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Review

Engineered nanomaterial applications in perinatal therapeutics

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ABSTRACT

Engineered nanomaterials (ENM) are widely used in commercial, domestic, and more recently biomedical applications. While the majority of exposures to ENM are unintentional, biomedical platforms are being evaluated for use in individualized and/or tissue-targeted therapies. Treatments are often avoided during prenatal periods to reduce adverse effects on the developing fetus. The placenta is central to maternal-fetal medicine. Perturbation of placental functions can limit transfer of necessary nutrients, alter production of hormones needed during pregnancy, or allow undesired passage of xenobiotics to the developing fetus. The development of therapeutics to target specific maternal, placental, or fetal tissues would be especially important to reduce or circumvent toxicities. Therefore, this review will discuss the potential use of ENM in perinatal medicine, the applicable physiochemical properties of ENM in therapeutic use, and current methodologies of ENM testing in perinatal medicine, and identify maternal, fetal, and offspring concerns associated with ENM exposure during gestation. As potential nanoparticle-based therapies continue to develop, so does the need for thorough consideration and evaluation for use in perinatal medicine.

Contents

1. Introduction

Many therapies are limited during pregnancy to avoid untoward risk to the mother, placenta, or fetus. This can lead to a hiatus of normal treatment until gestation is complete, in some cases permitting the progression of disease. Therapies targeted to individual maternal or fetal tissues, while circumventing unintended

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toxicities, could allow for the development of perinatal medicine treatments.

Nanotechnology is a novel field, growing at an exponential rate. In recent decades, the use of engineered nanomaterials (ENM) has expanded to include the prevention and treatment of disease. These materials may be used in wound dressings, implantable devices, imaging platforms, and as a backbone/scaffolding for therapeutics. Engineered particle-based therapies allow for an adapted, tissue-targeted, or individualized treatment strategy. These compounds offer distinct advantages as therapeutic agents including improved bioavailability, controlled drug release, and increased drug targeting efficiency [1]. Consumers, including pregnant women, may be exposed to nanoparticles through ingestion or use of over-the-counter personal care products including sunscreens, toothpastes, cosmetics, and dietary supplements (Weir). Many diagnostics and treatments for diseases of the mother are avoided during pregnancy to prevent fetal harm; this is especially true during the first trimester of gestation [2,3]. With respect to oncology treatments, chemotherapeutic agents are not prescribed during the first trimester, but deemed safer during the second and third trimesters; all other treatments (radiation, hormone and immunotherapy) are postponed until after delivery, delaying maternal treatment. Therefore, the potential role for nanotechnology in maternal, placental, and/or fetal therapies is extremely valuable.

The health and function of the placenta, as a barrier and transporter organ, plays a vital role within the fields of perinatal health and maternal-fetal medicine. Perturbation of placental function can limit transfer of necessary nutrients, reduce the removal of fetal waste, allow undesired passage of xenobiotics to the developing fetus, and alter placental metabolism. Understanding placental function and toxicity with the application of novel ENM biomedical platforms is crucial to the advancement of effective and safe perinatal therapies.

In this review we will: [1] describe the perinatal methodologies and physiological challenges of using ENM for tissue-targeted or personalized medicine, [2] identify the physiochemical considerations to be addressed during the development of biomedical and theranostic devices on a nanomedical platform, and [3] discuss maternal and fetal toxicological concerns.

2. Development of perinatal therapies using engineered nanomaterials

The development of safe and effective ENM therapeutics for use in pregnant women demands a comprehensive understanding of ENM toxicity, uptake, and transport at the maternal-fetal interface. The close apposition of the maternal and fetal circulations within the placenta facilitates maternal-fetal exchange. Placental transfer occurs via three processes: passive diffusion, transporter-mediated transport, and endocytosis/exocytosis [4]; however transfer of ENM will likely be via passive diffusion or transporter-mediated transport. Rapid diffusion of small, lipophilic molecules across the maternofetal barrier is proportional to membrane surface area, membrane permeability, and concentration gradient, and is inversely proportional to diffusion distance (membrane thickness). Concentration gradient across the placental barrier is predominantly influenced by the rate of blood flow across the membrane. Further, the limited transport of hydrophilic molecules at the maternal-fetal interface suggests limited placental permeability of lipid insoluble molecules in the absence of transporters [4]. For hydrophilic or charged molecules that do not rapidly diffuse across plasma membranes, transporter proteins in the plasma membrane allow for rapid exchange down (facilitated diffusion) or against (active transport) a concentration gradient [4]. Thus, it can be speculated that active transport mediates the exchange of ENM across the placental barrier for ENM characterized by a chemical composition compatible with binding sites of transporters located in the brush boarder membrane.

The application of ENM targeted drug therapy for pregnancy-related conditions represents an opportunity to improve maternal and fetal care (Fig. 1). The generation and characterization of ENM designed to specifically target placental transporters to ensure transfer or prevent placental drug transfer to the fetal compartment, especially during critical periods of fetal formation, represents a promising avenue for the treatment of pregnancy-related conditions. Indeed, ENM uptake and transport at the placental barrier is an important consideration in pharmacological treatment during pregnancy due to the potential for direct and indirect adverse maternal and fetal effects.

2.1. Engineered nanomaterials as therapeutic platforms

The design and manufacturing of ENM for biomedical applications has evolved over several decades since the establishment of nanotechnology in the 1980s [5]. These anthropogenic materials are produced from larger bulk material to take advantage of physiochemical properties provided at the nanoscale. The potential role of nanotechnology for targeted applications in medicine is characterized by ENM stability, biocompatibility, and efficient delivery [6]. ENM design focuses on the manipulation of particle size, chemical construct, shape, and surface charge, each of which play a key role in biocompatibility and toxicity (Fig. 2).

2.1.1. Route of exposure and biological interactions

The distribution of ENM during pregnancy is different than that in the non-pregnant state, given the physiologic modifications to support the growing fetus. These include increased respiration rate, blood volume, and cardiac output, along with adaptations to immune function. Therefore, considerations for the route of exposure and biological interactions during the development of nanotherapeutics for perinatal medicines will be crucial.

When ENM come in contact with complex biological environments, they encounter an assortment of proteins. The spontaneous adsorption of proteins on the surface of ENM, called the protein corona, mediates the interactions at the nano-bio interface. The composition and pattern of the protein corona is dynamic and depends on the physiochemical properties of ENM and conditions of the surrounding environment including protein composition and distribution, functional groups, exposure time, temperature, and pH [7–9]. Within the systemic circulation, serum proteins are rapidly adsorbed by ENM onto their surface, marking them for removal by the mononuclear phagocyte system. Intentional modification of particle surface composition by the covalent attachment of polyethylene glycol (PEG) has been reported to increase the blood half-life of all ENM regardless of surface charge [10]. Therefore, the route of ENM administration (injection vs. inhalation or ingestion) and maternal exposure may play a critical role in further determining ENM surface chemistry and thereby systemic distribution [11–14].

ENM studies conducted in pregnant rats have been based primarily on traditional biomedical routes of medicinal administration, intravenous [15–19] and gastric [15] exposure. Recently, inhaled silver naïve nanoparticles were identified in the placenta and fetus after chronic nose-only inhalation [20]. These exposures also paired with elevated maternal cytokines [20].

2.1.2. Size

A nanomaterial, by definition, refers to particles measuring between 1 and 100 nanometers (nm) in a single dimension of the primary particle size. Therefore, particles within this size may range from as small as a quantum dot (2 nm in each dimension) to as large

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