Preterm Birth Prevention
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Preterm birth (delivery before 37 weeks of gestation) is a significant risk factor for maternal and perinatal mortality. Despite intensive efforts to develop preventive and treatment interventions intended to delay delivery until term, preterm birth continues to be one of the most important problems facing contemporary obstetrics. The incidence of preterm birth remains stubbornly high, hovering around 10% to 11% of all pregnancies in the United States, with numerous and often overlapping etiologies, including preterm rupture of amniotic membranes, cervical insufficiency, decidual hemorrhage, multiple gestation, infection, and maternal stress.1

Interventions to reduce preterm birth have been studied in different at-risk populations, including those with a prior preterm birth or a short (<25 mm) cervix in the current pregnancy. For patients with a short cervix, interventions that have been studied include supplemental vaginal progesterone, cervical cerclage, and cervical pessary. Despite these interventions, the overall rate of preterm birth and obstetric outcomes has remained largely unchanged. Thus far, only the field of neonatology can quantify significantly improved perinatal outcomes.2,3

In the past, small pilot studies of tocolytic agents, home uterine activity monitoring, intramuscular progesterone, and screening for preterm birth risk factors have shown effectiveness at delaying delivery until term. However, results of larger, adequately powered studies of these interventions have been mixed and meta-analyses inconclusive or disputed.4-7 The lack of large, rigorously conducted trials limits evidence-based obstetric interventions. When small studies have shown benefit, the intervention may be widely accepted and used clinically (eg, electronic fetal monitoring) before subsequent larger studies with appropriate power and more rigorous study designs conclusively show no benefit. This paradigm has led to significant financial costs to patients and health care systems without benefit. Perhaps this tension in seeking to find an intervention to prevent preterm birth is best exemplified by the use of intramuscular 17α-hydroxyprogesterone caproate, the approval of which was recently revoked by the US Food and Drug Administration.8-10 Additionally, these well-intentioned interventions may potentially harm pregnant people and their fetuses (eg, β-mimetic tocolytic agents).11

Given this history of unsuccessful obstetric interventions, one can understand the enthusiasm of the obstetric community for new treatments that could decrease the rate of preterm birth. Thus, the development of an intravaginal pessary that could prevent preterm birth in at-risk individuals was considered a promising potential advance. There are several hypotheses as to why a pessary could reduce preterm birth. A pessary provides physical support to the uterus, theoretically transferring some of the weight of the enlarging gravid uterus from the cervix to maternal pelvic structures. The pessary alters the uterine-cervical angle to be more acute and posterior, and theoretically shifts the weight of the pregnancy off the cervix and toward the anterior lower uterine segment. The pessary compresses the cervix and could favorably alter the cervical-vaginal paracrine environment toward a milieu that promotes pregnancy maintenance and decreases premature cervical ripening. Additionally, the placement of the pessary and perception of benefit may reduce maternal anxiety, a known risk factor for preterm birth.

Perhaps the best studied pessary for preterm birth prevention was developed by Arabin and Alfirevic12 in the late 1970s; prior to this, obstetricians primarily used pessaries designed to treat pelvic organ prolapse. Since the introduction of the Arabin pessary, early case series and nonrandomized controlled studies found benefit of the pessary and proposed it as an alternative to cervical cerclage.13,14 In the first randomized clinical trial of pessary for women with a short cervix, the Arabin pessary was associated with a significantly reduced rate of preterm birth.15 However, a subsequent randomized clinical trial did not demonstrate benefit of pessary for pregnant individuals with a cervical length less than 25 mm.16 The more recent randomized trials have also yielded mixed results.16-19

Based on these results, the Eunice Kennedy Shriver National Institute of Child Health and Human Development-sponsored Maternal-Fetal Medicine Units Network report in this issue of JAMA20 on their large, adequately powered TOPS study (Trial of Pessary in Singleton Pregnancies With a Short Cervix), in which 544 women were randomized to pessary placement at 16 to 23 weeks of gestation (n = 280) or to usual care (n = 264). Almost all women in the study cohort were treated with vaginal progesterone. The Arabin pessary was not effective at preventing preterm birth in this very high-risk obstetric population. All participants in the study had a cervical length less than 25 mm at the time of second trimester screening, indicating that the investigators selected a population of pregnant people with a high likelihood of preterm birth.

Perhaps the most notable result from the study is the increased perinatal mortality risk in pregnant patients in the pessary group (13.1%) compared with the control group (6.8%). This troubling finding has not been reported in prior pessary studies, and the precise reasons for this increased
risk are not clear. Clinical data regarding these perinatal deaths are provided in eTable 3 in the article’s Supplement 3, and the majority occurred prior to viability, when no obstetric or neonatal intervention is likely to improve outcome. The data and safety monitoring board wisely advised ending the study before complete enrollment due to study futility and the increased perinatal mortality risk in the pessary group.

The TOPS trial has several notable strengths. The participants in the pessary and control groups were exceptionally well matched, strengthening comparisons. Given the high preterm birth rate of 45% in the cohort, the investigators clearly identified a population at very high risk of preterm birth. The investigators applied a structured standardized approach to the patients, with care taken to standardize cervical length measurements and application of the pessary, thus decreasing potential bias. Even though the predetermined sample was not collected, the total number of patients enrolled was relatively large and there was sufficient power to make valid conclusions. While one could criticize the study for the extensive time required to acquire the sample, the fact that the authors were able to continue to recruit successfully through the COVID-19 pandemic lockdown is testament to the focus and dedication of the nurse coordinators and research staff at the clinical sites.

A key weakness of the study is the inability to determine the root causes of the excess perinatal deaths in the pessary group to determine if this was attributable to pessary use or some other confounding factor. Should pessary use be determined to be a proximate cause of the fetal and neonatal deaths, then widespread use should be discouraged or perhaps even banned. Another weakness is the open-label nature of the study design, as there simply is no way to blind participants or study staff as to which patients received the intervention. Vaginal progesterone was used by nearly all study participants; thus, determining any interactions between pessary and vaginal progesterone for preventing preterm birth was not possible in this population. However, the rigor of the study protocol, as evidenced by the comparable nature of the 2 study groups, helps to mitigate bias in the data.

Is this the end of use of the Arabin pessary to prevent preterm birth? Perhaps. Other similar studies are ongoing, including with twin gestations (NCT02518594), and the inevitable update of systematic review and meta-analysis will incorporate these and other results. Until then, the Arabin pessary should continue to be used only in the context of clinical trials with appropriate sample size, study design, and safety monitoring. Most likely, however, the Arabin pessary will join the ranks of intramuscular progesterone, home uterine activity monitoring, and tocolytics as yet another unsuccessful clinical intervention for the prevention of preterm birth.

Until a better appreciation is gained of the root causes of preterm birth, simplistic, mechanical approaches such as the pessary are unlikely to succeed. In a recent interesting comment, Stock and Aiken21 note that 3 key directions of research should be addressed, including identifying the early pathologies that lead to preterm birth, developing an individualized evaluation of both fetal and maternal responses to threatened preterm labor, and better understanding the timing of birth to balance the risks of continuing the pregnancy vs delivery so as to optimize both fetal and maternal outcomes. Most interventions address the end result of the pathologic process leading to preterm cervical ripening or contractions and, hence, are unlikely to be successful. Strategies that address the pathophysiology that leads to preterm parturition are more likely to be successful. The application of machine-based deep learning and patient-specific interventions may hold promise in helping identify patients at risk with development of a prevention strategy that improves outcomes.

ARTICLE INFORMATION
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