Placenta and Reproductive Medicine

REVIEW ARTICLE

Alternative drug delivery systems for pregnancy-related disorders: A focused review

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ABSTRACT

Objectives: Several innovations are being developed and marketed in the drug delivery systems for treating various disorders. Novel drug delivery techniques, such as bioengineered liposomes, nanoparticles, and exosomes, can selectively target the placenta or fetus. This allows for the administration of 'fetal-friendly' drugs during pregnancy with minimal risk of off-target effects. Due to their unique size and drug-encapsulating properties, they will be prominent in treating pregnancy-related disorders. This review's objective was to summarize currently developed innovative and alternative drug delivery systems for pregnancy-related disorders, along with their advantages and clinical relevance. **Methods:** This process used a defined search strategy of indexed publications from databases like Google Scholar, PubMed, Embase, Medline, Scopus, and UTMB library from 2000 to 2020 and included methods to assess the quality of the evidence retrieved. **Results:** Pregnancy is a unique physiological condition where some of the drugs will be lifesaving to the mother, but they can be toxic to fetal tissue**.** It is mandatory to research on the novel drug delivery systems. Although there was a substantial quantity of research has been carried out on maternal-placental-fetal drug uptake, transfer, and toxicity, therapeutic evaluations of innovative and alternative drug delivery systems in pregnancy remain in their infancy. **Conclusions:** In this review, we highlighted the physiological considerations of the placenta and summarized recent research work on alternative drug delivery systems used in pregnancy and their potential applications in clinical reality.

Key words: drug delivery, pregnancy, placenta, liposomes, nanoparticles, exosomes

INTRODUCTION

Pregnancy-related complications, including pre-eclampsia, preterm birth, fetal growth restriction, and placental abruption, affect more than 1 in 6 pregnancies, leading to significant maternal and perinatal morbidity and mortality. According to the United States Centers for Disease Control and Prevention (US CDC, 2019), about 700 maternal mortalities resulting from complications of pregnancy or delivery were reported in the United States.[1] In 2018, the maternal mortality rate was 17.4 per 100,000 live births, a significant increase from 12.7 per 100,000 live births in 2007. Maternal mortality review committees suggest that the majority of deaths could have been avoided no matter what when they occur with early diagnosis and eminence care before, during, and after pregnancy. The neonatal mortality rate in the United States for the year 2018 was 5.7 deaths in 1,000 live births.[2] In the United States, over 21,000 infant deaths were reported in 2018 due to congenital disabilities, prematurity of various organ systems due to preterm birth, maternal complications, sudden death syndrome, or Injuries as major leading causes. Current intervention strategies in pregnancy are not entirely

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successful due to the inadequacy of effective drug delivery systems, contributing to rising rates of adverse pregnancy outcomes and neonatal and maternal mortalities. Although many factors are involved in pregnancy-related deaths, a better understanding of various types of drug delivery systems available to treat pregnancy-related disorders, which enhance the bioavailability of therapeutic agents for their pharmacological effect, will help clinicians provide effective treatment for pregnancy complications.[3]

There are likely two patients during pregnancy: the mother and her fetus. Diagnosing the right patient and providing appropriate intervention is critical. Regardless, the placental transfer of drugs is one of the significant factors to be considered during pregnancy. If a drug can cross the placenta, depending on various factors like dose, frequency, route of administration, and gestational age, the effect of the drug on fetal development will have possible effects.[4,5] Due to unique physiological condition during pregnancy where interventions present a distinctive concern as certain medications can affect the fetal growth and organ development[6] contributing to teratogenicity. Thus, drug pharmacokinetics were considerably altered by physiological changes related to the progression of pregnancy.[7,8] Teratogenic effects related to the use of diethylstilbestrol in 1917 and thalidomide in the 1960s have raised safety concerns about medication use during pregnancy and lactation.[9] To avoid these incidents in the future, the United States Food and Drug Administration (USFDA) established strict regulations regarding drug labeling and the use of medications in pregnancy, requiring demonstrations of the safety and efficacy of any drug before it becomes approved.[10] However, there are several drugs used in pregnancy complications as per the USFDA classification that were inevitable to overcome the adverse effects. For example, labetalol and atenolol, used to treat hypertension in women with preeclampsia, are associated with fetal growth restriction. Tocolytic drugs used to suppress preterm labor were associated with several complications, such as acute fetal distress, chorioamnionitis, fetal immaturity, thyrotoxicosis, hypocalcemia, and suspected fetal cardiac or renal anomaly. Adopting novel drug delivery systems is mandatory to overcome the adverse effects and improve pharmacological activity.

This review focuses on the current research and alternatives in selected targeted drug delivery systems, utilizing liposomes, nanoparticles (NPs), and exosomes that can cross the placenta to advance the treatment of feto-maternal diseases encountered during pregnancy (Figure 1).

PHYSIOLOGICAL CONSIDERATIONS

During the drug development process for pregnancy-related disorders, the transport of drugs through a placental barrier is one of the major concerns. Although the placenta functions as the primary interface between the maternal and fetal circulations and protects pregnancy by providing nutrients to the growing fetus, it can act as both a drug target, a drug barrier, and a possible target of any toxicity.[11,12] The human placenta at the latter half of gestation has a villous, haemomonochorial arrangement, *i.e.*, maternal blood is in uninterrupted contact with the fetal villi, which are comprised of a single layer of syncytiotrophoblast separating maternal blood from fetal vessels.[13] Between the fetal endothelium and the syncytiotrophoblast layer are connective tissues interspersed with occasional cytotrophoblasts and immune cells such as macrophages. The placenta plays a vital role in maternal-fetal physiology, such as nutrient and gas exchange, fetal immunoprotection, and preparing an environment for fetal growth.[14,15] Through spinal arteries in the intervillous space, maternal blood enters and submerges the outer lining of the villi, the syncytiotrophoblast. The syncytiotrophoblast layer is a polarized, multi-nucleated epithelium lacking lateral cell membranes. Therefore, there is no "paracellular" or "between cell" transport pathway.[16] Fetal blood enters arteries on the basal surface of the placenta, which branch into villous capillaries. Once the transfer occurs, nutrient-rich blood returns to the fetus *via* the umbilical vein. The two membranes of the syncytiotrophoblast, the syncytial microvillous membrane at the maternal side and the basal membrane at the fetal side regulate placental transport.[17,18] Figure 2 depicts the anatomy of the placental barrier and drug transport mechanism in the maternal-fetal interface.

Drug transport across the placenta involves passive diffusion through placental transporters and metabolic enzymes.[19] Cytochrome P450 is a critical metabolic system in the liver and placental metabolism. Placental cytochrome enzymes metabolize endogenous compounds, vitamins, and xenobiotics. For example, *CYP19A11* metabolizes glyburide and exhibits limited transplacental passage. *CYP11A1* metabolized Vitamin D3, plant sterols, cholesterol, and other steroids. Before the fetus receives the drug, various physiological changes, including changes to placenta blood flow, hepatic drug-metabolic enzyme activity, and renal elimination, may affect the overall amount of drugs and their metabolites that cross the placenta.[20] Due to these barriers, the accessibility of therapeutics to treat pregnancy complications is severely deficient. However, recent achievements in advanced drug delivery systems have improved the treatment of pregnancy-associated disorders.

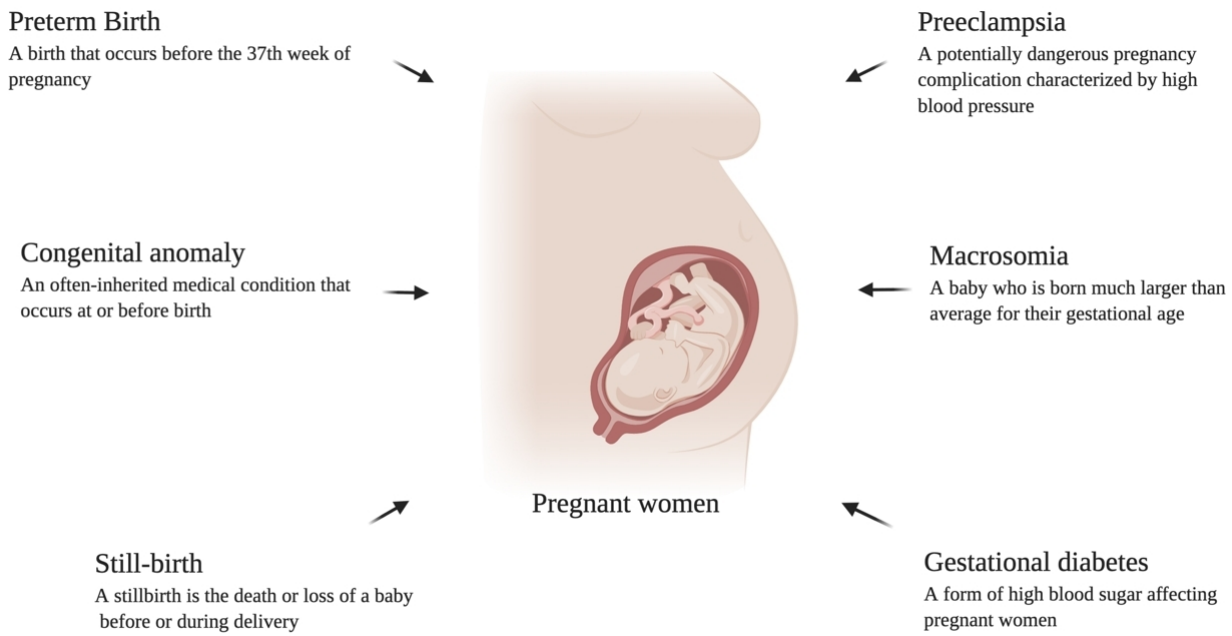

Figure 1. Complicated disorders lack of pharmacotherapy during pregnancy. This image was created by BioRender.

Recent advances in new technologies have improved drug delivery during pregnancy. These include liposomes, exosomes, and NPs that target the placenta and fetal tissues. Table 1 summarizes alternative and advanced drug delivery systems.

LIPOSOMAL DRUG DELIVERY SYSTEMS

Liposomes are amphiphilic molecules comprised of an aqueous core separated from the aqueous environment by a lipid bilayer. First discovered by Bangham and his co-workers in 1961, they consist of hydrophilic and hydrophobic molecules. Over the past 40 years, the clinical utility of liposomes for drug delivery[33] has been investigated. Recently, several advancements have been made in the liposomal drug delivery system for pregnancy-related disorders.[34–36] Polyethylene glycol (PEG) was used as a steric stabilizer for liposomes, and depending on how PEG is linked to the lipids, the physiological and biophysical properties were determined.

Generally, there are four types of liposomal delivery systems (Figure 3): (1) conventional liposomes, (2) sterically-stabilized liposomes (*e.g.*, PEG related liposomes), (3) ligand-targeted liposomes, and (4) liposomes containing combinations of the first three types.[37] Conventional liposomes are the first generation of phospholipids and cholesterol enclosing a hydrophilic core. Although these formulations reduced the toxicity of drugs with narrow therapeutic indexes, such as doxorubicin and amphotericin B, conventional liposomes are rapidly cleared from the bloodstream due to opsonization by plasma components as well as uptake by cells of the reticuloendothelial system mainly found in the liver and the spleen.[38] Next-generation liposomes were developed to enhance their stability and bioavailability in systemic circulation. They consist of a hydrophilic polymer, PEG. They offered improved circulation times utilizing steric barriers and reduced side effects. This revolutionary invention enhanced the therapeutic efficacy of encapsulated agents by reducing *in vivo* opsonization with serum components and rapid recognition by the reticuloendothelial system.

Further, it has been improved to third-generation liposomes with a ligand-targeted liposomal drug delivery system, which proposed site-specific delivery of drugs with a vast potential when decorated on the surface of nanocarriers.[39] Liposomes were decorated with different ligands such as antibodies, peptides/proteins, and carbohydrates to target the specific delivery of drugs to designated cell types or organs *in vivo*, which selectively express or over-express specific ligands. However, there is still a controlled *in vivo* performance due to poor pharmacokinetics and immunogenicity. With a combination of the above design platforms, the newer generation of liposomal drug delivery to improve liposomal targeting and associated drug delivery was developed and called theranostic liposomes.[40] Thus, dynamic and adaptable technology offered by liposomes to enhance the systemic efficacy of therapeutics in various diseases.

Table 1: Advanced drug delivery systems used during pregnancy

Serial number	Type of drug delivery system	Drug loaded	Target	Activity	References
1	Liposomes	Dofetilied	Oxytocin receptor	Inhibit myometrial contractions	21
2	Liposomes	Indomethacin	Oxytocin receptor	Targets uterus to reduce contractions	22
3	Unilamellar liposomes	Warfarin	Placenta	Crossed placenta Associated with risk of stillbirth	23
4	Cationic liposomes	siRNA	Outer cell layer of placental villi	Protecting fragile nucleic acids from degradation by nucleases	24
5	Liposomes	siRNA	Syncytiotrophoblast	Targets pregnancy related pathologies	25
6	PEGylated liposomes	Arginine-glycine-aspartic acid peptide	Integrin avB3 in the placenta	Induces preeclampsia like symptoms in mouse model	26
7	Liposomes	Bupivacaine	Analgesia	Provides pain relief post-cesarean section	27
8	Topical liposome	Aloe vera gel extract	Skin pigmentation	Treats melasma in pregnant women	28
9	Biodegradable nanoparticles	Antiretroviral drug	Vagina	Reducing risk of vaginal HIV infection	29
10	Placenta type CSA nanoparticles	Doxorubicin	Trophoblasts	Inhibit tumor growth and metastasis	30
11	Poly (PLGA) acid nanoparticles	siRNA	Host cell receptor in vagina	Reduces HSV-2 infection	31
12	Exosomes	Super repressor (NF-kB inhibitor)	Fetal membranes	Delays preterm birth	32

siRNA, small interfering RNA; HIV, human immunodeficiency virus; CSA, chondroitin sulfate A; HSV-2, herpes simplex virus 2; NF-κB, nuclear factor-kappa B.

Antibody-conjugated liposomes that bind to oxytocin receptors were developed by Paul *et al.*,[22] who reported that these immunoliposomes, when loaded with nifedipine (a calcium channel blocker), salbutamol (a beta-2 adrenergic receptor agonist) or rolipram (a phosphodiesterase-4 inhibitor), eliminated human and mouse myometrial contractions *in vitro*. *In contrast,* dofetilide-loaded liposomes (a potassium channel blocker) showed increased duration of contractions. Consistent with *in vitro* results, indomethacin-loaded immunoliposomes localized to murine uterine horns and mammary tissue but not maternal brain and fetus, and were influential in lessening rates of lipopolysaccharide (LPS)-induced preterm birth in mice. These findings suggested that oxytocin receptor-targeted liposomes have a potential clinical advantage in targeting the myometrium in reducing preterm birth. Similarly, Hua and Vaughan have reported that targeting myometrial tissue and avoiding adverse effects by circumventing non-targeted tissues for existing therapies, specifically targeting oxytocin receptors by liposomes, is compelling.[21]

Encapsulated liposomes often inhibit drug absorption and regulate its pharmacological activity to reduce drug transportation across the placental barrier. In many situations drugs can be life-saving for mother but it can be harmful to the fetus. Liposomes can be used as carriers for small molecule chemicals by maintaining safe therapeutic concentrations in the maternal circulations and produce an adequate pharmacological response with a minimal transplacental transfer. Bajoria *et al.*[23] have described that the lipid composition of cationic small unilamellar liposomes has significantly reduced encapsulated warfarin transportation across the human placenta. Since the clinical observation of warfarin use during pregnancy is associated with the risk of stillbirth, congenital anomalies, and intracranial hemorrhage, regulating its transfer during the pregnancy period is essential. Lack of detectable levels of intact liposomes in the fetal circulation is suggestive of failure of its transfer across the placenta. It is also consistent with a study carried out by Kaga *et al.*[41] which showed in *in vivo* model that hemoglobin loaded liposomes were not transferred from the mother to the fetus at a late stage of pregnancy. These findings will provide novel drug delivery methods using liposomes by which the mother can be treated by pharmacological agents with minimal exposure.

The knockdown of pathologically relevant genes by ribonucleic acid (RNA) interference is a dominant method. Small interfering RNAs (siRNAs) are double-stranded RNA oligonucleotides able to induce the silencing of a target gene *via* RNA interference. For many diseases, siRNAs have been extensively established as practical biomedical genetic therapy applications. siRNA technique will provide the specificity and it could be manipulated in the development of therapeutic approaches for pregnancy disorders.[42,43,25] However, due to the lack of stability in biological fluids and the hydrophilicity of siRNA, it hinders their transport to the target tissue and cellular uptake—Liposome-based formulations are considered carriers for siRNA to

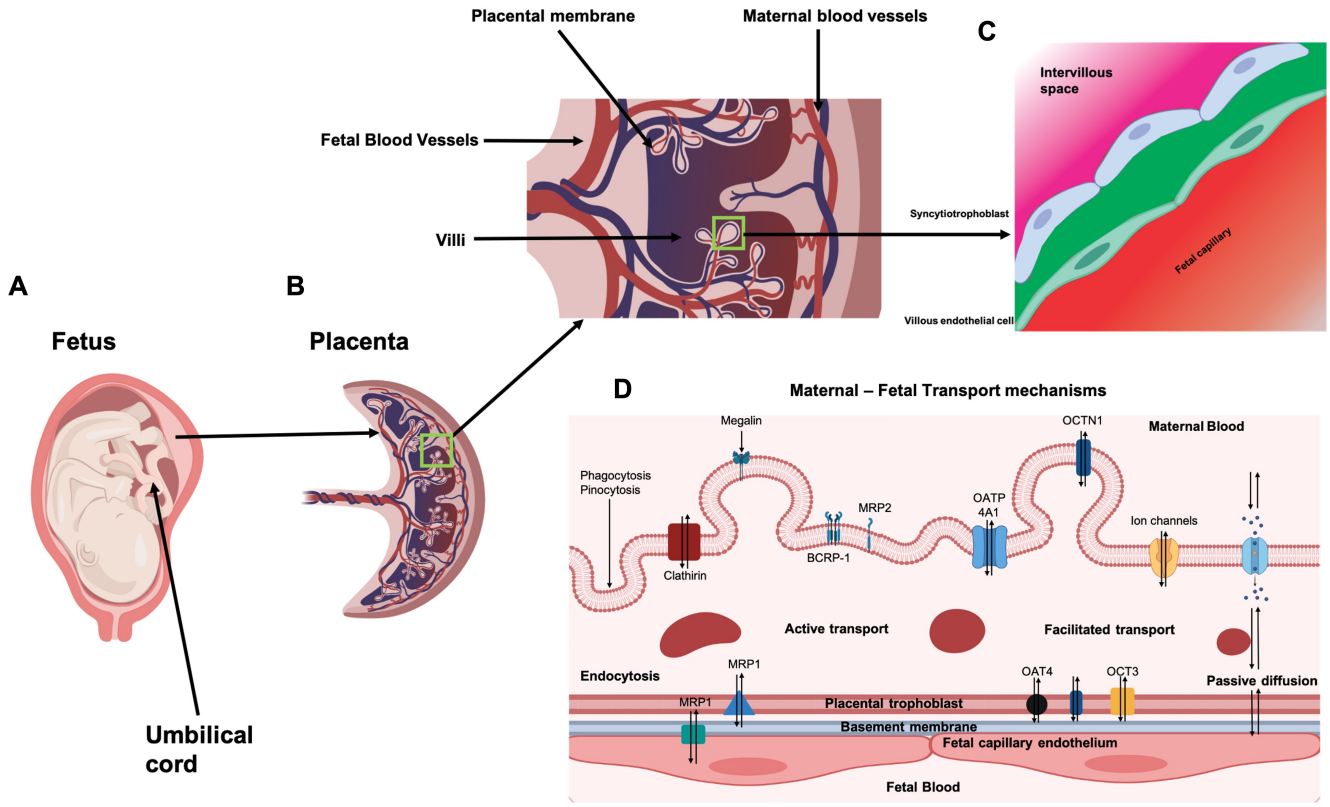

Figure 2. Physiology of human placenta and transport mechanism in the placental barrier. (a) Fetus attached to the umbilical cord (b) Cross-sectional view of the placenta (c) Cross-sectional view of villus that depicts the placental barrier's intervillous space, villous endothelial cells, and syncytiotrophoblast. (d) Transport mechanism within the placental barrier. It represents the list of transporters present in the placental trophoblast and fetal capillary endothelium. MRP, multidrug resistance-associated protein; OAT, organic anion transporter 4; OCT, organic cation transporter 3; BCRP, breast cancer resistance protein; OATP4A1, organic anion transporting polypeptide 4A1; OCTN, novel organic cation transporter. This image was created by BioRender.

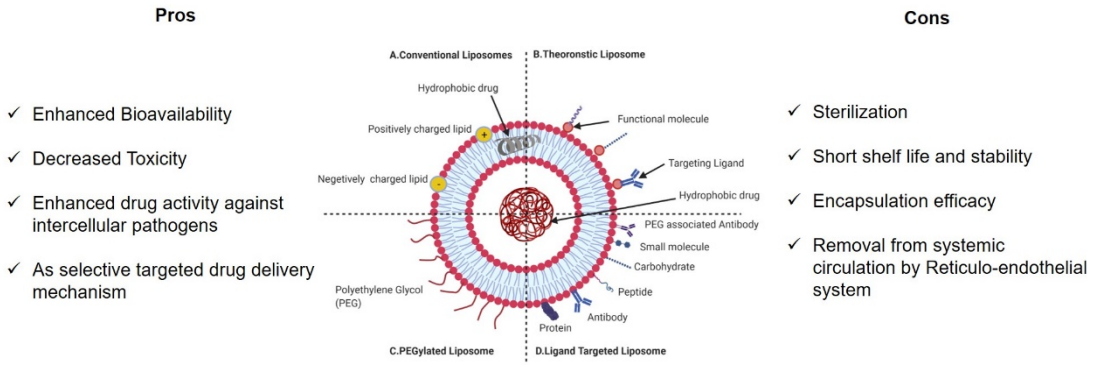

Figure 3. Schematic representation of the different liposomal drug delivery system types and their pros and cons. This image was created by BioRender.

placental cells. Liposomes can be one of the best alternative approaches to deliver siRNA to the target tissues by protecting fragile nucleic acids from degradation by nucleases and delivery to the outer cell layer of placental villi, and it can also be modified to restrict off-target effects in the fetus.[24] Valero *et al.*[25] have reported that liposomes can be used as carriers to deliver siRNA into the syncytiotrophoblast, a key target site in many pregnant-related pathologies. This study used three different formulations of cationic liposomes to deliver siRNA, improve their delivery, and facilitate greater cellular internalization. The liposomal siRNA technique has been tested in mouse models of pregnancy disorders.

Apart from the drug delivery systems, liposomes were also determined to a developed mouse model for studying pregnancy disorders. Yu *et al.*[26] have developed arginine-glycine-aspartic acid peptide (RGD)-modified PEGylated cationic liposomes and encapsulated them

with H19x siRNA to induce preeclampsia-like symptoms in a mouse model. Although small amounts of RGD-liposomes were detected in fetal tissues, the drug was primarily distributed in the placental tissues and targeted integrin avB3 in the placenta. It was proven that the RGD-PEG-liposomal siRNA technique is safe and target-specific delivery to the placenta for a robust knockdown in an *in vivo* model to study the effect of preeclampsia. With the efforts of many scientists, liposomes have evolved into novel drug delivery systems and many liposomal drugs have been approved for clinical trials and are available on the market for cancer treatment. Along with several advancements in liposomal research, some of the liposomal therapies have entered the clinical phase for pregnancy-related disorders. A retrospective clinical study on liposomal bupivacaine's impact on post-cesarean analgesia was reported by Parikh and colleagues.[27] As a practical addition in reducing opioid use postoperatively and to recovering from cesarean pain, liposomal bupivacaine with incisional administration can be a helpful adjunct.[27] Conversely, Prabhu *et al.*[44] reported that liposomal bupivacaine incisional block at the time of cesarean delivery did not decrease postoperative pain scores among opioid-naïve women undergoing scheduled cesarean delivery. Although these two studies were contradictory, further studies must explore injection volume and the effective loading of bupivacaine in liposomes.

Along with several disorders of pregnancy, melasma is a dermatological condition (skin pigmentation) during pregnancy.[45] Even though hydroquinone is available as a first treatment for melasma, natural medicine like Aloe vera gel (AGE) has a better therapeutic effect. To improve the bioavailability of AGE extract for topical application, Ghafarzadeh and Eatemadi developed topical liposome-encapsulated Aloe vera for treating melasma in pregnant women.[28] A double-blinded, randomized clinical trial was conducted with two groups of pregnant women with melasma in their second trimester. One group of women was treated with liposome-encapsulated AGE, and the other was kept as a control group (n = 90). After five weeks of treatment, there was a significant decrease in the occurrence of melisma, with an increase in parity of 39%. Although there is no difference between the groups regarding the family history of melasma, occupation, sunscreen usage, and hours of sun, there was a significant difference between the control and experiment groups regarding the melasma area severity index score. It was concluded that liposome-encapsulated AGE was grander than average AGE in decreasing the severity of melasma in pregnancy due to their ease of percolation.

Thus, liposomal drug delivery systems had significant advantages relative to free drugs by reducing the side effects and their passive accumulation at the sites of increased vasculature permeability.[34,46] Compared to unentrapped drugs, liposomal drugs have reduced extravasation into tissues with stretched endothelial junctions and significantly reduced side effects. With all these advantages, liposomal drug delivery has evolved as a conventional technology platform and has gained considerable clinical acceptance. Although liposomes have several advantages, they have challenges like bioavailability and controlled release of drugs from liposomes, rapid clearances by the liver and spleen, and Intracellular drug delivery.[37,47] Although our primary focus is on literature published between 2000 and 2020, a substantial number of publications have come out in the past four years, and we seek readers for those articles,[48–51] as well to get recent updates.

NP DRUG DELIVERY SYSTEMS

NPs, as the name implies, are tiny particles that size up to 20–100 nm in diameter (Figure 4). They have a significant advantage of exhibiting an extremely great surface area per unit mass because of their unique size.[52] NPs also exhibit increased drug half-life of drugs, resulting in lower doses administered and target delivery to specific tissues or organs.[53] These essential characteristics of NPs are considered a revolutionary advancement in drug delivery systems that determine transcellular or paracellular diffusion or endocytic uptake.[54–56]

The development of NP-based technologies and their delivery systems constantly expanded to clinical use for various disease conditions.[54,57–59] Ham *et al.* have developed biodegradable and chemical drug-loaded NPs for vaginal antiretroviral drug therapy.[29] PLGA NPs encapsulated CCR5 chemokine inhibitor, and PSC-RANTES provided sustained release and increased uptake into *ex vivo* cervical tissue compared to free drugs. McConville and colleagues had achieved in human clinical trials of 1% tenofovir gel in reducing the risk of vaginal human immunodeficiency virus (HIV) infection.[60] Zhang *et al.* have synthesized placental-type chondroitin sulfate A (CSA) NPs that can precisely bind to a definite placental-type CSA expressed on trophoblasts in human and mouse placentae.[30] Cellular uptake of this drug was shown in choriocarcinoma JEG3 cells, and no adverse effects on maternal tissues were reported.

Interestingly, it was reported that doxorubicin-loaded plCSA NPs inhibited tumor growth and metastasis. For treating pregnancy complications, NPs decorated with plCSA could efficiently deliver enormous amounts of therapeutic drugs. Besides chemical compounds' incorporation into NPs, siRNA-loaded NPs were also

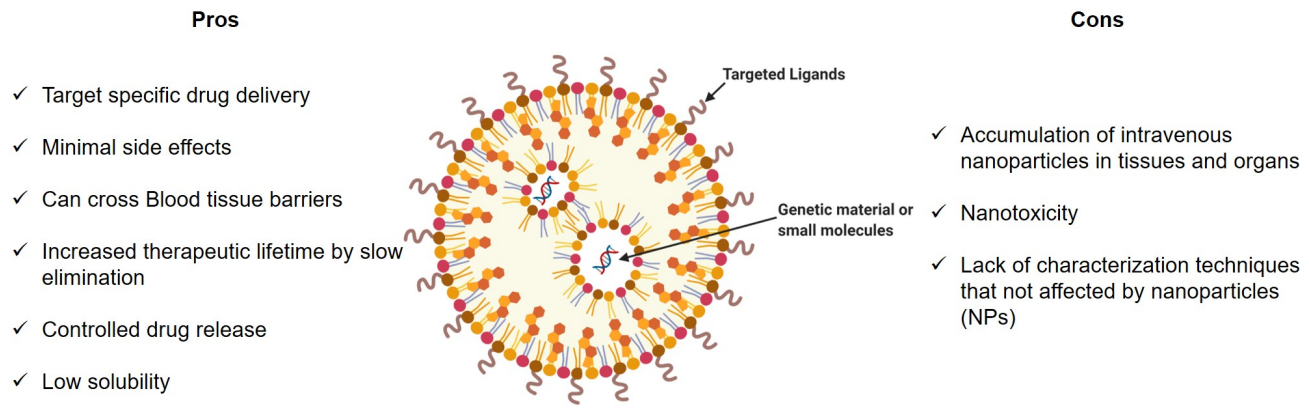

Figure 4. Schematic representation of Nanoparticle drug delivery systems and their pros and cons. This image was created by BioRender.

innovative.[31,61] Steinbach *et al.*[61] demonstrated that vaginal infection could be protected by siRNA delivery *via* poly (lactic-co-glycolic) acid PLGA NPs, which were loaded with siRNA complexes targeting a host cell receptor integral to vaginal herpes simplex virus 2 (HSV-2) infection in mice. Mice treated with NP-encapsulated siRNA have shown 20%–60% survival against 100% lethality in animals treated with control scrambled RNA. The infection led to a series of papers detailing biodegradable 1% tenofovir loaded NP formulation for vaginal use.[61] Although there have been several advancements in NP drug delivery systems, particularly in pregnancy-related issues like progesterone conjugated NPs and oxytocin receptor-targeted NPs, many of these studies have halted at clinical trials due to their unanticipated toxicity effect on the fetal tissues.[21,62]

Titanium dioxide (TiO_2) NPs, widely used in food products, toothpaste, cosmetics, and paints, might be exposed to pregnant women. Lee *et al.*[63] demonstrated no significant TiO_2 NP-related toxicity in pregnant animals or concerning embryo-fetal development. However, oral administration of a high dose of TiO_2 NPs to pregnant Sprague-Dawley rats between gestation days 6 to 19 leads to an increased level of TiO_2 in the maternal liver, brain, and placenta. Subcutaneous administration of TiO_2 NPs to pregnant mice at 3, 7, 10, and 14 days reached the fetus and affected fetal development. On the contrary, Takeda *et al.*[64] reported that NPs were detected in the testes and brains of offspring six weeks after birth, along with various functional and pathological disorders.

Similarly, Intratracheal infusion of Carbon NPs in pregnant mice at days 7 and 14 of gestation showed partial vacuolation of seminiferous tubules in gonads from offspring, and daily sperm production was significantly decreased. These studies suggested that the placenta is permeable to some forms of NPs in rodents and can cause harmful pregnancy-related issues unless the dosing and route of NPs administered are optimized. However, it would be necessary to determine the NP toxicity in the human reproductive system before conducting the clinical trials.[65]

EXOSOMES AS DRUG CARRIERS

Exosomes are small membrane-bound extracellular vesicles (EVs; 40–160 nm in diameter) formed during the fusion of multivesicular endosomes with the plasma membrane (Figure 5). They play a crucial role in intercellular communications, delivering various biomolecules like endogenous proteins and nucleic acids that are reflective of the physiological state of the recipient cell to target cells, which can have biological effects.[66–68] Recently, it has been established that exosomes play a role in communication between placental cells and maternal tissues to regulate their biological functions.[69,70] Exosomes are predicted to be safe therapeutic vehicles because of their endogenous origin and lack of immunogenicity. It has been shown that mesenchymal stem cell-derived EVs have therapeutic potential against cardiovascular disease, liver injury, renal injury, and neural injury.[71,72]

Teratoma formation and embolization are significant concerns for stem-cell-based therapeutics, which can lowered by exosome-based therapeutics.[73] Protein transduction methods are widely used to encapsulate therapeutic proteins in exosomes. Recently, advanced technologies such as exosomes for protein loading *via* optically reversible protein-protein interactions (EXPLORs) have been developed to encapsulate desired cargo, including drugs, in exosomes.[74] In this technique, the successful loading of cargo proteins into exosomes during their biogenesis stage has been accomplished by integrating a reversible protein-protein interaction module controlled blue light with the endogenous process of exosome biogenesis. Yim *et al.*[74] have also

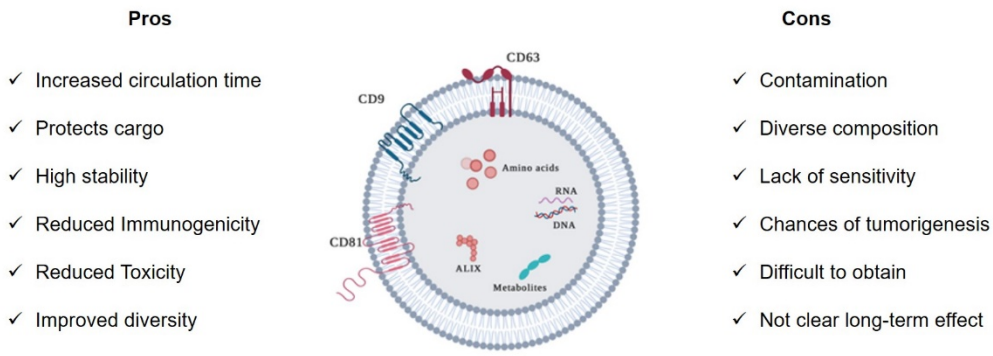

Figure 5. Schematic representation of exosomes, including their markers and pros and cons. This image was created by BioRender.

developed super repressor IB protein (SR), which inhibits the translocation of nuclear factor-kappa B (NF-κB) in inflammatory conditions and successfully loaded them into exosomes using EXPLOR technology. SR-encoded exosomes have significantly inhibited tumor necrosis factor-induced translocation of the p65 subunit of NF-κB in HeLa cells, suggesting potential anti-inflammatory properties of SR and its usefulness in various inflammatory pathologies. Sheller-Miller *et al.* have reported that SR-loaded exosomes delay LPS-induced preterm birth in mouse models and reduce pro-inflammatory cytokines levels, interleukin-1β (IL-1β) and IL-8. In this model, intravenous administration of SR reduced fetal inflammatory response responsible for infection-associated preterm birth in a mouse model of pregnancy. This decrease in cytokine production is likely due to inhibition of NF-κB translocation into the nucleus. This data suggests that exosomes can be engineered to carry pharmaceutical agents, cross placental barriers, and reduce the risk of infection-induced inflammation associated with preterm birth.[74,32]

Exosomes therapeutic efficacy in delivering small molecules, proteins, siRNA, miRNA, and nucleic acids has been studied primarily on various cancers. However, it can also be a significant line of drug delivery systems to treat disorders during pregnancy. Due to their unique properties like inherent small size and nature's cellular products, considered as nature's delivery systems, allow for the delivery of biological molecules by avoiding phagocytosis or degradation by macrophages.[75] Despite their unique properties, a definite ideal purification technique for isolating high-purity exosomes is lacking. Current isolation protocols yield low quantities of exosomes, and large-scale production of exosomes for clinical utility can be expensive. Integrative studies using therapeutics cargo and functional exosomes, or hybrid exosomes mimetic, are becoming critical.[76] Exosomes' involvement in tumor progression and their role in releasing antigens from the membrane during tumor growth are massive concerns.[77] Designing artificial exosomes or mimetics can overcome potential disadvantages such as unwanted immune reactions. Thus, exosome drug delivery systems can be a novel therapeutic area for drug delivery systems for chemical and biological molecules for cellular therapy in pregnancy-related issues.

CONCLUSIONS AND FUTURE DIRECTIONS

In this comprehensive review, we examine the intricate functions of the placental barrier at the maternal-fetal interface, elucidating its pivotal role in regulating maternal-fetal interactions. Additionally, we explore cutting-edge drug delivery methodologies poised to transform the management of pregnancy-related disorders. A refined understanding of the distinct advantages and challenges associated with these diverse drug delivery approaches is crucial for navigating the complexities of pharmacotherapy during pregnancy. While these innovative drug delivery platforms promise to enhance therapeutic efficacy by selectively targeting the placenta while minimizing fetal exposure, significant hurdles persist, particularly in achieving specificity and mitigating potential toxicities in clinical settings. Future directions for pregnancy-specific drug delivery systems include the development of reproductive tissues targeted NP systems, enhancement of liposome-based delivery, leveraging exosome-mediated delivery, improving biodegradable NPs, advancing the application of cationic liposomes, integrating topical liposomes and conducting thorough preclinical and clinical studies to ensure safety and efficacy. Personalizing drug delivery systems based on genetic and environmental factors also presents a promising avenue. The seminal research findings presented herein underscore the considerable potential of diverse drug delivery technologies in addressing pregnancy complications, laying a solid foundation for these future advancements in pregnancy-specific drug delivery systems.

DECLARATION

Author contributions

Kammala AK: Conceptualization, Writing—Original draft preparation. Lintao RCV: Writing—Reviewing and Editing. Menon R: Supervision, Project administration. All authors have read and approved the final version.

Ethics approval

Not applicable.

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could potentially create a conflict of interest.

Data availability statement

No additional data.

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