Preterm birth and its complications are the leading causes of infant morbidity and mortality worldwide. Infants born preterm have a significantly higher likelihood of dying during the neonatal period than term infants. Getting the interventions right will inevitably save millions of infants and their families. Over the years, numerous studies have investigated the impact of vaginal progesterone in preventing recurrent preterm birth. However, there are still many shortcomings in our evaluation and understanding of its effectiveness.

A recent study in *JAMA Network Open* by Nelson et al. investigates the association between vaginal progesterone and prevention of recurrent spontaneous preterm births. This study suggests no overall reduction in recurrent preterm birth or when evaluating for both severity and frequency of prior preterm births among participants who took vaginal progesterone compared with controls. They found recurrent preterm birth in cases significantly higher than their 3 to 1 matched historical controls (24.9% vs 16.3% respectively, *P* < .001; unadjusted odds ratio [OR] of 1.6; 95% CI, 1.2-2.1; adjusted for matched case-control OR of 1.8; 95% CI, 1.3-2.4). Many important risk factors exist for preterm births. However, the ability of healthcare professionals to mitigate and prevent these risks has been traditionally challenged by the high rates of unplanned pregnancies in the US and limited access to preconception care, most commonly among populations with historically higher risks for preterm births, which were mostly participants in Nelson et al.²

### Vaginal Progesterone for Preterm Birth

Studies have shown the influence of serum progesterone on successful pregnancy outcomes as it plays a critical role in uterine contractility, cervical dilatation, and onset to the progression of labor. The American College of Obstetrician and Gynecologists (ACOG) recommends that patients with prior spontaneous preterm birth and singleton pregnancy be offered progesterone supplementation (either vaginal or intramuscular) to prevent recurrent preterm birth, which is endorsed by the Society for Maternal-Fetal Medicine. In most cases, therapy is started around 16 to 20 weeks' gestation and continued until 36 weeks or until delivery.

Although this is a current practice backed by ACOG, some scientists have different opinions based on their research findings. Various studies have been conducted to evaluate this effectiveness in preterm birth prevention but with conflicting results and lack of consistent outcomes. Nelson et al.² suggest that vaginal progesterone was not associated with a reduction in risk of recurrent preterm birth; a notable feature of the study was the significantly higher rate of preterm births in those who use vaginal progesterone compared with historical controls.

A systematic review and meta-analysis also reported no convincing evidence for the effectiveness of vaginal progesterone in preventing recurrence in singleton pregnancies with prior spontaneous preterm births. The authors also found no significant differences between vaginal progesterone and the placebo in other adverse perinatal outcomes. Nonetheless, other studies have reported the effectiveness of vaginal progesterone on preterm birth prevention. A randomized clinical trial by Fonseca et al. investigated prophylactic administration of progesterone by vaginal suppository and reported a significant association with preventing recurrent preterm birth in women who have a short cervix or other clinical characteristics. Therefore, the significantly positive impact...
of vaginal progesterone on preterm births seems to be very selective as this influence differs across obstetrics history or the reproductive status of the woman.

There have also been studies about the best mode of progesterone administration to prevent preterm birth, either vaginal or intramuscular, but there has been no convincing evidence to date on its effectiveness in either way of administration. Blackwell et al® conducted a multicenter, international, randomized clinical trial in 93 centers both within and outside the US, that investigated whether 17α-hydroxyprogesterone caproate (17-OHPC) prevented recurrent preterm birth in singleton gestations (PROLONG Study). They reported no significant differences in either the frequency of preterm births or neonatal morbidity index between the intervention group with 17-OHPC and placebo (relative risk [RR], 0.95; 95% CI, 0.71-1.26 and RR, 1.12; 95% CI, 0.68-1.61 respectively).® These reports call for action and more research. Health care professionals may begin to consider dialogue or intensify discussions concerning whether the protocol for vaginal progesterone use in patients with previous stillbirth should be reviewed for modifications or suspension.

Barriers to Adherence to Vaginal Progesterone Treatment

Nelson et al² reported high levels of nonadherence to vaginal progesterone, and they found this to be mostly due to adverse effects of treatment among the cases in their cohort. Adequate information about maternal outcomes after vaginal progesterone therapy and adverse effects have been scarce. Other factors that could lead to noncompliance may include the physical impact of the medication like irritation or discomfort on the pelvis from frequent administration, the risk of pelvic trauma during repeated insertion, the timing of administration, conflict with intercourse, and so on. Previous randomized clinical trials also reported significantly increased psychosocial disorders at 24 weeks’ gestation after periods of either vaginal or intramuscular progesterone use in pregnant women.⁹ Thus, more important factors to consider in the real-life situation may include further need assessment from women on their perception and satisfaction with its use.

Pregnancy as a Unique Progesterone Increasing State

Progesterone belongs to a class of hormones called progestogens. It is a steroid hormone that uses an intracellular receptor signaling pathway in its mode of action. Progesterone is the main hormone of the corpus luteum and the placenta and is secreted by the ovarian corpus luteum during the first 10 to about 12 weeks of pregnancy, after which the placenta takes over its production. One of its most important functions is to regulate and maintain pregnancy by decreasing the vasculat tone of the uterine myometrium, thus suppressing myometrial activity and aiding in the retention of the embryo during implantation and fetal growth up until normal delivery.

Implications for Current Practice Review

In the fight against preterm births and perinatal morbidity and mortality, a more comprehensive evaluation of vaginal progesterone will be important as current evidence in its prevention of recurrence in singleton pregnancy is currently far from overwhelming. The report from the recent studies on vaginal progesterone to prevent recurrent preterm birth demonstrate the critical need to investigate its effectiveness further.²⁻⁵ The need to consistently ensure shared decision-making process in the context of its use for this purpose as recommended by ACOG is of paramount importance. This gives important opportunities for the health care workers to know the patients’ preferences, and it also allows the patients to fully express their opinions and share their experiences on the treatment. The recent findings of even higher recurrent preterm births among women who use vaginal progesterone compared with controls is worth further research even though historical
controls were investigated. Therefore, a call to action is needed to evaluate the current practice and more research on the existing evidence. Furthermore, researchers should consider incorporating more critical checkmarks in the current use of vaginal progesterone to prevent recurrent preterm delivery while we await more benefits of its effectiveness in the near future.

ARTICLE INFORMATION

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