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Placental exosomes: A proxy to understand pregnancy complications

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Abstract

Exosomes (30–150nm particles), originating from multivesicular bodies by the invagination of the endosomal membrane, are communication channels between cells. Exosomes are released by various cell types and cargo proteins, lipids, and nucleic acids reflecting the physiologic status of their cells of origin and cause functional changes in recipient cells, which are likely dependent on their quantity and/or cargo contents. Recently, placental exosomes, produced by various placental cell types, have been isolated from maternal blood using the placental protein-specific marker, placental alkaline phosphatase (PLAP). PLAP-positive exosomes are seen in maternal blood as early as the first trimester of pregnancy and increase as gestation progresses, with maximum numbers seen at term. Although the functional relevance of placental exosomes is still under investigation, several studies have linked placental exosomes changes (quantity and cargo) reflecting placental dysfunctions associated with adverse pregnancy events. Since placental exosomes can be isolated from maternal blood, they are liquid biopsies reflecting placental functions. Hence, they are useful as biomarkers of placental functions and dysfunctions obtainable through noninvasive approaches. This review summarizes the biogenesis, release, and functions of exosomes and specifically expounds the role of placental-specific exosomes and their significance associated with pregnancy complications.

Keywords

microvesicles; pregnancy; parturition; PLAP; signaling

Introduction

The placenta is the most important fetal-in-origin intrauterine organ that is essential for the growth and survival of fetus and maintenance of pregnancy¹. All maternal-fetal

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communications needed to maintain a healthy pregnancy are controlled and regulated by the placenta². Hence, any dysfunctional placental communication system can be detrimental to the survival of the fetus. Cell-to-cell communication is one of the most common molecular mechanisms in organisms, mediated through direct cell-to-cell contact, soluble factors, or intracellular nanotubes. Various modes of communication between feto-placental and maternal-placental systems exist; the most common method is mediated by endocrine factors³. Various autocrine and paracrine communication modes have been reported⁴. In recent years, because of their high-efficiency cell communication function, exosomes, members of the extracellular vesicle family, have received significant attention and generated enthusiasm among placental researchers. Exosomes cargo various cellular metabolic products from the cell of origin and traverse through tissues and biological fluids and function as communication mediators. Several recent reports have explored their usefulness as communication mediators as well as indicators of placental physiologic and pathophysiologic status. In this review, we provide a brief overview of exosomes and the potential role of placental-specific exosomes in pregnancy physiologies and pathologies.

The source and function of exosomes: What are exosomes?

Exosomes is one kind of extracellular vesicles (EVs) which was thought to be cellular 'debris' but actually plays an important role in intercellular communication. Variety of EVS exists and they are classified based on their origin and biogenesis, size and function. EVs (50nm–2µm) are released from different cell types including human placenta that can produce a wider variety of EVs. Macrovesicles (Syncytial Nuclear Aggregates, 20µm–> 100 µm)⁵, micro vesicles (0.2–1µm)⁶, apoptotic bodies (800–5000 nm) and nanovesicles (20–100 nm)⁷.

Exosomes, which belong to the nanovesicles were first reported by Rose Johnstone from sheep reticulocytes in 1970⁸; however, as we know now they also produced by various cell types, such as immune cells, epithelial cells, and tumor cells^{9–12}. Exosomes originate in endosomal compartments called multivesicular bodies (MVBs), which are formed by the invagination of the endosomal membrane. The formation of MVBs includes 2 known pathways: one is dependent on the endosomal sorting complexes required for transport (ESCRT) and the other is ESCRT-independent¹³. ESCRT is a complex protein that forms networks to guide protein sorting and MVB vesicle formation¹⁴. The vesicles are called intraluminal vesicles when they are inside the MVBs; otherwise, they are called exosomes once the contents of the MVBs are released into the extracellular environment by cell membrane exocytosis¹⁵.

Composition, biogenesis, and release of exosomes

Exosomes are cup-shaped or sphere-shaped with a diameter of about 30–150 nm and a density of about 1.13–1.19g/mL¹⁵. All exosomes contain protein, raft-associated lipids, ceramide, other sphingolipids, and phosphoglycerates^{16–18}. The proteins commonly associated with exosomes include membrane transport and fusion proteins, tetraspanins, heat-shock proteins, proteins involved in multivesicular body biogenesis, lipid-related proteins, and phospholipases. As mentioned above, one of the key components of exosomes

includes ESCRT proteins and tetraspanins. ESCRT proteins consist of approximately 30 proteins that assemble into 4 distinct complexes (ESCRT-0, -I, -II and -III) with associated proteins (eg, VPS4, VTA1, ALIX) that are involved in the formation and secretion of exosomes^{19–20}. Tetraspanins, organizing web or recruiting molecules, contribute to exosomes' assembly and biogenesis^{21–22}. The most common tetraspanins of exosome biogenesis include CD63, CD9, and CD81. Because of their involvement in exosome biogenesis, tetraspanins are often used as markers to detect exosomes in various preparations as well as used for exosomes' separation and purification²³.

Selection and packaging of cargo by exosomes are still a mystery²⁴. Although various theories have emerged on how exosomes package a specific cargo, the precise mechanism or process of selection of a given cargo are still not well defined²⁵. However, it is well known that cellular physiology impacts cargo selection and packaging. Based on proteomic analysis, Mathivanan et al²⁶ have reported that exosomes may contain over 4400 different proteins and other molecules. The release of exosomes from a cell is dependent on their membrane cholesterol content²⁷. Exosomes that are rich in cholesterol get secreted, whereas those that contain less cholesterol are directed to lysosomes, where they are digested²⁴. Once formed, exosomes are released from a cell with the help of various molecules. Two well-reported molecules that help with release processes are Rab-GTPases and SNARE proteins (soluble N-ethylmaleimide-sensitive fusion attachment protein [SNAP] receptors)^{28–29}. Thus, exosomes' biogenesis, cargo packaging, and secretion are well-orchestrated events regulated by the physiologic status of the cell. Cells also release exosomes in response to specific stimulants. For example, oxidative stress, infection, allergies, and inflammation are factors that can cause increased release of exosomes. Similarly, tumor cells constitutively release exosomes^{30–31}. Once released, exosomes interact with recipient cells by fusion with the plasma membrane, via receptor-mediated uptake or by internalization via endocytosis or macropinocytosis^{32–33}. The protein and lipid composition are unique in exosomes from different cells of origin, enabling them to be used as a biopsy that reflects the physiology of the cell of origin. In Figure 1, we show characteristics of exosomes isolated from cell culture media and biologic samples and essential features to be included when describing exosomes.

Exosome functions

Exosomes were, until recently, considered cellular metabolic waste disposal units³⁴. However, recent technological advances have provided more in-depth knowledge on exosomes and their functions. It is now believed that cellular communication is one of the basic functions of exosomes. The way exosomes deliver cargo and function at target cells often depends on the surface molecules and the cargo they carry. This behavior remains a “black box” in exosome research. Exosomes can impact neighboring cells once released into the extracellular fluid and distant cells by systemic spread through biologic fluids. Exosomes are found in many biological fluids, including blood, urine, epididymal fluid, saliva, amniotic liquid, malignant and pleural effusions of ascites, lavage fluid, bronchoalveolar fluid, synovial fluid, and breast milk^{35–46}. Thus, exosomes can be considered autocrine and paracrine contributors of cellular functions.

Several studies have linked exosomes to various cellular biologic functions. A few functional examples of exosomes include the following: 1) the presence of major histocompatibility complex (MHC) class I and II molecules on exosomes from antigen-presenting cells can inactivate CD8+ and CD4+ T-cells to induce specific immune responses^{47–49}; 2) exosomes with prostaglandins are involved in the inflammatory response by platelets⁵⁰; 3) exosomes play a role in cancer development as functional mediators of tumor-stroma interaction⁵¹, including migration, treatment resistance, and metastasis⁵²; 4) circulating levels of exosomes are associated with the onset and clinical course of critical illness, including acute myocardial injury, acute kidney injury, and other organs failure⁵³; and 5) exosomes may also spread various microbial particles (viruses, or microbial antigens) associated with disease processes⁵⁴.

Earlier we mentioned various modes of exosomal communications. Exosomes enable intercellular communication, not by direct cell-to-cell contact, but by transferring specific cargo contents to a recipient cell. They can confer epigenetic changes in the recipient cells by delivering microRNAs. For example, exosomes secreted by mast cells containing mRNA and siRNA (small interferenceRNA) are shown to impact translation of target genes in the recipient cell⁵⁵. Exosome cargo, especially miRNAs, have been very well reported. miRNAs are small noncoding RNAs that play an important role in regulating gene expression and biological processes. miRNAs from exosomes work on communication and information transmission by acting on cells directly. Thus, exosomes also play a part in immune response and antigen presentation⁵⁴, inflammation, blood clotting, and angiogenesis⁵⁶.

Exosomes are now being considered biomarkers of different diseases in various biologic samples. Tumor-derived exosomes are rich in specific miRNAs, which may serve as tumor markers^{57–59}. Exosomes isolated from biological fluids and their cargo of miRNA and proteomes can help in the diagnosis and treatment of cancer or immune diseases^{60–62}. The characteristics and functions of exosomes suggest that exosomes will play an important role in the etiology, development, diagnosis, and treatment of diseases.

Exosomes in pregnancy

The role of exosomes in pregnancy and parturition are still being elucidated. Exosomes are reported to be involved in early pregnancy. Exosomes isolated from endometrial epithelial cells and uterine mucus promote embryo implantation as well as facilitate communication between the endometrium and embryo in normal pregnancy^{63–64}. Recently, Machtinger reviewed EVs' function in the human reproduction system and reported that EVs may contribute to oocyte and sperm maturation, fertilization, prevention of polyspermy, and embryo implantation by mediating intercellular communication⁶⁵. Carlos Salomon's group showed a promising report that exosomes isolated from first-trimester placental mesenchymal stem cells can increase endothelial cell migration and vascular tube formation. The report also indicated that exosomes from cytotrophoblast cells promote extravillous trophoblast invasion by promoting activation of associated pathways mediated by matrix metalloproteinases (MMPs) and mitogen-activated protein kinases (MAPK)⁶⁶.

Exosomes are reported to regulate maternal immune system and contribute to the pregnancy establishment⁶⁷ through both immunostimulatory and immunosuppressive modulations. Antigen presenting cells (dendritic cells, macrophages and B cells) release exosomes with immunostimulatory capabilities, which activate immune effector mechanisms^{68–69}. In contrast, exosomes released from epithelial cells focus on immunosuppressive resulting in inhibition of the host immune system and modify maternal immune responses and allow fetal development and survival during pregnancy^{70–71}.

Placental exosomes

Placental exosomes may regulate maternal physiological functions and fetal development. Taylor et al first described circulating “shed placental fragments” in 2002 and speculated that they may contribute to fetal immune tolerance⁷². Placental exosomes are reported to take part in the pathology of pregnancy, such as hypertensive disorders⁶⁶, gestational diabetes, preterm birth, and premature rupture of membranes. This article summarizes the features and functions of placental exosomes and expounds their clinical significance in the occurrence and development of complications during pregnancy.

Characteristics and functions of placental exosomes

Placental exosomes are secreted by various placental cells during pregnancy^{73–75}, which are rich in growth factors, DNA fragments, miRNAs, and messenger RNAs. Nilsson and Baranov's group isolated exosomes from ex vivo placental explant cultures from first trimester normal pregnancies and reported that placenta-specific enzyme placental-type alkaline phosphatase (PLAP) was a unique marker of placenta exosomes^{75–76}. Alkaline phosphatase is present in all tissues in humans but is particularly concentrated in the liver, bile duct, kidney, bone, intestinal mucosa, and placenta. PLAP is an integral membrane protein (enzyme) unique to the placenta, which lacks the last 24 amino acids compared to the other alkaline phosphatase, so they present certain characteristics, like heat stability, substrate specificity, and resistance to chemical inactivation⁷⁷. PLAP expression has been found in primary trophoblasts—cytotrophoblast cells and ED27 trophoblast-like cells, both isolated from first-trimester chorionic villi—and in JEG-3 cells (an extravillous trophoblast cell lines)⁷⁷. Two major functions of PLAP have been reported so far: 1) to assist the transfer of maternal IgG to the fetus at the placenta surface^{78–80} and 2) to stimulate DNA synthesis and cell proliferation in fibroblasts so that it can improve the survival of fetal fibroblasts^{81–82}. Recent studies by the Menon laboratory have shown PLAP immunoreactivity in both amnion and chorion cells of the fetal membranes (unpublished data). So, it is likely that PLAP is fetal tissue-specific rather than just placenta-specific. PLAP⁺ exosomes are now widely used to isolate fetal-specific exosomes from maternal biologic fluids because they are placenta-specific⁸³. The function of placental exosomes in normal pregnancy is mainly reported in 4 main areas: 1) maternal-fetal communication⁸⁴, 2) transferring of gene information to target cells to regulate fetomaternal metabolic homeostasis⁸⁵, and 3) inhibition of maternal T-cell signals may lead to immune tolerance⁷², 4) regulate angiogenesis and endothelial cell migration^{77,86}. Placental exosomes can be found in the maternal peripheral blood in vivo, with significant differences found between pregnant and nonpregnant subjects⁸⁷. The total number of placental-derived exosomes

increases during the first trimester, as early as sixth week of pregnancy, even when the intervillous circulation is not fully established^{83,88}. Taylor et al⁵⁴ have shown that the concentration of exosomes at 28 weeks' gestation in maternal peripheral blood was ~20-fold greater than that observed in nonpregnant women. Salomon et al⁸⁹ have shown that placental exosomes' concentration in maternal plasma increases by 6 fold in normal pregnant women as gestation progress, with the maximum concentration reported at term. Placental exosomes transport various miRNAs and mRNAs⁹⁰, and the cargo and its concentrations change during pregnancy⁸⁵.

The kinetics of release and biological activities of placental exosomes are regulated by the microenvironment (eg. oxygen pressure, glucose concentration, inflammation). Increasing glucose concentration—such as seen in pregnancy-induced diabetes, imbalanced insulin resistance, and abnormal regulation of central nervous system—and any variation of oxygen pressure could influence the rate of release of exosomes from primary trophoblasts and also influence the contents and their biological activity against target cells⁸⁹. Placental exosomes were associated with maternal uterine blood flow and placental weight at delivery, suggesting that determination of placental exosomes and their cargo contents in maternal blood (liquid biopsies) can be a superior noninvasive method of detecting placental function. The detection of placental-related miRNAs in exosomes, whose expression levels are associated with gestational status and fetal physiologic status, has opened a new avenue for predicting disease progression and detecting therapeutic effects⁸⁵.

The significance of placenta exosomes in pathologic pregnancies

Placental exosomes play an important role in pathological pregnancies⁹⁰. The precise role of placental exosomes in the pathogenesis of pregnancy complications is still in the preliminary stages of investigation by various laboratories. Reports suggest that the varied presence of various proteins in placental exosomes, including quantity and contents, can be linked to placental dysfunction associated with preeclampsia, pregnancy-induced diabetes, and preterm birth⁸⁵.

Placental exosomes and preeclampsia

Preeclampsia is a common and one of the most serious complications of pregnancy, especially in the third trimester of pregnancy. Preeclampsia and associated hypertensive disorders are responsible for nearly 40% of premature births^{91–92}. Limited intervention or management strategies exist due to its unclear pathogenesis. Deficient trophoblast cell infiltration and unsuccessful uterine spiral artery remodeling lead to abnormal placental blood flow, causing the development of hypertension and proteinuria. The role of placental exosomes are investigated in the pathogenesis of preeclampsia due to the following reasons: 1) the variations in quantity and cargo protein contents in placental exosomes and 2) the impact of placental exosomes on maternal immune tolerance. Redman et al⁹³ reported that shedding of vesicles and debris from trophoblast cells into the maternal circulation contributes to the vascular inflammation and endothelial injury, which is associated with the pathophysiology of preeclampsia. Shomer et al found that the vascular protein related to inflammation and vascular proliferation was higher in peripheral blood microvesicles when

vasculopathy existed in preeclampsia patients, suggesting that microvesicles played an important role in the occurrence of vascular disease during pregnancy⁹⁴. Placental microvesicles, in general, are reported to modulate basic peripheral blood immune cell activation and response to LPS in normal pregnancy. Interestingly, this response is significantly enhanced in patients with preeclampsia^{93,95–96}, suggesting that placental microvesicles from trophoblast cells can take part in immunizing and generating an inflammatory response that may contribute to the etiology of preeclampsia. Vargas et al⁹⁷ reported that the expression of syncytiotrophoblast-specific protein-2 (syncytin-2) in exosomes decreased significantly in the eclampsia group. Syncytin-2 is a kind of human endogenous retrovirus (HERV) protein that impacts placental development and trophoblast cell fusion. It plays a more important role in mediating cell fusion than syncytin-1, in terms of expression, cellular localization, and function⁹⁸. These data are thus indicative that syncytin-2 strongly impacts placental development and that trophoblast cell fusion involves more than 1 HERV envelope protein. Finally, placental exosomes from extravillous trophoblast cells affect the function of vascular smooth muscle by decreasing migration and lead to abnormal changes in blood pressure and renal dysfunction⁹⁹.

It is also speculated that placental exosomes may contribute to preeclampsia pathogenesis through an immune-mediated mechanism. The function of placental exosomes in the immune system is mainly reported in the following 4 aspects: 1) suppression of T-cell signaling pathways⁷², 2) impairment of cytotoxicity by reducing the active NK cell receptor¹⁰⁰, 3) apoptotic activity regulated by FasL and TRAIL pathway created by exosomes¹⁰¹, and 4) placental exosomes express TGFB and PD-L1 in Treg activation⁷⁶. It was previously thought that the etiology of preeclampsia was linked to an abnormal maternal immune tolerance, which led to an incomplete invasion of trophoblasts. However, recent studies have shown that both abnormal immune tolerance and maternal immune system hyperactivity contribute to the pathogenesis of preeclampsia⁹⁶. So, the imbalance of the immune system induces the occurrence of preeclampsia through the variety of the placental exosomes, including the contents, volume, and origin. The increased quantity and the variation of the contents in placenta exosomes together with the change of function create the systemic inflammatory response and abnormal maternal immune tolerance. Therefore, it is likely that placental exosomes may play an important role in the etiology of preeclampsia. Salomon's group postulated that the cellular origin of exosomes and/or exosomal content (eg, proteins) might be an important determinant of the dysfunctional state of placenta. For example, syncytin-2 (as mentioned above) is markedly downregulated in exosomes derived from preeclamptic placentas compared to healthy pregnancies⁵⁹. Many researchers believe that the pathophysiology of preeclampsia occurs during the early stages of pregnancy. It is speculated that placental exosomes in peripheral plasma could be an excellent biomarker for the prediction and diagnosis of preeclampsia. In summary, placental exosomes play an important role in the pathogenesis of preeclampsia by the variations of their contents and their imbalance impact on the immune system. Further characterization is required to better understand the usefulness of exosomes as a novel biomarker in the prediction, diagnosis, and treatment effect of this complicated pregnancy complication.

Placental exosomes and GDM

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders during pregnancy. Hyperglycemia, hyperinsulinemia, and hypoxia are major pathophysiologic alterations associated with metabolic disorders during pregnancy, which may adversely affect the maternal-fetal vascular exchange and placentation. GDM can cause abnormal placental function, leading to preterm birth, fetal distress, fetal death, and other adverse pregnancy outcomes. Salomon et al¹⁰² found that maternal blood glucose levels affect the release of placental exosomes by early gestational trophoblasts, while elevated levels of blood glucose impact the biological activity of placenta exudates and induce the emergence of maternal insulin resistance. A longitudinal study by Salomon C concluded that the concentration of total exosomes and placental exosomes in plasma in a GDM group was higher than the control group; however, the contribution of placental exosomes to the total exosome concentration (as determined by exosomal PLAP/total exosomes) was lower than the normal group¹⁰³. This study also reported that the bioactivity of placental and nonplacental exosomes was associated with changes in the inflammatory environment, modulating the maternal glucose metabolism in presymptomatic women⁹⁷. So, we can speculate that the concentration of serum exosomes is related to the occurrence and development of GDM. The exosomes can activate the immune and inflammatory system of GDM patients and accelerate the progress of disease. Santovito D¹⁰⁴ has reported that exosomal miRNA is dysregulated in diabetes patients, and the adiponectin pathway, which is associated with glycemic control, regulated the exosomal miRNA profiling. Almohammadi et al¹⁰⁵ identified that the abundance of miR-518a-5p, miR-518b, miR-518c, miR-518e, miR-520c-3p and miR-525-5p in placental exosomes from GDM women is increased when compared with the normal ones. Interestingly, the concentration of placental exosomes is related to placental mass, and the mass increases significantly in GDM patients⁹⁷, likely contributing to excessive release of placental exosomes compared to normal gestations. Thus, changes in exosomes' concentration, composition, and/or bioactivity (ie, interaction with maternal cells) may participate in the pathogenesis of GDM, and the exosomes could be a bio-marker in the prediction of GDM^{106–107}.

Placental exosomes and preterm birth

Very few studies investigated the role of placental exosomes in preterm birth. Our laboratory is currently studying the contribution of feto-maternal exosomes in preterm birth. Recent studies have shown that senescent fetal membranes at term produce exosomes, and in vitro studies mimicked these conditions showing that exosomes from fetal cells reflect oxidative stress and sterile inflammation. These exosomes can traverse through feto-maternal tissues and are capable of causing functional changes related to parturition in maternal tissues^{108–110}. In preterm birth, we postulate that these exosomes can be generated by premature senescence activation in response to oxidative stress or inflammation-inducing risk factors to cause preterm labor. The roles of placental exosomes are yet to be explored in preterm birth and preterm prelabor rupture of the membranes (pPROM).

Other Placental EVs in pregnancy

The placenta is an organ that performs all vital functions for the growth and survival of the fetus. Placental cells, including trophoblasts, syncytiotrophoblasts and mesenchymal stem cells, secrete soluble endocrine mediators and EVs. Although the main idea of this paper is major in the placenta exosomes, the other EVs also pay attention to the researchers. SNA is the biggest vesicles which has been thought to be the end of the life cycle of syncytiotrophoblast. They contain a lot of nuclei and fetal protein, RNA and other factors and can be found in the early pregnancy. The content in SNA can influence the behavior of maternal cells and may have some relationship with the morbidity and clinical symptoms of preeclampsia¹¹¹. In contrast to exosomes that are produced inside the cell, the exact origin of placental micro- and nano- vesicles excluded exosomes is still unclear, however, the amount of vesicles increased with increasing gestational age¹¹². Syncytiotrophoblast microparticles (STBMs) that derived from syncytiotrophoblast (STB) play a role in the endothelial system, interact with immune components and contribute to systemic inflammation¹¹². They provide the basis for supporting normal pregnancy and are closely related to the pathogenesis of preeclampsia^{113–115}.

Conclusion

Placental exosomes that can arise from trophoblast cells are unique with a high efficiency of fetal-maternal communication (Figure 2). The biomarkers that include the syncytiotrophoblast-specific proteins (miRNAs, proapoptotic molecules FasL and TRAIL, and TGFB) can be detected in placental-specific (PLAP⁺) exosomes in maternal peripheral blood and urine, which made the noninvasive detection of placental exosomes and determination of placental physiology a possibility. The function of placental exosomes includes cell communication, immune response, antigen presentation, inflammation, blood clotting, angiogenesis, and induced downstream signals; they are located in susceptible cells for protein exchange and transfer of nucleic acids and other substances, which have an important role in the physiological and pathological pregnancy. We conclude that placental exosomes have a promising future in the pathogenesis of pregnancy, diagnosis, and treatment of pregnancy complications if an accurate and specific isolation method can be found.

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Figure 1. Basic exosome characteristics

Exosome study reports normally include a minimum of 4 modes of characterization. An example of placental membrane cell- (amnion) derived exosome analysis is represented in this figure.

(A) Exosome shape: Transmission electron microscopy with negative staining is often used to determine exosome shape. Amnion cell-derived exosomes isolated from culture media shows classic shape of exosomes. Similarly, exosomes isolated from amniotic fluid also had similar morphology.

(B) Size and concentration of exosomes: Exosomes are generally between 30–150 nm in size. Nanoparticle tracking analysis is also used to estimate quantity of exosomes. Amnion cells produce exosomes with an average size of 138.6 nm and a mean of 2727 exosomes/cell.

(C) Western blot analyses are often performed using exosome homogenates. Isolated exosomes should show specific markers (CD9, CD81, Alix, and HSC70). In addition, markers to determine the cell of origin are also often included in analysis. In this figure, Nanog, an amnion stem cell marker, is analyzed to show amnion cell specificity of exosomes.

(D) Flow cytometric analysis is also used to demonstrate exosome markers. CD63 analysis is shown in this figure.

Figure 2. Placental exosomes in normal and pathologic pregnancies

Placental cells shed exosomes as early as 6th week of pregnancy, and their numbers gradually increase as gestation progresses. The maximum number of placental exosomes are seen at term. **(A)** The contents of these exosomes include proteins, lipids, DNA, and various forms of RNAs. It is hypothesized that pregnancy complications that impact placental function can be reflected in **(B)** exosome cargo and **(C)** contents. In summary, multitudes of physiologic alterations can cause placental dysfunction, contributing to various mechanisms, but not limited to, activation of pathological pathways, altered cell communication, immune tolerance imbalance, and cell migration and invasion. These dysfunctional pathophysiologic changes can be reflected in exosomes and in their quantity and contents. Understanding the changes in exosome quantity and cargo may increase their usefulness as a biomarker of placental function.

The reviewer point was "Standard deviation value should be presented"