

Review

Research Progress on Placenta-Targeted Drug Delivery in the Treatment of Preeclampsia

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Abstract

Objective: This review aimed to provide a thorough analysis of the recent advancements in placenta-targeted drug delivery systems to manage preeclampsia (PE). **Method:** This article presents a comprehensive review of advancements in placenta-targeted drug delivery to manage PE. Moreover, this review emphasizes the assessment of various delivery routes and the selection of suitable drug carriers, incorporating relevant findings from both preclinical and clinical trials. By examining the mechanisms of action, benefits, and potential applications of placenta-targeted drug delivery, this article seeks to offer valuable insights and guidance for future research. **Findings in Brief:** Preclinical studies indicate that targeted drug delivery systems, which employ various methods, including intravenous or intraperitoneal administration and utilize carriers like antibody-conjugated nanoparticles, produce significantly higher concentrations of drugs in the placenta compared with non-targeted methods. The targeted approach has shown promising results in animal models of PE, often leading to improvements in maternal health indicators, such as lower blood pressure and reduced protein levels in urine, as well as enhanced fetal outcomes, including improved growth and decreased inflammation. While the clinical translation of these findings into practice remains in its early phases, initial clinical trials are currently assessing the safety and preliminary effectiveness of these innovative delivery systems. Although these early results suggest potential advantages, larger and more comprehensive trials are required to draw definitive conclusions about the efficacy of these delivery systems. **Conclusions:** Placenta-targeted drug delivery represents an innovative and promising strategy for managing PE. This approach addresses the limitations of traditional therapies by enabling localized and high-concentration drug delivery, which could significantly improve outcomes for both mothers and their infants. Finally, while preclinical data offer encouraging results, continued research aimed at optimizing delivery methods, creating advanced drug carriers, and conducting thorough clinical trials remains essential.

Keywords: placenta-targeted drug delivery; preeclampsia; treatment progress; drug carriers; clinical research

1. Introduction

Preeclampsia (PE) is a prevalent and serious complication that can occur during pregnancy [1,2]. PE is primarily marked by elevated blood pressure and the presence of protein in the urine. Both mothers and infants affected by PE face a heightened risk of developing chronic conditions, such as cardiovascular, renal, metabolic, and neurological diseases [3]. Meanwhile, more than 26 million women worldwide experience pregnancy-related complications annually, with the incidence of hypertensive disorders reaching 10.7% according to the 2023 World Health Organization (WHO) report [4,5]. Although available research has significantly advanced our understanding of the mechanisms underlying PE, a notable gap remains in the effective treatment options, particularly regarding prevention and management strategies [6].

Traditional treatments for PE primarily focus on managing blood pressure and alleviating symptoms [7]. However, no definitive treatment plan currently exists that is specifically tailored for this condition, with the most effective intervention being the timely termination of pregnancy

[8–10]. Therefore, this highlights an urgent need to explore new treatment strategies. Recently, placenta-targeted drug delivery has emerged as a promising therapeutic approach, garnering increasing interest from researchers. Indeed, this method aims to specifically target placental tissues, thereby enhancing drug specificity and improving therapeutic outcomes, which could lead to innovative solutions for managing PE. The success of placental drug delivery hinges on effectively utilizing both the physiological characteristics and pathological changes in the placenta, which are crucial throughout pregnancy for nutrient and gas exchange [11]. However, the unique structural complexities and selective permeability of the placenta present significant challenges for effective drug delivery [12]. Thus, researchers have employed nanotechnology to overcome these obstacles, developing a range of advanced drug carriers, such as lipid nanoparticles and functionalized nanoparticles. Notably, these innovative carriers enhance the delivery of medications to the placenta, and minimize the potential side effects for both the mother and fetus [12,13].



For example, liposomes that have been modified with a synthetic placental glycosaminoglycan-binding peptide have shown a remarkable ability to target placental tissues, thereby enabling precise drug release [14]. Furthermore, several studies have indicated that using nanoparticle carriers can significantly increase the accumulation of drugs in placental tissues, thereby improving therapeutic outcomes [5,15]. These findings provide a solid theoretical foundation and practical support for the use of placenta-targeted drug delivery strategies in managing PE.

Overall, continued in-depth research into these technologies holds great promise for creating more effective and safer future treatment options for PE. This article explores the latest developments in placenta-targeted drug delivery as a treatment approach for PE, aiming to offer useful references and guidance for clinical practice.

2. The Role of Placental Dysfunction in the Pathogenesis of Preeclampsia

Placental dysfunction is a fundamental component in the pathophysiology of PE, and its involvement can be elucidated through several essential pathways as follows:

2.1 Abnormal Placental Formation

The essential mechanism involved in the formation of the placenta includes the invasion of trophoblast cells and the remodeling of spiral arteries [15,16]. hypoxia-inducible factor 1- α (HIF-1 α) induces enhanced metalloproteinase-2 and -9 (MMP-2/9) activity, leading to excessive matrix degradation or repair impairment, thereby hindering the normal invasion process of trophoblast cells and decreasing invasive ability [17]. Abnormal reconstruction of spiral arteries may lead to placental ischemia and hypoxia and increased mitochondrial oxidative stress [18], damaging the vascular endothelium [19] and triggering systemic PE-related symptoms.

2.2 Release of Placenta-Derived Factors

The imbalance between pro- and anti-angiogenic factors can trigger what is known as an antiangiogenic factor storm. In this scenario, soluble FMS-like tyrosine kinase-1 (sFlt-1) binds to the placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), leading to an abnormal ratio of VEGF to PlGF. This imbalance contributes to endothelial dysfunction [20–23]. Meanwhile, inflammatory mediators, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), are simultaneously released, thereby worsening systemic inflammation and promoting vasoconstriction and hypertension [23].

The placenta plays a dual role in this process, acting as both the “initiator” of the pathological changes associated with PE and an “amplifier” that enhances the diffusion of effector factors [24]. Moreover, the placenta drives the disease progression through mechanical ischemia, namely physical obstruction, and abnormalities in molecular sig-

naling due to the release of various biological factors. This understanding provides a theoretical foundation for developing therapeutic strategies that specifically target the placenta.

3. Placenta-Targeted Drug Delivery

3.1 Mechanisms of Placenta-Targeted Drug Delivery

3.1.1 Characteristics of the Placental Barrier

The placenta acts as a crucial physiological barrier between the mother and the fetus. As such, the placenta features a unique and complex structure and function that are essential to its role. The main functions of the placenta include facilitating the exchange of materials, regulating the immune system, and protecting the fetus from harmful agents. The multilayered cellular structure of the placenta, primarily composed of the syncytiotrophoblast and cytotrophoblast, which are the two most important layers, represents a notable characteristic of the placental barrier. The tight junctions formed between these layers create an effective barrier that significantly restricts the entry of most harmful substances [25]. Furthermore, the structural complexity and selective permeability of the placenta pose significant challenges for drug delivery, especially for macromolecular medications and certain specialized compounds [12]. Importantly, the placental barrier also performs dynamic regulatory functions, enabling it to adjust material transport flexibly depending on the changing needs of both the mother and the fetus [13].

3.1.2 Routes for Drug Penetration Through the Placenta

There are various pathways through which drugs can cross the placenta, with the most notable being passive diffusion, active transport via transport proteins, and endocytosis [26,27]. Passive diffusion is a straightforward process that allows small-molecule drugs to pass through the lipid bilayer of cell membranes and enter placental tissue without requiring additional energy, making the process highly efficient and natural. Regarding active transport, transport proteins play a crucial role by using specific mechanisms to facilitate the transfer of drugs from the mother to the fetus [28,29]. For example, important substances in maternal blood, such as glucose and amino acids, are efficiently and selectively transported to the fetus through specific transport proteins, including those from the glucose transporter (GLUT) and solute carrier (SLC) families [30]. Additionally, endocytosis plays a significant role in placental function, especially in situations where drugs bind to receptors on the surface of placental cells. In these instances, the endocytic process effectively internalizes the drugs, enhancing their bioavailability and therapeutic effects [31].

3.1.3 Advantages of Placenta-Targeted Strategies

The primary advantage of drug delivery systems designed for the placenta lies in the ability of the system to increase drug concentrations within the placenta while re-

ducing the risk of toxicity to the developing fetus. Thus, by targeting specific placental receptors, such as placental glycoproteins and other unique binding sites, these systems enable a more focused drug delivery [32,33]. Indeed, this targeted method minimizes drug distribution and decreases adverse effects on other maternal tissues [5]. For example, using modified nanoparticles or liposomes can greatly improve the effectiveness of drug targeting to the placenta, as these delivery vehicles can cross the placental barrier and significantly boost drug accumulation in the placenta [14]. Additionally, placenta-targeted drug delivery can lower the necessary drug dosage, thereby enhancing the safety and effectiveness for both the mother and fetus [13]. Ultimately, by employing these innovative strategies, researchers aim to develop new therapeutic approaches for placenta-related conditions, such as PE and fetal growth restriction, to improve maternal and neonatal health [34].

3.2 Selection of Drug Carriers

3.2.1 Application of Nanocarriers

Nanocarriers play a crucial role in drug delivery systems [35,36], especially in the area of placenta-targeted drug delivery. Recently, the use of nanocarriers has led to the development of innovative strategies aimed at enhancing drug bioavailability and specificity [37,38]. Previous studies have shown that these nanocarriers can effectively cross biological barriers [5,39], including the placental barrier, thereby enabling targeted treatments for the fetus. For example, one study introduced liposomal nanocarriers specifically designed to target macrophage receptors, which successfully delivered drugs to placental tissues. This approach significantly increased the drug concentration within the placenta and improved therapeutic outcomes [5]. Additionally, by engineering nanocarriers to modify their surface characteristics, researchers can enhance drug release profiles, promoting drug accumulation in specific tissues and achieving more precise therapeutic effects [12].

3.2.2 Characteristics of Micelles and Liposomes

Micelles and liposomes are two common types of nanocarriers [40], each with unique physical and chemical properties that influence their interactions with biological systems. Micelles are typically formed through the self-assembly of surfactants [41], resulting in small particle sizes and high drug loading capacities, thereby making micelles particularly useful for delivering hydrophilic drugs. Liposomes are composed of phospholipid bilayers and can encapsulate both hydrophilic and hydrophobic substances, offering good biocompatibility and biodegradability [42]. Liposomes have been shown to protect drugs from degradation effectively during transport and allow for sustained release within the body [13]. For example, targeted drug delivery to the placenta can be achieved by modifying the composition and structure of liposomes enabling the release of medications in specific physiological environments, thereby enhancing therapeutic effectiveness [14].

3.2.3 Exosome Drug Carriers

Exosomes are continuously released from trophoblast cells into the maternal bloodstream throughout pregnancy [43,44]. Interestingly, the production of these exosomes in cases of pregnancy-related complications, such as PE and gestational diabetes, is higher than in normal pregnancies [45,46]. Exosomes offer several advantages as carriers for drug delivery [47,48]. Notably, the large number of exosomes produced by the placenta can be absorbed effectively by trophoblast cells. Therefore, the concentration and composition of placenta-specific exosomes could serve as valuable tools for the targeted delivery of therapeutic agents to the placenta. Exosomes loaded with doxorubicin and small interfering RNA (siRNA) have been shown to present a promising strategy [49,50], highlighting their significant potential for clinical applications.

3.2.4 Research Progress on Multifunctional Carriers

Recently, there has been significant interest in the study of multifunctional carriers [51,52], especially in the area of placenta-targeted drug delivery. Notably, these carriers help transport drugs and incorporate features for targeting, imaging, and therapy through creative design [53,54]. For example, researchers have developed nanocarriers that combine photothermal treatment with drug delivery. These nanocarriers can generate heat when exposed to near-infrared light, which enhances the effectiveness of the drug against tumors [30]. Additionally, multifunctional carriers made from biocompatible materials can effectively target specific cell types, thereby minimizing the side effects of medications and improving the safety and effectiveness of treatments [55]. This innovative approach to designing multifunctional carriers opens up new possibilities for advancements in drug delivery systems, particularly in the development of precision therapies within complex biological environments.

Several studies have demonstrated favorable short-term efficacy using these carriers; however, these delivery systems often lack comprehensive assessments regarding the durability of efficacy and the potential adverse effects, thereby complicating the risk evaluation for clinical use [56,57]. In reconciling various research perspectives and findings, it is crucial to recognize that the effective execution of placenta-targeted drug delivery hinges on the optimization of drug carriers and the enhancement of targeting mechanisms. Certain studies have underscored the promise of nanocarriers in augmenting the efficiency and selectivity of drug delivery, whereas other studies have concentrated on aspects such as biocompatibility and drug release dynamics. A comparison of the advantages and disadvantages of various carriers in the placenta-targeted drug delivery system is shown in Table 1 (Ref. [56–61]).

Table 1. Comparative analysis of placenta-targeted drug delivery systems.

Carrier type	Advantages	Disadvantages	Suitable drugs
Folate-modified liposomes [56]	• High biocompatibility • Strong folate receptor targeting (placenta/tumor ratio = 15:1)	• Low drug loading capacity (<5%) • Rapid clearance by mononuclear phagocyte system	siRNA, small-molecule antioxidants
PLGA-PEG nanoparticles [57]	• Dual pH/enzyme-responsive release • High drug loading (10%–20%) • Scalable production	• Significant burst release (>30% on day 1) • Poor long-term stability	Proteins, IL-10
Anti-TfR1 antibody conjugates [58]	• High placental penetration (>60% transplacental efficiency) • Macromolecule-compatible	• Immunogenicity risks • High production costs (USD 500–1000 per dose)	Dexamethasone, nucleic acids
Cationic polymers (PEI) [59]	• High nucleic acid encapsulation (>90%) • Stable DNA/RNA complexes	• Cytotoxicity (LD₅₀ = 50 µg/mL) • Short placental retention (<6 h)	CRISPR-Cas9, shRNA
Gold nanorods [60]	• NIR-controlled release • Compatibility with photothermal therapy • Real-time imaging capability	• Low placental accumulation (<3% ID/g) • Potential metal toxicity	Small-molecule chemotherapeutics
Placental exosomes [61]	• Natural targeting (homing effect) • Low immunogenicity • BBB penetration capacity	• Difficult isolation (yield <0.1 µg/10⁶ cells) • Complex drug loading	miRNA, anti-inflammatory peptides

Notes: PLGA-PEG, poly (lactic-co-glycolic acid)-polyethylene glycol; TfR1, transferrin receptor 1; NIR, near-infrared radiation; BBB, blood-brain barrier; ID/g, injected dose per gram tissue; PEI, polyethyleneimine; LD, lethal dose; IL-10, Interleukin-10; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-crispr-associated protein 9.

All numerical ranges represent averaged literature values from the referenced studies.

Production costs are based on 2023 clinical-scale manufacturing estimates.

Toxicity data for PEI are derived from trophoblast cell viability assays conducted *in vitro*.

3.3 Preclinical Research Results

3.3.1 Overview of Animal Model Studies

Preclinical investigations into placenta-targeted drug delivery for managing PE primarily rely on animal models to assess the effectiveness and safety of various pharmacological agents [62]. Recently, numerous animal models, including mice, rats, and rabbits, have been used to mimic the pathophysiological conditions associated with PE, allowing researchers to study the effects of drugs on both the placenta and the maternal organism [63,64]. For example, transgenic mouse models can provide deeper insights into the mechanisms that lead to placental dysfunction and evaluate the impact of targeted therapeutic agents [5]. These models help in understanding how drugs are distributed and metabolized within the placenta, and aid in identifying any potential toxicity to both the mother and the fetus. Therefore, by employing these animal model studies, researchers can more effectively assess the clinical potential of placental-targeted pharmacotherapies.

3.3.2 Evaluation of Drug Efficacy

When evaluating the effectiveness of pharmaceuticals, preclinical studies often employ various methods to assess drugs designed for targeted delivery to the placenta [62]. Notably, these investigations and analyses have demonstrated that using modified liposomes as drug carriers can significantly increase drug concentrations within the placenta, leading to improved therapeutic outcomes. Specifically, placenta-targeting liposomes can achieve drug accumulation in the placenta that is up to 94 times higher than that of free drugs, highlighting the substantial potential of targeted delivery methods in medical treatments [12]. Additionally, the use of combination therapy has shown remarkable synergistic effects. For example, experiments using mouse models have revealed that administering two different drugs simultaneously greatly enhances therapeutic efficacy in addressing placental dysfunction, which underscores the importance of multidrug strategies in clinical practice [13]. These research findings provide crucial theoretical foundations for future clinical trials.

3.3.3 Safety and Toxicity Studies

Safety and toxicity assessments are essential elements of preclinical studies [65]. In research aimed at drug delivery to the placenta, various animal models have been employed to assess the toxicity of different pharmaceuticals. For example, high doses of certain medications have been shown to lead to liver damage in both mothers and fetuses, as well as adverse effects in other organs [13]. Additionally, research into nonspherical nanoparticles as drug delivery systems has revealed their effectiveness in transporting drugs within cells; however, these nanoparticles can also cause cytotoxic effects at certain concentrations [66]. Therefore, it is crucial to conduct thorough toxicity evaluations, including both acute and subacute toxicity trials,

to ensure the safety of drug delivery systems targeting the placenta. Such studies provide critical safety data to inform future clinical applications, to reduce potential risks to both mothers and their fetuses during the treatment of conditions such as PE.

3.4 Clinical Research Dynamics

3.4.1 Design of Major Clinical Trials

The design of clinical trials focused on placenta-targeted drug delivery for managing PE is becoming a significant area of research. Current studies indicate that drug delivery systems specifically designed for the placenta can significantly increase drug concentrations in this organ, thereby improving therapeutic outcomes. For example, researchers have developed liposomes that attach to macrophage proteins, allowing for effective targeting of the placenta after maternal administration, and increased drug accumulation in placental tissues [5]. Additionally, the design of clinical trials is starting to incorporate various innovative nanocarriers, such as polymeric nanoparticles and viral vectors, which have shown benefits in targeting efficiency and drug release mechanisms [12]. When planning these clinical trials, researchers typically consider several important factors, including the baseline characteristics of participants, methods of drug administration, dosage levels, and follow-up durations, to maintain the scientific integrity and effectiveness of the trials.

3.4.2 Interpretation of Clinical Results

Initial findings in clinical investigations focused on a placental-targeted drug delivery system have indicated that this method shows significant promise in managing PE. For example, studies have revealed that using targeted liposomes for drug administration can notably improve placental function while also reducing the incidence of maternal hypertension [12,13]. Additionally, drug delivery systems designed specifically for the placenta not only increase the concentration of the drug at the site but also help to reduce systemic side effects for both the mother and fetus [13]. However, researchers caution against hastily interpreting clinical outcomes, emphasizing the importance of evaluating effectiveness through the analysis of changes in clinical indicators and biomarkers to improve understanding of the efficacy and safety of the treatment [13].

3.4.3 Challenges in Clinical Application

Despite the promising outcomes, significant challenges hinder the translation of placental-targeted drug delivery systems into clinical practice, while the safety evaluation remains of utmost importance. Patients suffering from PE often present with various comorbid conditions, making the safety profile of medications in this patient population critically significant. While the potential for using a placental-targeted drug delivery system in treating PE seems encouraging, several major obstacles exist

to the clinical implementation. First, the unique physiological structure and function of the placenta pose challenges for effective drug delivery, particularly in ensuring that therapeutic agents can cross the placental barrier without jeopardizing the fetus [12]. Second, during the clinical translation process, existing placenta-targeted drug delivery systems face issues related to drug stability, release kinetics, and targeting specificity [13,67]. From a regulatory standpoint, no specific approval standards currently exist for drugs that target the placenta. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), require drug developers to present adequate data on placental selectivity to prevent irreversible harm to the fetus from drugs that may cross the placental barrier. However, existing animal models often fail to accurately mimic the intricate nature of the human placenta-fetus barrier, which creates significant challenges for evaluating how effectively drugs distribute and the potential off-target effects within the placental tissue. Furthermore, validating the long-term safety of placenta-targeted drugs necessitates extensive longitudinal studies that cover various stages of fetal development. These studies are not only time-consuming but also costly, which can hinder the process of translating findings into clinical practice. Additionally, conducting clinical trials with pregnant women involves navigating complex ethical considerations. On the one hand, potential participants may decline to join studies due to concerns about fetal risks. Conversely, in critical situations where the health of the mother is at stake, treatment choices must balance the need to “save the mother” against the imperative to “protect the fetus”. Unfortunately, current medical ethical frameworks lack specific standards for assessing the benefits and risks associated with placenta-targeted therapies. This highlights the urgent need for future research that brings together various disciplines to develop dynamic regulatory and ethical guidelines that prioritize the safety of both mothers and their infants [68].

3.5 Future Research Directions

3.5.1 Prospects for Personalized Treatment

Tailored therapeutic approaches show great potential in managing PE. As the understanding of researchers on the underlying mechanisms of diseases deepens, researchers are exploring ways to develop individualized treatment plans based on the unique pathological characteristics and biomarkers of each patient. For example, PE is closely associated with issues such as placental dysfunction [69], maternal inflammatory responses [70], and abnormalities in angiogenesis [71]. Therefore, treatment strategies that specifically address these mechanisms could lead to improved clinical outcomes [30]. Additionally, personalized treatment involves assessing the genetic predisposition, lifestyle choices, and existing health conditions of a patient to reduce side effects and enhance the effectiveness of the therapy. Future research should focus on identifying

biomarkers that can monitor placental function and maternal health in real time, allowing for timely adjustments to treatment plans and truly realizing the concept of personalized medicine [33].

3.5.2 Development of New Drugs

The development of new pharmacological agents is crucial for improving the management of PE. Recent advancements in nanotechnology and bioengineering have led researchers to create targeted drug delivery systems specifically aimed at the placenta. This innovative approach seeks to increase the concentration of therapeutic agents in the placenta while reducing potential side effects for both the mother and fetus. For example, targeted lipid nanoparticles have proven effective in delivering drugs directly to the placenta, which significantly enhances their bioavailability [5]. Additionally, there is ongoing research on various pharmacological treatments for PE, such as antioxidants [72,73], anti-inflammatory medications [74,75], and new antihypertensive agents—all to improve placental blood flow and function to reduce the incidence of PE [13]. Future research should focus on conducting clinical trials to determine the safety and effectiveness of these new therapeutic agents, as well as to explore the potential use of these agents in different patient populations.

4. Conclusions

Targeted drug delivery to the placenta is emerging as a promising new approach for treating PE; thus, this delivery system is drawing increasing attention from researchers. Recent progress in understanding placental physiology and pathology has led to the identification of more specific targets and therapeutic strategies. While these diverse research paths provide valuable insights for implementing a placental-targeted drug delivery system in clinical settings, differing opinions could also potentially be drawn. Therefore, future studies should aim to integrate these varied findings to create a more comprehensive treatment framework. Additionally, collaboration across disciplines is crucial for advancing this field. Experts in pharmacology, obstetrics, fetal medicine, and pharmaceutical engineering should work together to enhance the research and application of the placental-targeted drug delivery system. Such partnerships can deepen research insights and accelerate the clinical use of innovative therapies, ultimately benefiting patients. Moreover, future placental-targeted drug delivery systems are set to evolve further in the treatment of PE, with strong potential to play a vital role in improving maternal and infant health. By continuously improving drug carriers, enhancing targeting accuracy, and promoting interdisciplinary collaboration, the future clinical applications of placenta-targeted drug delivery look promising. However, researchers must remain vigilant to ensure that the drive for innovation does not compromise safety and long-term effects, thereby achieving real clinical benefits.

Author Contributions

FC designed and drafted the protocol documents for registration. JD designed of the work and revised the draft. Both authors contributed to editorial changes in the manuscript. Both authors have read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-3.5 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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