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REVIEW ARTICLE

A Review on Nanoparticle-Based Drug Delivery Systems for Treating Placental Dysfunction

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Abstract: The placenta plays a significant role during pregnancy. Preeclampsia and fetal growth restriction are two serious obstetric complications influenced by placental dysfunction. Currently, prophylaxis is often administered too late to avoid disease manifestation, and there is no effective treatment for placental dysfunction during the perinatal period. However, with the recent integration of nanoscience and medicine, it is anticipated that innovative and effective nanotherapies will be developed to address the difficulty of managing placental dysfunction. Nanoparticle drug delivery is now safe and precise, utilizing intelligent nanoparticles capable of loading drugs, ligands, and other therapeutic substances specifically targeted at the placenta. Placental malfunction seriously jeopardizes maternal and fetal health, frequently resulting in issues such as intrauterine growth restriction and preeclampsia. This article provides an introduction to nanoparticles in medicine, types of nanoparticles used, targeted drug delivery systems, benefits of nanoparticles in medicine, challenges and limitations, and applications in specific diseases. As conventional treatment options are limited, creative methods are needed to improve results. Due to their special physicochemical characteristics and ability to pass through biological barriers, nanoparticles have become attractive options for targeted drug administration.

Keywords: Placental Dysfunction; Nanoparticles; Pregnancy; Targeted Therapeutic Delivery.

1. Introduction

Nanomedicine, the application of nanotechnology for the treatment, prevention, monitoring, and control of biological diseases, has been widely applied in the field of placental dysfunctions and oncology [1]. The clinical therapeutic effect of nanomaterials requires precise targets (receptors and/or cells) that can be specifically identified by nanoparticles and are suitable for the delivery system to improve the efficacy of the original drug and minimize side effects [2]. These precise targets include proteins, macrophages, dendritic cells, endothelial cells, and tumor cells. When nanoparticles (NPs) contact and break down their targets, the drug is released to assert its therapeutic function [3]. There are many types of nanomaterials and nanocarriers used for drug delivery to treat diseases, including liposomes, dendrimers, micelles, polymeric micelles, polymeric nanoparticles, and metallic nanoparticles [4]. Fetal growth restriction (FGR) is defined as a pathologic decrease in the rate of fetal growth, with the most frequent etiology being uteroplacental dysfunction due to an inadequate supply of nutrients and oxygen to support normal aerobic growth of the fetus [5]. For symmetrical FGR, fetal chromosomal anomalies, structural anomalies, and fetal infections should be carefully excluded [6]. Consequent to the uteroplacental vascular maladaptation of endovascular trophoblastic invasion, there is increased vascular resistance and decreased blood flow to the placenta in the choriodecidual compartment [7].

2. Pathophysiology of Placental Insufficiency

The cause of inadequate placentation is the genesis of both FGR and preeclampsia (PE). Three phases can be identified in the pathophysiology of placental insufficiency, which is still complicated and multifactorial, affecting both the mother and the fetus [8].

Phase 0: A healthy placentation during phase 0 is mostly dependent on the mother's interaction with either the fetal or the paternal antigens [9].

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Phase 1: The placenta is exposed to oxidative stress and hypoxia during phase one because of poor vascularization, causing the placenta to emit pro-inflammatory cytokines and anti-angiogenic substances into the mother's blood circulation [10]. Maternal systemic endothelial dysfunction is caused by an imbalance of several circulating molecules, including placental-like growth factor (PlGF), soluble FMS-like tyrosine kinase-1 (sFlt1), and tumor necrosis factor-alpha (TNF-a) [11].

Phase 2: Although placental insufficiency syndromes can be attributed to early gestation or even preconception, phase 2 refers to the late gestational period when symptoms first appear [12].

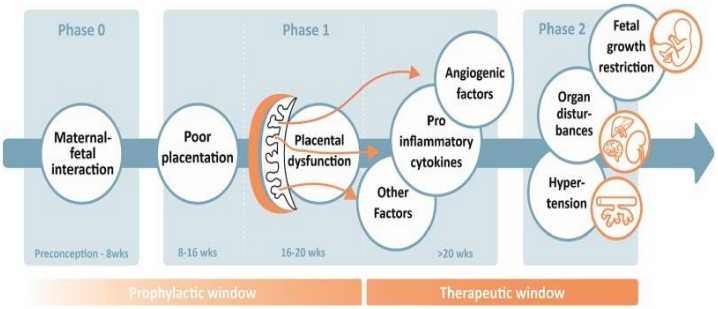

Figure 1. Pathophysiology of Placental Dysfunction

3. Diagnosis

Prenatal care providers use ultrasound or prenatal exams to diagnose placental insufficiency. An ultrasound can measure the size and location of the placenta and the fetus in addition to detecting blood flow between them [13]. If the fetus appears smaller than average on the ultrasound or if the fundal height measurement is smaller than expected, a placenta problem may be suspected [14]. Providers also consider the mother's concerns and fetal movement, which may provide clues about the pregnancy's status [15]. MRI imaging has been discovered to offer more details to help identify and treat placental insufficiency [16, 17]. Reduced flow voids between the placenta and the uterus can be interpreted as a sign of lower uteroplacental perfusion [18]. MRI imaging also offers strong soft-tissue contrast, allowing placental-MRI to identify anomalies related to the placenta, such as hemorrhages and infarctions, suggesting a high risk of placental insufficiency and downstream FGR [19]. Placental dysfunction disrupts nutrient and oxygen supply to the fetus, leading to growth restrictions and potential complications in pregnancy, such as preeclampsia and fetal distress [20]. Early detection and management are crucial to mitigate risks and ensure a healthy pregnancy outcome [21].

Table 1. Treatments for Placental Dysfunction

Treatment	Mechanism of Action	Advantages	Limitations
Aspirin	Inhibits thromboxane A2 production	Reduces risk of preeclampsia and FGR	May cause bleeding complications
Low Molecular Weight Heparin	Anticoagulant and anti-inflammatory properties	Improves placental perfusion and fetal growth	Requires daily injections
Sildenafil Citrate	Vasodilator, increases uterine blood flow	Enhances placental function and fetal growth	Limited data on long-term safety
Vitamin D Supplementation	Modulates immune function and angiogenesis	May reduce risk of preeclampsia and FGR	Optimal dosage and timing unclear
Antioxidants (Vitamins C and E)	Reduce oxidative stress and improve endothelial function	Potential to prevent preeclampsia and FGR	Inconsistent results in clinical trials
Folic Acid	Essential for DNA synthesis and cell division	Reduces risk of neural tube defects	No significant effect on placental dysfunction
Metformin	Improves insulin sensitivity and reduces inflammation	Potential to prevent preeclampsia and FGR	Limited data on safety during pregnancy
Pravastatin	Pleiotropic effects, improves endothelial function	May reduce risk of preeclampsia and FGR	Safety concerns during pregnancy
Nanoparticle-based drug delivery	Targeted delivery of therapeutic agents to the placenta	Enhances drug efficacy and reduces side effects	Still in experimental stages

4. Nanomedicine during Pregnancy

Nanotechnology enables particular uses in medicine, from focused treatments to more sensitive diagnostics. Nanomedicines offer a way to enhance prenatal care that will directly and permanently benefit the mother and the unborn child [22]. When a medicine molecule is encapsulated or associated with a nanoparticle, its fate is determined by the properties of the nanoparticle rather than its own physicochemical properties [23]. This provides control over the drug's final location and release schedule. For instance, water-soluble small molecular weight medications are quickly removed from the bloodstream by the kidneys, restricting their accessibility to the targeted tissue [24]. When encapsulated in a nanoparticle, such a medication can evade renal clearance and often have an extended duration of circulation [25].

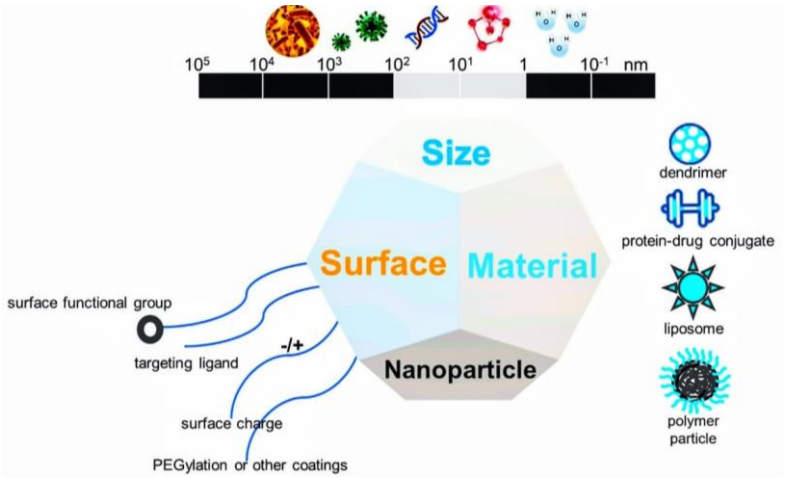

Figure 2. The biophysiochemical properties of nanomaterials for drug delivery in placental dysfunction

4.1. Types of Nanoparticles

Four primary classes of nanoparticles have been studied in recent years for prenatal treatment with maternal and placental targets: liposomes, polymers, silicon nanoparticles, and quantum dots [26].

4.1.1. Liposomes

Liposomes were among the first nanoparticles studied as medicinal carriers, with the first formulation licensed for clinical use in 1992 [27]. Amphiphilic (phospho)lipid molecules form a bilayered spherical vesicle through self-assembly, with hydrophilic heads and hydrophobic tails. Medications can be incorporated in the lipophilic membrane or encapsulated inside the hydrophilic core [28]. The second generation of liposomes, known as poly(ethylene glycol) (PEG)-coated or "stealth" liposomes, was created to lessen the limitation of quick detection and absorption by macrophages in the liver and spleen [29].

4.1.2. Polymers

Polymeric nanoparticles are perhaps the most adaptable drug delivery technique. Many monomers can be combined to form a single polymer, with an endless variety of natural or manufactured monomers available [30]. These monomer combinations can be arranged in diblock, triblock, random, or alternating configurations, which can be stable or biodegradable depending on their lengths and connectedness in a branching or linear manner [31]. Various polymer nanoparticle forms have been characterized in the setting of placental medication administration, including poly(lactic-co-glycolic acid) (PLGA), polystyrene nanoparticles, and poly(amidoamine) (PAMAM) dendrimers [32].

4.1.3. Quantum Dots

Quantum dots (QDs) are the tiniest nanoparticles used in medication delivery, with special optical and electrical characteristics [33]. One of their intrinsic fluorescence qualities is the ability to transform a spectrum of light into distinct hues, which may be very important in theragnostic applications that integrate therapy and diagnosis [34]. The fluorescence provides localization information, and once the goal accumulation has been reached, a drug release trigger can be given [35].

4.1.4. Silicone Nanoparticles

Silicon (Si) nanoparticles are a kind of quantum dots with the same appealing properties as previously mentioned for theragnostic applications, but at smaller sizes [36]. The bigger porous Si nanoparticles enable surface property change and high loading capacities due to their rich surface chemistry and large internal surface area [37]. Customized pore sizes and volumes can be created by electrochemical synthesis, controlled from the micron to nanometer scale [38]. It is also possible to chemically engineer porous Si surfaces to regulate the kind, quantity, and rate of release of pharmacological payloads [39].

4.2. Effect of Different Nanomedicines on Fetal Growth

In the majority of studies, fetal growth is based on fetal or pup weight, reported at various times (from GD18 up to at time of birth) [40]. Beneficial treatment effects on increasing fetal or pup weight were demonstrated in eight investigations [41]. The Jones group conducted preclinical studies in which they injected hIGF-1 into their trophoblast-specific gene delivery systems using an invasive FGR animal model (uterine branch ligation), in addition to their in vitro functioning studies [42]. They discovered higher fetal birth weights on GD20 [43]. Yu et al. assessed that the fetuses' weights were higher than those of the control rat group, in addition to the reduced maternal outcome caused by siRNA-sFlt1-PAMAM [44]. Cureton et al. found that multiple nitric oxide injections enhanced the fetal outcome on GD18 [45].

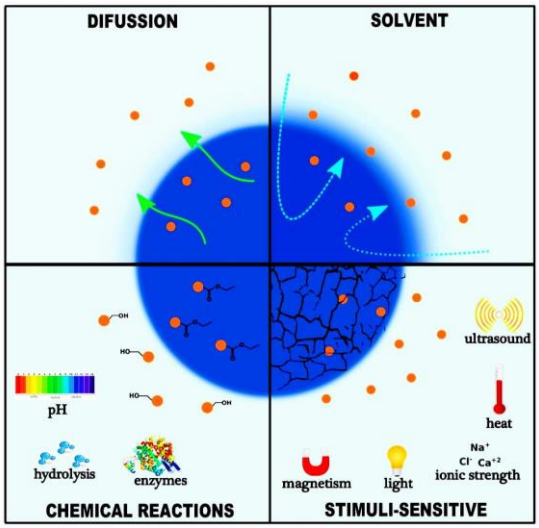

Figure 3. Mechanisms for controlled release of drugs using different types of nanocarriers.

4.3. Effect of Different Nanomedicines on Prolonging Pregnancy

In the human situation, premature birth is frequently the outcome of PE and FGR. Enhancing the preeclamptic symptoms may allow the pregnancy to last longer, giving the fetus additional time to mature [46]. Since most animal models of PE and FGR do not induce preterm birth, the impact of nanoscale drug delivery techniques on gestational extension has not been particularly studied in these animals [47, 48]. Nevertheless, in animal models of forced preterm birth, a number of nanomedicines have been demonstrated to prolong pregnancy and offer useful data regarding prevention of transplacental transit, the impact of administration route, and the efficacy of therapy [49]. Two research, for example, used animal models of premature birth and showed that giving indomethacine-encapsulated targeted liposomes can prolong pregnancy [50].

Table 2. An overview of targeting approaches of nanomedicines in complicated pregnancies for placenta insufficiency syndromes

Targeting Approach	Mechanism of Action	Advantages	Limitations	Examples
Passive Targeting	Enhanced permeability and retention effect	Increased drug accumulation in the placenta	Non-specific targeting	PEGylated liposomes, polymeric nanoparticles
Active Targeting (Ligand-mediated)	Specific binding to placental receptors or antigens	Improved placental specificity and drug delivery	Potential immunogenicity, complex manufacturing process	Antibody-conjugated nanoparticles, peptide-modified nanocarriers
Size-based Targeting	Utilization of size-dependent placental transport pathways	Enhanced transplacental passage of small-sized particles	Limited drug loading capacity for smaller particles	Nanoparticles < 100 nm in size
Charge-based Targeting	Electrostatic interactions with placental surface charges	Increased placental retention and cellular uptake	Potential toxicity and non-specific interactions	Cationic liposomes, cationic polymeric nanoparticles
Magnetic Targeting	Magnetic field-guided localization of magnetic nanoparticles	Externally controlled drug delivery to the placenta	Requirement of external magnetic field, potential toxicity	Iron oxide nanoparticles, magnetic liposomes
Stimuli-responsive Targeting	Activation or release of drugs in response to specific placental stimuli	Spatiotemporal control of drug release in the placenta	Complex design and manufacturing, potential immunogenicity	pH-sensitive nanoparticles, enzyme-responsive nanocarriers
Biomimetic Targeting	Mimicking the properties of natural placental components or cells	Enhanced placental compatibility and reduced immunogenicity	Limited scalability and reproducibility	Platelet membrane-coated nanoparticles, extracellular vesicle-inspired nanocarriers
Combination Targeting	Utilization of multiple targeting strategies for synergistic effects	Improved targeting efficiency and specificity	Increased complexity and potential for adverse interactions	Dual-ligand targeted nanoparticles, size and charge-optimized nanocarriers

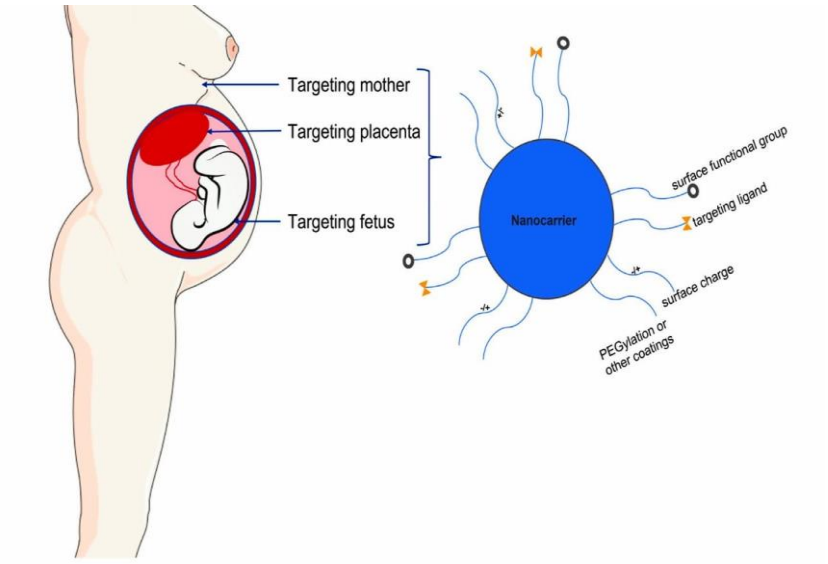

Figure 4. Schematic illustration demonstrating placental targeted drug delivery and nanoparticles applied in pregnancy

5. Conclusion

Nanomedicines offer a promising therapeutic approach during (difficult) pregnancies, primarily through fetal toxicity reduction and placental regulation of drug interaction. Some nanomedicines have been demonstrated to successfully stop encapsulated drugs from passing through the placenta, which is anticipated to significantly lower the likelihood of prenatal adverse consequences. Additionally, several of these nanomedicines improved the health of the mother and the fetus in animal models of placental insufficiency, proving that the target tissue can receive efficacious medication concentrations. Although these initial animal findings are promising, additional investigation is required to fully comprehend the biology of this complex disease before considering application in clinical settings. Nanoparticles enable focused medication delivery, increased therapeutic efficacy, and fewer systemic adverse effects, making them a promising treatment option for placental malfunction. Additional investigation and clinical trials are required to verify their safety, efficacy, and enduring effects on the health of expectant mothers and fetuses. However, their creation marks a noteworthy advancement in the treatment of pregnancies affected by placental dysfunction

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