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Role of Placental Extracellular Vesicles in the Physiology and Pathology of Pregnancy

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ABSTRACT

Extracellular vesicles are membrane-limited nanovesicles of endosomal or plasma membrane origin present in most biological fluids. They are capable of transporting various substances and are considered biomarkers of pathological conditions. In preeclampsia, increased levels of placental extracellular vesicles containing antiangiogenic factors have been observed. Moreover, placental extracellular vesicles in preeclampsia are characterized by low strongly anti-inflammatory factor levels and increased high-mobility group nuclear protein levels, indicating cellular damage. Similar to other pathological conditions, the onset of preeclampsia is accompanied by increased extracellular vesicle concentrations, which are detectable as early as 11 weeks of gestation. This review aimed to highlight the role of extracellular vesicles in the course of pregnancy and in the development of preeclampsia. Full-text review and original research articles published in Russian and English were comprehensively analyzed using the eLibrary.Ru, Google Scholar, and PubMed databases, covering the period from 1989 to 2024. The search employed the following keywords: *плацентарные внеклеточные везикулы* (placental extracellular vesicles), *внеклеточные везикулы во время беременности* (extracellular vesicles during pregnancy), and *внеклеточные везикулы и преэклампсия* (extracellular vesicles and preeclampsia). Severe preeclampsia has been associated with a significant increase in the number of extracellular vesicles of various origins. Several authors have demonstrated that placental extracellular vesicles can enter the fetal circulation; however, whether they induce a harmful effect on the fetus remains unclear. Placental extracellular vesicles play a crucial physiological role during pregnancy. They serve as indicators of gestational progression, which makes it possible to quantify them for the prediction of various pregnancy complications.

Keywords: extracellular vesicles; pregnancy; implantation; preeclampsia; prediction.

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Роль плацентарных внеклеточных везикул в физиологии и патологии беременности

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АННОТАЦИЯ

Внеклеточные везикулы — мембранные нановезикулы эндосомального или плазматического происхождения, присутствующие в большинстве жидкостей организма. Внеклеточные везикулы способны переносить различные вещества, и в последнее время рассматриваются как биомаркеры различных патологических состояний. Установлено, что при преэклампсии наблюдается увеличение уровня плацентарных внеклеточных везикул, содержащих антиангиогенные факторы. Кроме того, при преэклампсии плацентарные внеклеточные везикулы характеризуются низким содержанием факторов с выраженным противовоспалительным действием и высоким уровнем ядерных белков высокой мобильности, что отражает повреждение клеток. При развитии преэклампсии, как и при многих других патологических состояниях, наблюдается увеличение количества внеклеточных везикул, причём уже с 11-й недели гестации. Целью данного обзора является освещение роли внеклеточных везикул в процессе развития беременности, а также при присоединении преэклампсии. Проведён анализ опубликованных полнотекстовых научных обзорных и оригинальных статей на иностранном (английском) и русском языках с использованием баз данных eLibrary.Ru, Google Scholar и PubMed за период с 1989 по 2024 год. Для поиска были использованы следующие ключевые слова: «плацентарные внеклеточные везикулы», «внеклеточные везикулы во время беременности», «внеклеточные везикулы и преэклампсия». Установлено, что при тяжёлой преэклампсии наблюдается статистически значимое увеличение внеклеточных везикул различного происхождения. Ряд авторов показал, что плацентарные внеклеточные везикулы попадают в кровоток плода, однако остаётся нерешённым вопрос, оказывают ли они повреждающее действие на организм плода или нет. Плацентарные внеклеточные везикулы имеют важное физиологическое значение во время беременности: они являются индикаторами течения процесса гестации, что обуславливает возможность определения их количества с целью прогнозирования различных осложнений беременности.

Ключевые слова: внеклеточные везикулы; беременность; имплантация; преэклампсия; прогнозирование.

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Extracellular vesicles are membrane-limited nanovesicles originating from the endosomal or plasma membrane and occur in most biological fluids. They contain fragments of the producer cell membrane, including surface receptors/ligands. The composition of the extracellular vesicles depends on the producer. Extracellular vesicles are usually divided into exosomes (50–150 nm) and microvesicles (100–1000 nm). Exosomes are of endocytic origin and are released from cells by the fusion of a multivesicular endosome with the outer plasma membrane. In contrast, the microvesicles bud directly from the cell surface. Both types of extracellular vesicles cause various biological effects [1, 2]. The International Society for Extracellular Vesicles recommended using the term *extracellular vesicles* because of the complexity of isolating and distinguishing vesicle subtypes [3].

The main components of extracellular vesicle membranes are cholesterol, sphingomyelins, and phosphatidylcholines, with a significant enrichment in sphingomyelin, gangliosides, and phosphatidylserine [4, 5]. Because of the presence of a lipid bilayer, extracellular vesicles are highly stable and are protected from degradation in the extracellular environment [6, 7]. Additionally, extracellular vesicles may also contain prostaglandins, leukotrienes, endocannabinoids, or lysophospholipids [8, 9]. Extracellular vesicles can transport proteins that were previously considered intracellular and nonsecreted. Various nucleic acids, including DNA, mRNA, microRNA, and tRNA, are also components of the extracellular vesicles [10]. Extracellular vesicles that contain mRNA affect protein synthesis, whereas those with microRNA and tRNA regulate protein translation through RNA-induced silencing [10]. Because of their structure, extracellular vesicles can be biomarkers of various pathological conditions [7, 10].

This review aimed to highlight the role of extracellular vesicles during pregnancy as well as in the development of preeclampsia. We analyzed full-text scientific reviews and original articles, in foreign (English) and Russian languages, published from 1989 to 2024 using the *eLIBRARY.RU*, *Google Scholar*, and *PubMed* databases. The following keywords were used for the search: *плацентарные ВВ (placental extracellular vesicles)*, *ВВ во время беременности (extracellular vesicles during pregnancy)*, and *ВВ и преэклампсия (extracellular vesicles and preeclampsia)*.

ROLE OF EXTRACELLULAR VESICLES IN IMPLANTATION

Implantation is a multi-stage process that includes several stages [5]. Animal experiments have shown that the morula stage embryo enters the uterus on the 6th day, before forming a blastocyst with an inner cell mass and a blastocoele, or central cavity, surrounded by a monolayer of trophoblast cells. After the rupture of the zona pellucida, the inner cell mass (the embryo and associated extraembryonic membranes) takes on an ovoid and tubular shape and begins to elongate until it occupies the entire length of the uterine horn

ipsilateral to the corpus luteum [11]. Elongation is important for the body to recognize pregnancy. Remodeling and proliferation of trophoblast cells [12] cause a significant increase in embryo length during elongation [13]. The paternal set of chromosomes is responsible for the development of the chorion, whereas the female set is responsible for the development of internal organs [14]. Apart from hormonal factors, intercellular communication between the endometrium and the fertilized egg is important for successful implementation [2, 12, 13]. There is a recent accumulation of evidence indicating the role of extracellular vesicles in the intercellular communication [2].

Extracellular vesicles exert their biological effects through interaction with the surface or intracellular receptors of the recipient cell, resulting in the expression of certain genes [15]. Extracellular vesicles are an important component of the reproductive system of humans and animals [1, 2, 10, 15]. Endometrial extracellular vesicles are involved in the regulation of blastocyst implantation. Their number is maximal in the secretory phase, i.e., it depends on the phase of the menstrual cycle, which is necessary for synchronizing the development of the embryo and the endometrium [16]. Experiments on rats showed that endometrial extracellular vesicles containing miRNA-30d increased the adhesive capacity of trophoblasts. Their number also increases in women during the implantation window [17]. More than 200 microRNA fragments and more than 1000 different proteins have been isolated from extracellular vesicles produced by human endometrial ECC-1 (endometrial cancer cell line) cells contain [18]. Extracellular vesicles increase the adhesive capacity of trophoblast cells through focal adhesion kinase signaling and increasing fibronectin [18, 19].

When the blastocyst contacts the endometrium, a hematoma is formed, the purpose of which is to fix the fertilized egg and regulate the depth of chorion invasion [20]. During the blastocyst implantation, the trophoblast differentiates into a cytotrophoblast (outer layer) and a syncytiotrophoblast (inner layer). As the blastocyst grows, a layer of syncytial cells, the syncytiotrophoblast, is formed in the cytotrophoblast. Cytotrophoblast cells secrete a substantial amount of proteolytic enzymes that promote the lysis of the endometrial stroma. The walls of the spiral arteries and syncytiotrophoblast cells form finger-like protrusions from which villi are formed. The fetus' blood and mother's do not mix due to the peculiarities of placental blood flow: the fetal blood from the umbilical arteries enters the capillaries of the villi protruding into the intervillous space, which is washed by the mother's blood. The intervillous space is supplied with blood by the spiral arteries of the endometrium, which are in a state of gestational remodeling, i.e., dilated and full-blooded. The remodeling of spiral arteries is controlled by natural killers, which stimulate the synthesis of angiogenic factors: VEGF (vascular endothelial growth factor), angiopoietins, and matrix metalloproteinases MMP-2 (matrix metalloproteinase-2) and MMP-9 (matrix metalloproteinase-9) [21].

ROLE OF PLACENTAL EXTRACELLULAR VESICLES DURING PREGNANCY

Sabapatha et al. (2006) isolated placental extracellular vesicles using gel chromatography and identified them using antibodies against placental alkaline phosphatase (PLAP). Later, extracellular vesicles were isolated from trophoblast cell cultures and placental tissue [22]. Approximately $1-2 \times 10^{11}$ extracellular vesicles, 10%–20% of which are PLAP-positive placental extracellular vesicles, circulate in the plasma of pregnant women at the early stages of gestation [22]. The number of extracellular vesicles gradually increases toward the third trimester and does not depend on the sex of the fetus or the mother's body mass index [23, 24]. A comparable number of extracellular vesicles circulates in the fetal bloodstream, of which approximately 45% originate from the placenta [25].

The primary and most important role of the extracellular vesicles is their participation in the formation of the fetoplacental blood flow through their involvement in the remodeling of spiral arteries [21].

Placental extracellular vesicles are involved in the regulation of immunological reactions [1, 2, 9]. The fetus is essentially an allograft. For the successful development of pregnancy, immunological tolerance must occur, most often by inhibiting the activation of maternal T-lymphocytes (T cells) and natural killer (NK) cells [26]. This is achieved through the expression of UL16-binding proteins (ULBP1–5) on extracellular vesicles, as well as proteins encoded by genes associated with chain I of the major histocompatibility complex (MHC)–MIC. Interaction with these ligands causes a selective and dose-dependent decrease in the activity of the NKG₂D receptor, which is present on NK cells, and CD8⁺ and γ - δ -on T cells [27, 28]. Placental microvesicles also express B7 ligands, including B7–H3, which causes suppression of T cell activation. The presence of the HLA-G5 isoform (human leukocyte antigen G5) in microvesicles protects fetal tissue from attack by maternal immune cells [27].

The expression of syncytin-1 by placental extracellular vesicle suppresses the production of tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ), important pro-inflammatory agents associated with early pregnancy loss and preeclampsia [29]. Mikaelyan et al. (2019) showed a decrease in mitochondrial proteins in microvesicles circulating in the maternal bloodstream during the development of fetal growth retardation syndrome [30].

In addition to their anti-inflammatory activity, placental extracellular vesicles have pro-inflammatory effects, manifested in their activation of macrophages and release of cytokines, including TNF- α (tumor necrosis factor- α), MIP-1 α (macrophage inflammatory protein-1 α), interleukin (IL)-1 α , IL-6, IL-8 and IL-1 β from endothelial cells [31].

ROLE OF PLACENTAL EXTRACELLULAR VESICLES IN THE GENESIS OF PREECLAMPSIA

Preeclampsia is a multisystem pregnancy complication characterized by hypertension after gestational week 20, proteinuria and/or edema, as well as a high incidence of adverse pregnancy outcomes for the mother and fetus. Insufficient remodeling of spiral arteries, oxidative stress, dysfunction of the vascular endothelium in the mother, and systemic inflammation are important in the pathogenesis of preeclampsia [32–34].

Preeclampsia is characterized by an increase in the level of placental extracellular vesicles containing antiangiogenic factors, i.e., soluble fms-like tyrosine kinase-1 (sFlt-1) and endoglin. These components a pronounced damage to the endothelium, contribute to a decrease in the activity of endothelial nitric oxide synthetase (eNOS), and affect platelet function [35, 36]. Placental extracellular vesicles in preeclampsia contain low levels of microRNA-548c-5p, which have a pronounced anti-inflammatory effect and high levels of nuclear high-mobility proteins, which indicate cell damage [35–39]. An increased content of placental extracellular vesicles in preeclampsia, which occurs as early as gestational week 11, can be used for the early diagnosis of preeclampsia [40].

Han et al. (2020) conducted a series of experiments with placental extracellular vesicles obtained from pregnant women with preeclampsia. After isolation, extracellular vesicle culture was administered to non-pregnant mice, which developed hypertension and proteinuria. The authors found that placental extracellular vesicles caused vasoconstriction, increased the influx of calcium ions into vascular smooth muscle cells, and contributed to a decrease in cerebral perfusion [41].

In our previous study we found that, in severe preeclampsia, there is a statistically significant increase in erythrocytes, placental extracellular vesicles, as well as extracellular vesicles with tissue factor and lipopolysaccharide of Gram-negative microorganisms; in moderate PE, there is an increase in extracellular vesicles with tissue factor and lipopolysaccharide of Gram-negative microorganisms [42].

Several previous studies have demonstrated that placental extracellular vesicles can enter the fetal circulation; however, whether they exert a detrimental effect on the fetus remains unresolved [25, 43].

There are numerous publications demonstrating the possibility of using the occurrence of fetal microvesicles in the maternal bloodstream to diagnose various intrauterine pathologies [44–46].

CONCLUSION

Placental extracellular vesicles play an important physiological role during pregnancy: they serve as indicators of gestational progression and can be quantified for the prediction of various pregnancy complications.

ADDITIONAL INFORMATION

Author contributions: I.G.M.: conceptualization, methodology, writing—review & editing; K.T.E.: methodology, investigation, formal analysis, writing—original draft; Yu. E.Yu.: conceptualization, writing—review & editing; N.R.M.: investigation, formal analysis, writing—original draft; M.Z.R.: investigation, writing—original draft. All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Informed consent: The authors obtained written informed consent from the patient for the publication of personal data in a scientific journal, including its online version. The scope of the published data was approved by the patient.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. И.Г.М. — концептуализация, методология, редактирование рукописи; К.Т.Е. — методология, исследование, анализ, создание черновика; Ю.Е.Ю. — концептуализация, редактирование рукописи; Н.Р.М. — исследование, анализ, создание черновика; М.З.Р. — исследование, создание черновика. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

Этическая экспертиза. Проведение исследования одобрено локальным этическим комитетом Казанского ГМУ (протокол № 8 от 29.10.2024). Все участники исследования добровольно подписали форму информированного согласия до включения в исследование.

Согласие на публикацию. Авторы получили письменное информированное добровольное согласие пациента на публикацию персональных данных в научном журнале, включая его электронную версию. Объём публикуемых данных с пациентом согласован.

Источник финансирования. Авторы декларируют отсутствие внешнего финансирования для проведения исследования и публикации статьи.

Раскрытие информации. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали три внешних рецензента, член редакционной коллегии и научный редактор издания.

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