Targeted nanoparticles in pregnancy: a new frontier in perinatal therapeutics

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Many of the clinically used medications during pregnancy are small molecules, with molecular weight <1000 g/mol, which readily cross the placenta from the mother to the fetus. This, in certain cases, leads to serious fetal side effects.[1] As an example, one of the most commonly used tocolytic medications, indomethacin (molecular weight 358 g/mol), freely crosses the placenta,[2] and is linked to fetal side effects such as antenatal closure of the ductus arteriosus,[3] oligohydramnios,[4] necrotizing enterocolitis,[5] and intraventricular hemorrhage.[6] Other medications that are limited in pregnancy due to related fetal exposure include warfarin[7] and antiepileptics.[8]

Minimizing fetal exposure to medications is one of the main challenges in developing safer medications to use in pregnancy. This can be achieved by selectively targeting the site of action of a specific drug, the uterus in the case of tocolytics. One of the main capabilities of nanomedicine, a field of research on the intersection of medicine and nanotechnology, is increasing safety and efficacy of a drug by vectoring it preferentially to the affected tissue.[9] The placenta can be perceived as a membrane, across which small molecules can readily pass to the fetus, causing the related side effects,[1] and nanoparticles can be engineered to prevent this from occurring.[10-12] Since a nanoparticle has hydrodynamic diameter several orders of magnitude larger than a low-molecular-weight drug, it will remain in the maternal compartment, without crossing the placenta to the fetus. By manipulating physical and chemical properties of the particles, such as size and surface chemistry,[10,11] fetal exposure to the drug can be minimized. Furthermore, targeted delivery of the drug to its intended site can significantly mitigate the risks associated with systemic drug toxicities to the mother and the developing fetus.

While the concepts of nanomedicine are being applied clinically for >2 decades in the fields of oncology and infectious diseases,[13-15] perinatal nanomedicine is in its infancy. Liposomes are nanoparticles built from phospholipid bilayers, the building blocks of cell membranes. Liposomes are Food and Drug Administration approved and currently being used in the clinical setting to reduce adverse effects and improve efficacy of various medications. Liposomes encapsulating doxorubicin,[16] amphotericin B,[17] and bupivacaine[18] are routinely used in oncology, infectious diseases, and analgesia. Within the past year, the first 3 reports from different groups across the globe focusing on targeted nanoparticles to the uterus[19] and placenta[20] for the therapy of pregnancy-related conditions were published.

In the current issue, Paul et al[21] report a potential solution to the limitation of tocolytic treatments for preterm labor and uterotonic agents for postpartum hemorrhage. Immunoliposomes are liposomes that use antibodies for targeting a specific organ or condition. Paul et al[21] present immunoliposomes conjugated to oxytocin receptor antibody, which target the oxytocin receptor on the pregnant uterus. In their report, they were able to demonstrate that immunoliposomes loaded with tocolytic drugs including nifedipine, indomethacin, salbutamol, and rolipram, significantly reduced both human and mouse uterine contractility ex vivo compared to untargeted liposomes. Additionally, uterine location of the tocolytic drug, indomethacin, was increased with the immunoliposomes, resulting in lack of transplacental passage of the liposome to the fetus, significant prolongation of pregnancy, and reduction in preterm birth. This study represents a potential of nanoparticles to overcome the pharmacological challenges posed by many medical therapies available in the field of obstetrics. The potential to reduce fetal exposure to medications and to optimize pharmacological effects by delivering a drug to its intended site of action is exciting and can lead to new opportunities in the treatment of high-risk pregnancies.

Homing nanoparticles to the tissue of interest based on targeting specific receptors overexpressed within the tissue can be done using different ligands. Paul et al used antibodies as the moiety to specifically target the oxytocin receptor on the pregnant uterus. Immunoliposomes have been studied for the past 3 decades[22] as a drug delivery system for the treatment of cancer and other conditions.[23,24] However, immunoliposomes have not yet entered the clinical arena. While several monoclonal antibodies are currently used for the therapy of cancer (eg, human epidermal growth factor receptor 2, HER2 antibody, trastuzumab[25]) and transplant rejection (eg, interleukin-2 receptor antagonists basiliximab and daclizumab[26]), administration of monoclonal antibodies carries the risk of acute immune reactions such as anaphylaxis, serum sickness, and the generation of antibodies.[27] Pathological conditions in pregnancy, such as preeclampsia and preterm birth, are proinflammatory in their nature[28] and characterized by immune cell activation, and administration of antibodies may potentially aggravate maternal symptoms. Therefore, although the fetal exposure to the drugs is significantly

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minimized and the pregnancy is extended, clinical translation of the delivery system reported by Paul at al can be hampered by the antibody, the targeting moiety.

Two other recently published reports explore the ability to target maternal tissues using either oxytocin receptor antagonist, atosiban, commonly used clinically in Europe,[19] or experimental cancer-targeting peptides to increase the delivery to the placenta.[20] Liposomes with atosiban as a targeting moiety were reported to have similar properties to those described by Paul et al. Namely, these oxytocin receptor antagonist-targeted liposomes increased the concentration of the tocolytic agent, indomethacin, in the uterus, prevented indomethacin passage to the fetus, and reduced the rate of preterm birth.[19] In therapeutic concentrations, atosiban was shown to be safe and not to induce adverse effects,[29] and the total administered dose of oxytocin receptor antagonist in the reported liposomal system was several times below the minimal therapeutic dose.

In another study, King et al[20] showed that, following intravenous injection, the tumor-homing sequences CGKRK and CRGDKGPDC (iRGD), targeting $\alpha v\beta 3/\alpha v\beta 5$ integrins on de novo–produced blood vessels, specifically localized on the placentas and uterine spiral arteries of pregnant mice and that liposomes decorated with the CGKRK or iRGD sequences were also able to successfully target these tissues in vivo. Similar to other studies, targeted liposomes released a fluorescent probe within the mouse placenta, with no transfer to the fetus and significantly enhanced placental growth, when carrying insulin-like growth factor-II.

Employing principles of nanomedicine in the field of obstetrics can significantly improve our current clinical practices. Targeting the drugs specifically to the maternal organs to treat conditions such as fetal growth abnormalities and preterm labor can revolutionize how we treat our high-risk patients. Existing and new therapeutics (eg, small interfering RNA, micro RNA, protein based) can be efficiently encapsulated in the nanoparticles and delivered to the site of their action in the mother's body, while avoiding fetal harm. However, as with any new developments, several important questions are posed and still remain to be answered. Most of these are related to short- and long-term safety of the administered drug delivery system as well as how effectively they treat pregnancy complications compared to current therapies. Targeted nanomedicines represent a new frontier in perinatology with a potential to meet unmet needs for new and improved therapies in pregnancy that obstetricians face at this time. Collective effort in perinatal medicine to translate these initial reports into clinical practice should be applied to improve maternal and fetal care. ■

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