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New hope for preventing preterm birth: The promise of vaginal nanoformulations

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Defined as birth before 37 completed weeks of gestation, preterm birth (PTB) accounts for the vast majority of perinatal morbidity and mortality.[1–3] Sadly, data collected by the World Health Organization indicate that the annual rate of PTB worldwide has not improved over the last several decades and is greater than 10% in most countries.[4] PTB rates are generally higher in the developing world; among industrialized nations, the United States (US) has the highest rate of PTB.[2] In the US particularly, advances in neonatology have occurred more rapidly than in the field of obstetrics, so that more and more neonates born closer and closer to the cusp of viability survive their neonatal intensive care unit stay, only to live with a constellation of medical challenges. The acute sequelae of PTB, such as respiratory distress syndrome and necrotizing enterocolitis, are replaced by lifelong respiratory, metabolic and neurologic abnormalities, including retinopathy of prematurity and cerebral palsy.[5] The personal and societal costs of PTB are enormous.

Currently, the only US Food and Drug Administration (FDA) approved drug for the prevention of PTB is hydroxyprogesterone caproate, aka Makena. However, the FDA is now calling for withdrawal of the approval of this drug, because of the lack of efficacy shown in the PROLONG trial.[6] Although not FDA approved, vaginal progesterone is the most successful drug therapy to prevent PTB and is administered to women who have had a PTB before and are at risk for delivering preterm. However, vaginal progesterone only reduces the incidence of PTB by one third.[7, 8] As far as tocolytics, the three most commonly used are magnesium sulfate, indomethacin and nifedipine. However, these drugs only delay birth for approximately 48 hours,[9, 10] which provides an opportunity to administer antenatal corticosteroids to promote lung maturity but does not increase gestational age or improve neonatal outcomes significantly. Beta mimetics, such as ritodrine and terbutaline, originally thought promising agents to prevent PTB, are now contraindicated due to toxicity.[10]

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Conflict of Interest

The author has a pending patent (13/536,94), titled "Administration of N,N-Dimethylacetamide and Its Monomethylated Metabolites for the Treatment of Inflammatory Disorders". The author is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and her research group.

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The paucity of pharmacotherapy to prevent PTB has resulted, at least partially, from concerns about potential teratogenic effects on the fetus and toxic effects on the mother, both of which result from off-target actions of drugs meant to function in either the cervix or the uterus. A useful first step for avoiding these complications is using the vaginal route of administration. Advantages of administering a drug vaginally include the presence of a dense network of blood vessels, large surface area, and ability to circumvent hepatic first-pass metabolism.[11] Most importantly, this route of administration takes advantage of the so-called “uterine first pass effect”. The uterine first pass effect allows drugs introduced into the vagina to be carried by the vaginal-cervical-uterine portal vascular system and accounts for why high concentrations of a vaginally administered drug accumulate in the cervix and uterus, while low concentrations accumulate in the systemic circulation.[12, 13] Still, there are several disadvantages related to the vaginal route of administration. These include potentially poor absorption,[14] alterations to the vaginal microbiome[15] and a thick cervico-vaginal mucous layer—a natural barrier rich in glycoproteins and lipids preventing drugs from reaching their target tissues higher up in the gynecologic tract.[16, 17]

The most promising advance to overcome these challenges is the revolution in pharmacology and pharmaceutics known as nanomedicine.[18–20] Vaginally administered nanoparticles loaded with drug cargo, specifically engineered for mucoadhesion[21] or mucopenetration,[22] can overcome the cervico-vaginal mucous barrier and be directed to the target tissue with reduced systemic drug levels and reduced penetration of the placental barrier. Several preclinical trials have demonstrated the utility of the vaginal nanoformulation approach.

In two different preclinical studies, we have shown that a vaginally administered self-nanoemulsifying drug delivery system (SNEDDS) can delay the onset of inflammation induced PTB.[23, 24] After reporting that a sphingosine kinase inhibitor (SKI II, Cayman Chemicals, MI, USA) can prevent PTB when administered intraperitoneally,[25, 26] we showed that a SNEDDS composed of oil, co-solvent and SKI II drug cargo significantly increased the number of pups rescued from PTB in lipopolysaccharide-induced mice.[23] In a second study, we showed that a similar vaginal formulation loaded with 17-alpha hydroxyprogesterone caproate (aka Makena) also delayed the onset of PTB and rescued a significant number of pups.[24] Work is now underway to test a vaginal nanoformulation of N,N-dimethylacetamide, a widely used drug excipient, which we have shown to be a candidate for re-purposing for PTB.[27–30] Finally, Ensign *et al.* have recently reported that a vaginal nanoformulation loaded with the histone deacetylase inhibitor Trichostatin A plus progesterone (P4) decreased inflammation-induced PTB by 50% in their murine model.[31]

The ability to direct efficacious levels of drug cargo to the cervix and uterus, while maintaining very low concentrations in the maternal systemic circulation and preventing significant amounts from crossing the placental barrier, heralds a new era in the long and unrewarding quest for drugs to delay PTB. The advent of nanomedicine raises the possibility of re-purposing existing drugs and testing new drugs that would otherwise not be candidates for obstetrical disorders. Efforts in the PTB drug development field should be refocused and vaginal nanoformulations should be placed in the spotlight.

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