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Engineered nanomaterial applications in perinatal therapeutics

S.B. Fournier[a], **J.N. D'Errico**[b], and **P.A. Stapleton**[a,b,*]

[a]Environmental and Occupational Health Sciences Institute, 170 Frelinghuysen Rd., Piscataway, NJ 08854, USA

[b]Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, 160 Frelinghuysen Rd., Piscataway, NJ 08854, USA

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.

Keywords

Perinatal; Maternal and fetal medicine; Placenta; Engineered nanomaterials; Nanotoxicology

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

*Corresponding author at: Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Environmental and Occupational Health Sciences Institute, Rutgers University, 170 Frelinghuysen Road, Piscataway, NJ 08854, USA. stapleton@eohsi.rutgers.edu (P.A. Stapleton).

Conflict of interest

The authors report no conflict of interest.

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 as a multi-walled carbon nanotube (20 nm in one dimension, but microns in length).

In a therapeutic context, size is an important parameter regarding circulation, distribution, placental transport, and fetal exposure to ENM. Indeed, size-dependent translocation of ENM varies across models, routes of administration, and particle type [21–24]. ENM excretion through the kidney is limited to <5.5 nm [25]. Physiological evidence suggests that hemochorial placental pore size measures around 10 nm, thereby preventing passive diffusion of larger ENM [26]. Recently, Wick et al., using an *ex vivo* human placental perfusion model reported the active transport and accumulation of 50 nm and 300 nm polystyrene particles in placental tissue [27]. Therefore, particles larger than 10 nm require an active transport support to maternal-fetal transfer; however, the transport mechanism is currently unidentified. In the few assessments conducted to evaluate ENM disposition pregnant rats, uptake of naïve ENM to the placenta following intravenous administration of gold (1.4 nm and 18 nm), silver (20 nm and 110 nm), or silica (25 nm and 50 nm) nanoparticles were size-dependent [14].

2.1.3. Chemical composition—Nanomaterials can be comprised of a wide variety of anthropogenically produced and biologically-derived resources. Anthropogenic bulk materials may be used to develop a structure or platform from which to build or promote cellular growth. Alternatively, biologically-derived biodegradable materials may be used to surround a pharmacological agent to direct release. For example, a protein- or lipid- based polymer may be used to deliver an antibiotic or antiviral medical to treat specific intrauterine infections.

Initial nanomaterial classification can be based on chemical composition. The most widely used bulk materials include: carbon, metals, plastic, and endogenously-derived (e.g. lipoprotein, lactic acid). Due to the unique chemical properties associated with material classification, each nanosystem is designed for specialized applications. Carbon-based applications are developed for their combined strength and electrical properties [28]. In physiological systems, this may make them ideal for gene or peptide delivery. Nanodiamonds have been explored as a delivery vehicle for bone morphogenetic proteins. These are approved for the promotion of bone growth, as an efficient alternative to conventional methods in medical and dental applications [29]. The unique surface properties of nanodiamond clusters, facilitates the loading and delayed release of proteins, and particle clearance by diffusion, altogether promoting more precise and sustained protein delivery [30].

Metallic nanoparticles range from low reactivity (titanium dioxide) to high reactivity (cadmium) materials. Nanosized titanium dioxide is widely used in domestic applications, including food, supplements, and personal care products [31]. Many biomedical applications exploit the magnetic properties of iron and magnesium that may aid in the development of imaging platforms [32]. Other metals including silver for antimicrobial properties or gold for heat production may be identified for use in a therapeutic context [33].

Polystyrene is a vinyl polymer being explored for fluorescence imaging. Quantum dots are classified as nanocrystals of semiconducting materials consisting of an inorganic core and an aqueous organic coated shell. In terms of medical applications, quantum dots have been utilized in a diagnostic capacity for fluorescence imaging of tissue as well as therapeutic delivery vehicles for protein or drugs [34,35]. Other chemicals may also be composited to create a layer particle: a magnetic diagnostic core with a therapeutic shell.

2.1.4. Shape—In a similar frame, ENM shape will be dictated by chemical construct. Nanoparticles may be synthesized in a variety of geometries, which can directly influence uptake and transport at the placental barrier. A comprehensive evaluation of the effect of shape on the cellular internalization of ENM reports the highest cellular uptake values for rods/tubes, followed by spheres, cylinders, and cubes [36]. In some cases similarities in the size and shape of ENM and intracellular components may confer the potential for direct physical interference of cellular processes [37]. Within a perinatal context, fibrous and/or sheet-like particles may be more appropriate for maternal applications unintended to pass the placental barrier; whereas fetal applications need to be small enough to pass the placental barrier. Accordingly, carbon-based nanomaterials may be developed as graphene sheets (wall-like scaffold), fullerenes (ball), single- (straw), and multi-walled (concentric tubes or a rolled graphene sheet) carbon nanotubes. Naïve titanium dioxide primary particles may be described as anatase, rutile, or brookite; all with the same chemical composition, but cleaved at differing angular axes [38]. The uptake and potential cytotoxicity of ENM coated with ligands may present an additional layer of complexity, as shape and dimension are factors known to alter ligand presentation to target receptors on cellular surfaces [39,40].

2.1.5. Surface chemistry/charge—Overall, modifications to ENM surface chemistry will increase or decrease the likelihood of particle-placental interactions. Surface modifications may be added to prevent placental transfer during maternal treatment, protecting the fetus from direct pharmacological interaction. Alternatively, variations may be tissue-targeted to specific placental receptors designed specifically for fetal use during prenatal therapy. Surface composition has been reported to affect accumulation of Au nanoparticles in murine fetal pups whereby ENM accumulation in fetal tissues was observed prior to gestational day 11.5 following a single intravenous injection to the dams of gold coated with ferritin, citrate or PEG in a saline solution. A greater maternal-fetal transfer of ferritin-coated and PEGylated nanoparticles compared to citrate coated nanoparticles was observed [41]. Using a similar experimental approach to Wick et al., investigation by Myllynen et al. reported finding no evidence that polyethylene glycol-coated gold particles up to 30 nm in diameter crossed the maternal-fetal barrier. Together these findings suggest an effect of material surface coating on transplacental transport of ENM.

Surface modifications offer an effective method to improve bioavailability and drug targeting efficiency. ENM surface functionalities mediate nano-bio interactions and are key determinants of overall stability. Alterations of surface chemistry include the addition of a functionalized group to a naïve nanoparticle surface or modifications within the biological environment. The addition of functionalized groups will not only increase particle size, but will also modify the hydrophilic or hydrophobic nature of the primary composition. Along with particle size, surface charge (and by default the hydrophilicity/phobicity) has been identified as a major factor affecting ENM translocation into a cell or through a physiological barrier [42].

The term “theranostics” has emerged to describe continuing efforts to combine diagnostic and therapeutic functions into a single platform for a more effective and tailored approach to diagnosis and treatment. Current approaches to cancer treatment demonstrate the utility of nanoparticle-based theranostics [43]. Tumor recognition and targeted delivery of therapeutics can be achieved using nanoplatforms loaded with targets known to bind to biomarkers expressed on the surface of cancer cells [44]. These theranostic and chemotherapeutic devices have a great potential in pre- and perinatal therapeutics, in maternal oncology patients. The development of these materials would focus on reducing ENM-placental interactions, using therapeutic agents that may avoid or evade placental transfer for fetal protection.

2.2. Nanomaterial toxicity in the perinatal environment

Nanoparticles are a promising tool for diagnostic and therapeutic medicine in maternal and fetal patient populations. It is crucial that these materials are prepared to mitigate detrimental effects during treatment. In this section we will discuss product development and toxicological testing models currently available.

2.2.1. Cellular models—Cell lines BeWo, Jar, and JEG-3 are commonly used *in vitro* models to mimic the placental barrier. The BeWo clone specifically models the cytotrophoblast layer of the placenta found in between the fetal and maternal interfaces and expresses adenosine triphosphate binding cassette (ABC) transporters specific to the maternal and fetal interfaces, including P-glycoprotein, breast cancer resistance protein (BCRP) and multidrug resistance-associated protein (MRP-1). This particular cell line is easily maintained and has similarities to the first trimester human placenta such as hormone secretion, close cell apposition, and apical microvillous projections [45]. Early studies provide evidence that cadmium triphosphate telluride and copper oxide nanoparticles, but not titanium dioxide, significantly decreased placental cell viability (at concentrations above 25 and 12 μg/mL, respectively) and the release of human chorionic gonadotropin (at concentrations above 1 and 3 μg/mL, respectively), showing placental dysfunction by altering hormonal secretion [46].

Safety testing using this cell line applied to Transwell inserts can allow for placental transport studies where quantification of uptake from the maternal (apical) and efflux to the fetal (basolateral) side is possible followed by a cell viability assay [47]. Validation of these transport studies using BeWo cell lines on Transwell inserts against rates detected in *ex vivo*

placental models for the same compounds are in agreement [45,47]. Transport of caffeine, benzoic acid, glyphosate, and antipyrine using BeWo cell culture and transwell inserts validate these models as translatable and potentially high-throughput models for the human placental transport of xenobiotics [48]. Transport of fluorescent polystyrene ENM over an *in vitro* Transwell insert seeded with a trophoblastic cell line demonstrated a greater transport rate for 50 nm compared to 10 nm particles [1]. In a related assessment, a size-dependent transport across a Transwell membrane insert was reported for particles loaded with dexamethasone at 146 nm as compared to 232 nm [49]. Future studies will need to evaluate ENM toxicity on transporter induction and efficiency within placental cells; however, BeWo have been validated against *ex vivo* models and is currently used for ENM transport studies [50–52].

Given the limitations of cell culture without the full context of the human body, recently developed organ-on-a-chip technology may be a superior alternative. This method uses microfluidic technologies to construct tissue surrounded by vasculature and interstitial fluid flow, enabling the cell to cell communication found *in vivo* [53]. Moreover, human cells can be applied for the recapitulation of human physiology. Recently has the first placenta-on-a-chip been created to simulate the exchanges between mother and fetus [54,55]. This new system not only promotes the unique placental process of syncytialization, but also the maternal-fetal barrier thinning that occurs throughout the progression of pregnancy. Transport through the bioengineered placental barrier has been confirmed by studying glucose and placental drug transfer rates compared against human placental tissue [54,56]. Although a more accurate *in vitro* model of the human organ, still the absence of full physiological responses found *in vivo*, including dynamic biofeedback, and neurological input, precludes the full *in vivo* extrapolation.

2.2.2. *In situ* assessments—Placental explant or *in situ* assessments may provide additional evidence on nanomaterial action within the maternofetal system. An *ex vivo* perfusion model utilizes mid- (E12-E14) or late- (E16-E18) gestation mouse placentas to allow for reproducible studies evaluating organ responses to environmental conditions [57]. Potential applications are complimentary to *in vitro* studies, and include assessing changes in placental *de novo* synthesis of molecules, molecular metabolism and transport during normal gestation or within the context of genetic modifications and environmental variables. Early studies were able to visualize infused fluorescently labeled dextran through the uterine and umbilical arteries with a two-photon imaging system [57]. While this methodology is currently unused with ENM, it holds exciting potential as a high throughput assessment for future studies.

The dual recirculation human placental perfusion model is an *ex vivo* alternative where transplacental transport of various substances can be studied in a controlled environment [58]. Briefly, intact placentas were obtained after uncomplicated term pregnancies were delivered, and were transported to the research laboratory within 20 min of delivery, the fetal and maternal sides were cannulated and the maternal side perfused with a dose-range of polystyrene beads suspended in warmed physiological salt solution. Viability and functionality of the placenta after nanoparticle perfusion were assessed by glucose consumption and lactate production. Using this model, Grafmueller et al. confirmed

nanomaterial translocation across the human placental barrier [59]. However, it is important to keep in mind the difficulties in accessing these tissues and the inherent variability within this model.

2.2.3. *In vivo* assessments—The distribution of ENM can vary dramatically between the pregnant and non-pregnant state, based on physiological adaptations associated with pregnancy. Few assessments have been conducted to determine the fate of ENM deposition or disposition during pregnancy. Of these whole body animal evaluations, evidence is provided for the significance of particle size on efficiency of uptake and transport. In pregnant rats, uptake and tissue deposition of naïve ENM from the blood following intravenous administration of gold (1.4 nm and 18 nm), silver (20 nm and 110 nm), or silica (25 nm and 50 nm) nanoparticles were size-dependent [14,15]. ENM deposition and accumulation of silver ENM was identified using ICPMS or hyperspectral analyses in the mothers' spleen, liver, and lungs, in addition to the endometrium, placenta, and fetus using [15,18,19]. Using radiolabeled C60 fullerenes, radioactivity distribution was measured in the liver, lungs, placenta, fetus, and milk of the lactating dam [16,17]. A single intravenous injection of quantum dots in pregnant mice late in gestation resulted in a size- and dose-dependent accumulation in the pups and a placental transfer of 0.23–0.61% of the intravenous dose [22]. Additionally, intravenous administration at gestational day 17 of 0.4 mg of 70 nm silica or 35 nm TiO_2 led to the presence of these particles in the mouse placenta, the fetal liver, and fetal brain as evidenced by TEM [24]. These studies demonstrate low concentrations of ENM distribution to the placenta and fetus after maternal injection [15–19]; however, given the anatomical differences between murine and human placenta, extrapolations must be made with caution [60].

While the focus of this review is to highlight the potential that engineered nanotechnologies provide to perinatal therapeutics, it would be remiss to ignore the potential toxicities associated with ENM exposure during gestation. There have been a number of recent review articles focusing on developmental toxicities associated with ENM exposures [61–65]. The general emphasis of these reviews has been to describe the teratogenic effects after unintentional exposure. One review has focused on the anatomical and systemic implications of gestational exposure on the offspring [66]. Disruption of the maternal environment has been shown to impact future health and survival of the fetus, which has more recently been identified as the "Barker Hypothesis" [67]. This theory also states that fetal development in a hostile environment may predispose for adult sensitivity to disease [67]. Nanoparticle exposure during gestation has led to the identification of a range of untoward effects on the health of the mother, fetus, and adult offspring [66]. Pulmonary exposure to ENM during gestation led to the development on a hostile gestational environment defined as endothelial cell [68] and vascular smooth muscle [69] dysfunction within the uterine and umbilical circulations. Alterations within offspring exposed to ENM during gestation have included neonatal and adult behavior, stunted growth, impaired neurologic function, immune reactivity, kidney injury, mitochondrial, epigenetic modifications, cardiomyocyte, coronary, and microvascular function [68,70–79]. Therefore, care should be taken to fully evaluate possible fetal consequences of maternal ENM exposure.

There is considerable evidence in animal models and humans supporting the influence of maternal health on preimplantation, gestation, and postnatal development after birth [80–82]. Additionally, systemic maternal inflammation in the rat model is associated with ENM exposure, and although maternal, exposes the fetus to maternal responses of increased cytokine, chemokine, or lipid mediators [83]. Cytokines may activate resident immune cells at the placental barrier and result in placental transfer of inflammatory factors, thereby inducing a hostile environment for the developing fetus [84,85]. Previous *in vitro* and *in vivo* studies corroborate that exposure to certain ENM will induce a proinflammatory response [86,87]. While an immune milieu is maintained during pregnancy by multiple cell types, where the body is tolerant to the product of conception while also remaining reactive to invading pathogens with potential adverse effects to the offspring; it is unclear to what effect ENM exposure may have on the regulation of this delicate homeostasis [88,89]. Future therapeutic development may want to consider the direct inclusion of an anti-inflammatory onto the ENM platform.

3. Conclusion

The use of nanoparticles during pregnancy may be a double-edged sword, as there is evidence showing increased maternal and fetal inflammation after naïve nanoparticle exposure; conversely, inflammation was attenuated for the fetus after exposure to nanoparticle-conjugated drug administration [81,90]. Intrauterine inflammation has been shown to enhance the transport of nanoparticles across the placenta, possibly facilitating placental and fetal accumulation [81]. Although enhancement of permeability across barriers has pharmaceutical advantages, there may be potential hazards, yet to be characterized during gestation. Surface modification and conjugates added to nanoparticle scaffold may further enhance penetration across biological barriers, such as the placenta, increasing persistence in these tissues. Nanoparticle-based therapy with antioxidant and anti-inflammatory properties can mitigate these outcomes to reduce immune-mediated damage [90]. Therefore, in addition to directing therapy to the primary site of treatment, intentional biomedical use of these devices should consider modifications to limit untoward side effects as perinatal therapeutics.

Maternal-fetal medicine is an arena with a critical need for targeted delivery of drug therapies as the developing fetus represents a vulnerable subgroup of the population. The placenta is a highly dynamic and complex organ that constitutes the boundary between the mother and developing fetus [67]; indeed, one of the most significant barriers to the development of drug therapy. The potential to modify ENM physiochemical properties (size, shape, and surface characteristics) for placental targeting or inhibition represents an exciting opportunity. Therefore, development of paradigm ENM for fetal medicine will focus on tissue-targeting materials to allow for the safe treatment of maternal and fetal conditions during gestation.

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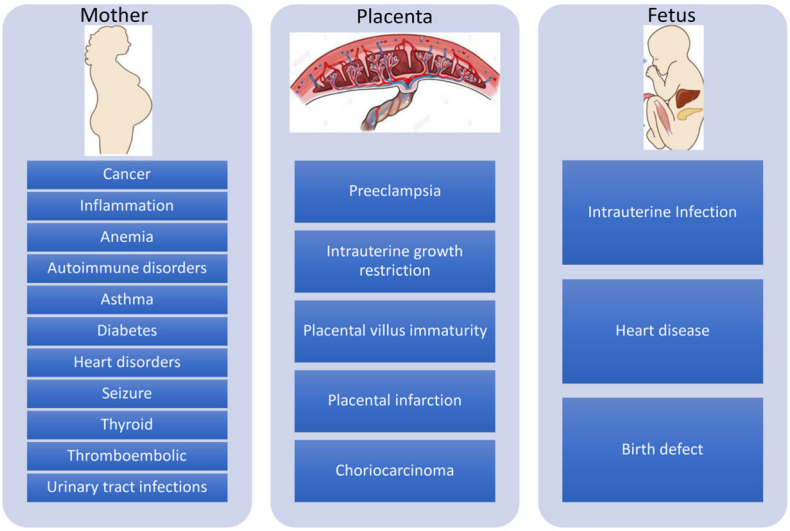

Fig. 1.

Perinatal conditions that may be treated using therapies developed on an engineered nanomaterial platform.

Fig. 2.

Physiochemical properties and biological concerns when considering the development of engineered nanomaterial platforms into biomedical therapeutics.