DOI: https://doi.org/10.17816/KMJ642505 EDN: SLZOIL

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

Ilshat G. Mustafin[1], Timur E. Kurmanbaev[2], Evgenii Y. Yupatov[3,4], Roza M. Nabiullina[1], Zarina R. Mukhametzyanova[1]

[1] Kazan State Medical University, Kazan, Russia;
[2] Kirov Military medical academy, Saint Petersburg, Russia;
[3] Kazan State Medical Academy — Branch of the Russian Medical Academy of Continuous Professional Education, Kazan, Russia;
[4] Kazan Federal University, Kazan, Russia

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.

To cite this article:
Mustafin IG, Kurmanbaev TE, Yupatov EYu, Nabiullina RM, Mukhametzyanova ZR. Role of placental extracellular vesicles in the physiology and pathology of pregnancy. *Kazan Medical Journal.* 2025. DOI: 10.17816/KMJ642505 EDN: SLZOIL

Submitted: 03.12.2024 **Accepted:** 10.03.2025 **Published online:** 13.05.2025

DOI: https://doi.org/10.17816/KMJ642505 EDN: SLZOIL

Роль плацентарных внеклеточных везикул в физиологии и патологии беременности

И.Г. Мустафин[1], Т.Е. Курманбаев[2], Е.Ю. Юпатов[3,4], Р.М. Набиуллина[1], З.Р. Мухаметзянова[1]

[1] Казанский государственный медицинский университет, г. Казань, Россия;
[2] Военно-медицинская академия им. С.М. Кирова, г. Санкт-Петербург, Россия;
[3] Казанская государственная медицинская академия — филиал Российской медицинской академии непрерывного профессионального образования, г. Казань, Россия;
[4] Казанский (Приволжский) федеральный университет, г. Казань, Россия

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 обусловливает возможность определения их количества с целью прогнозирования различных осложнений беременности.

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

Как цитировать:
Мустафин И.Г., Курманбаев Т.Е., Юпатов Е.Ю., Набиуллина Р.М., Мухаметзянова З.Р. Роль плацентарных внеклеточных везикул в физиологии и патологии беременности // Казанский медицинский журнал. 2025. DOI: 10.17816/KMJ642505 EDN: SLZOIL

Рукопись получена: 03.12.2024 **Рукопись одобрена**: 10.03.2025 **Опубликована online**: 13.05.2025

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 blastocele, 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 NKG_2D receptor, which is present on NK cells, and $CDC8^+$ 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-1α (macrophage inflammatory protein-1α), interleukin (IL)-1α, IL-6, IL-8 and IL-1β 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].

DOI: https://doi.org/10.17816/KMJ642505

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.

Ethics approval: The study was approved by the Local Ethics Committee of Kazan State Medical University (Protocol No. 8, dated October 29, 2024). All participants provided written informed consent prior to inclusion in the study.

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.

Funding sources: The authors declare no external funding was received for conducting the study or publishing the article.

Disclosure of interests: Authors have no explicit or potential conflicts of interests associated with the publication of this article.

Statement of originality: No previously published material (text, images, or data) was used in this work.

Data availability statement: The editorial policy regarding data sharing does not apply to this work, as no new data was collected or created.

Generative AI: No generative artificial intelligence technologies were used to prepare this paper.

Provenance and peer review: This paper was submitted unsolicited and reviewed following the standard procedure. The review process involved three external reviewers, a member of the editorial board, and the in-house scientific editor.

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.

REFERENCES

1. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol*. 2013;(200):373–83. doi: 10.1083/jcb.201211138

2. O'Neil EV, Burns GW, Spencer TE. Extracellular vesicles: Novel regulators of conceptus-uterine interactions? *Theriogenology*. 2020;(150):106–112. doi: 10.1016/j.theriogenology.2020.01.083 EDN: EROARI

3. Gould SJ, Raposo G. As we wait: coping with an imperfect nomenclature for extracellular vesicles. *J Extracell Vesicles*. 2013;2. doi: 10.3402/jev.v2i0.20389

4. Laulagnier K, Motta C, Hamdi S, et al. Mast cell- and dendritic cell-derived exosomes display a specific lipid composition and an unusual membrane organization. *Biochem J*. 2004;(380):161–171. doi: 10.1042/bj20031594

5. Skotland T, Hessvik NP, Sandvig K, et al. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. *J Lipid Res*. 2019;(60):9–18. doi: 10.1194/jlr.R084343

6. Simpson RJ, Jensen SS, Lim JW. Proteomic profiling of exosomes: current perspectives. *Proteomics*. 2008;(8):4083–4099. doi: 10.1002/pmic.200800109

7. Keller S, Ridinger J, Rupp AK, et al. Body fluid derived exosomes as a novel template for clinical diagnostics. *J Transl Med*. 2011;(9):86. doi: 10.1186/1479-5876-9-86 EDN: HRWNUY

8. Record M, Silvente-Poirot S, Poirot M, Wakelam MJO. Extracellular vesicles: lipids as key components of their biogenesis and functions. *J Lipid Res*. 2018;(59):1316–1324. doi: 10.1194/jlr.E086173

9. Subra C, Grand D, Laulagnier K, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. *J Lipid Res*. 2010;(51):2105–2120. doi: 10.1194/jlr.M003657 EDN: NZVXHF

10. Kosaka N, Iguchi H, Yoshioka Y, et al. Secretory mechanisms and intercellular transfer of microRNAs in living cells. *J Biol Chem*. 2010;(285):17442–17452. doi: 10.1074/jbc.M110.107821

11. Lonergan P, Fair T, Forde N, Rizos D. Embryo development in dairy cattle. *Theriogenology*. 2016;(86):270–277. doi: 10.1016/j.theriogenology.2016.04.040

12. Wang J, Guillomot M, Hue I. Cellular organization of the trophoblastic epithelium in elongating conceptuses of ruminants. *C R Biol*. 2009;(332):986–997. doi: 10.1016/j.crvi.2009.09.004

13. Wales RG, Cuneo CL. Morphology and chemical analysis of the sheep conceptus from the 13th to the 19th day of pregnancy. *Reprod Fertil Dev*. 1989;(1):31–39. doi: 10.1071/RD9890031

14. Giannubilo SR, Marzioni D, Tossetta G, et al. The "Bad Father": Paternal Role in Biology of Pregnancy and in Birth Outcome. *Biology*. 2024;(13):165. doi: 10.3390/biology13030165 EDN: UKBDPM

15. Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. *J Extracell Vesicles*. 2014;(3). doi: 10.3402/jev.v3.24641 EDN: YERXCY

16. Ng YH, Rome S, Jalabert A, et al. Endometrial exosomes/microvesicles in the uterine microenvironment: a new paradigm for embryo-endometrial cross talk at implantation. *PLoS One*. 2013;(8):e58502. doi: 10.1371/journal.pone.0058502
17. Vilella F, Moreno-Moya JM, Balaguer N, et al. Hsa-miR-30d, secreted by the human endometrium, is taken up by the pre-implantation embryo and might modify its transcriptome. *Development*. 2015;(142):3210–3221. doi: 10.1242/dev.124289
18. Greening DW, Nguyen HP, Elgass K, et al. Human endometrial exosomes contain hormone-specific cargo modulating trophoblast adhesive capacity: insights into endometrial-embryo interactions. *Biol Reprod*. 2016;(94):38. doi: 10.1095/biolreprod.115.134890
19. Evans J, Rai A, Nguyen HPT, et al. In vitro human implantation model reveals a role for endometrial extracellular vesicles in embryo implantation: reprogramming the cellular and secreted proteome landscapes for bidirectional fetal-maternal communication. *Proteomics*. 2019:e1800423. doi: 10.1002/pmic.201800423 EDN: PYHKSB
20. Iupatov EYu, Mustafin IG, Kurmanbaev TE, et al. Local hemostasis disorders underlying endometric pathology. *Obstetrics, Gynecology and Reproduction*. 2020;15(4):430–440. doi: 10.17749/2313-7347/ob.gyn.rep.2021.214 EDN: UNIBMF
21. Chen K, Liang J, Qin T, et al. The Role of Extracellular Vesicles in Embryo Implantation. *Front Endocrinol*. 2022;(13):809596. doi: 10.3389/fendo.2022.809596 EDN: HMFEHH
22. Sabapatha A, Gercel-Taylor C, Taylor DD. Specific isolation of placenta-derived exosomes from the circulation of pregnant women and their immunoregulatory consequences. *Am J Reprod Immunol*. 2006;(56):345–355. doi: 10.1111/j.1600-0897.2006.00435.x
23. Abolbaghaei A, Langlois MA, Murphy HR, et al. Circulating extracellular vesicles during pregnancy in women with type 1 diabetes: a secondary analysis of the CONCEPTT trial. *Biomark Res*. 2021;(9):1–10. doi: 10.1186/s40364-021-00322-8 EDN: DYTIWY
24. Bathla T, Abolbaghaei A, Reyes AB, Burger D. Extracellular vesicles in gestational diabetes mellitus: A scoping review. *Diab Vasc Dis Res*. 2022;19(2):14791641221093901. doi: 10.1177/14791641221093901 EDN: AEQNBA
25. Miranda J, Paules C, Nair S, et al. Placental exosomes profile in maternal and fetal circulation in intrauterine growth restriction – Liquid biopsies to monitoring fetal growth. *Placenta*. 2018;(64):34–43. doi: 10.1016/j.placenta.2018.02.006
26. Mincheva-Nilsson L, Baranov V. Placenta-derived exosomes and syncytiotrophoblast microparticles and their role in human reproduction: immune modulation for pregnancy success. *Am J Reprod Immunol*. 2014;72(5):440–457. doi: 10.1111/aji.12311
27. Kshirsagar SK, Alam SM, Jasti S, et al. Immunomodulatory molecules are released from the first trimester and term placenta via exosomes. *Placenta*. 2012;33(12):982–990. doi: 10.1016/j.placenta.2012.10.005
28. Hedlund M, Stenqvist AC, Nagaeva O, et al. Human placenta expresses and secretes NKG2D ligands via exosomes that down-modulate the cognate receptor expression: evidence for immunosuppressive function. *J Immunol*. 2009;181(1):340–351. doi: 10.4049/jimmunol.0803477
29. Than NG, Abdul Rahman O, Magenheim R, et al. Placental protein 13 (galectin-13) has decreased placental expression but increased shedding and maternal serum concentrations in patients presenting with preterm pre-eclampsia and HELLP syndrome. *Virchows Arch*. 2008;453(4):387–400. doi: 10.1007/s00428-008-0658-x EDN: JPJLYR
30. Mikaelyan AG, Marey MV, Sukhanova YuA, et al. Characteristics of the microvesule composition in physiological pregnancy and pregnancy complicated by the intrauterine growth restriction. *Obstetrics and Gynecology: News, Opinions, Training*. 2019;7(4):25–31. doi: 10.24411/2303-9698-2019-14002 EDN: PCAQOV
31. Atay S, Gercel-Taylor C, Taylor DD. Human trophoblast-derived exosomal fibronectin induces pro-inflammatory IL-1beta production by macrophages. *Am J Reprod Immunol*. 2011;66(4):259–269. doi: 10.1111/j.1600-0897.2011.00995.x
32. Preeclampsia. Eclampsia. Edema, proteinuria and hypertensive disorders during pregnancy, childbirth and the postpartum period. Clinical recommendations. Moscow, 2021. 79 p. (In Russ.)
33. Jung E, Romero R, Yeo L, et al. The etiology of preeclampsia. *Am J Obstet Gynecol*. 2022;226(2):S844–S866. doi: 10.1016/j.ajog.2021.11.1356 EDN: TABGLI
34. Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. *Am J Obstet Gynecol*. 2022;226(2):S1071–S1097. doi: 10.1016/j.ajog.2020.07.020 EDN: VHKXKU
35. Vargas A, Zhou S, Ethier-Chiasson M, et al. Syncytin proteins incorporated in placenta exosomes are important for cell uptake and show variation in abundance in serum exosomes from patients with preeclampsia. *FASEB J*. 2014;(28):3703–3719. doi: 10.1096/fj.13-239053
36. Salomon C, Guanzon D, Scholz-Romero K, et al. Placental Exosomes as Early Biomarker of Preeclampsia: Potential Role of Exosomal MicroRNAs Across Gestation. *J Clin Endocrinol Metab*. 2017;(102):3182–3194. doi: 10.1210/jc.2017-00672
37. Morgoyeva AA, Tsakhilova SG, Sakvarelidze NYu, et al. The role of extracellular vesicles in the development of endothelial dysfunction in preeclampsia. *Effective pharmacotherapy*. 2021;17(32):8–12. doi: 10.33978/2307-3586-2021-17-32-8-12 EDN: LMRRTF
38. Schuster J, Cheng SB, Padbury J, et al. Placental extracellular vesicles and preeclampsia. *Am J Reprod Immunol*. 2021;85(2):1–16. doi: 10.1111/aji.13297 EDN: BIAEQU
39. Gill M, Motta-Mejia C, Kandzija N, et al. Placental syncytiotrophoblast-derived extracellular vesicles carry active NEP (neprilysin) and are increased in preeclampsia. *Hypertension*. 2019;73(5):1112–1119. doi: 10.1161/HYPERTENSIONAHA.119.12707
40. McElrath TF, Cantonwine DE, Gray KJ, et al. Late first trimester circulating microparticle proteins predict the risk of preeclampsia< 35 weeks and suggest phenotypic differences among affected cases. *Sci rep*. 2020;10(1):17353. doi: 10.1038/s41598-020-74078-w EDN: RFXAFE
41. Han C, Wang C, Chen Y, et al. Placenta-derived extracellular vesicles induce preeclampsia in mouse models. *Haematologica*. 2020;105(6):1686. doi: 10.3324/haematol.2019.226209 EDN: SZTTNK
42. Mustafin IG, Kurmanbaev TE, Yupatov EYu, et al. Clinical and pathophysiological aspects of microvesicular composition of peripheral blood in pregnant women with preeclampsia. *Bulletin of modern clinical medicine*. 2024;17(3):36–43. doi: 10.20969/VSKM.2024.17(3).36-43 EDN: HYXWMT
43. Condrat CE, Varlas VN, Duică F, et al. Pregnancy-related extracellular vesicles revisited. *Int J Mol Sci*. 2021;22(8):3904. doi: 10.3390/ijms22083904 EDN: CVPKKE
44. Adamova P, Lotto RR, Powell AK, Dykes IM. Are there foetal extracellular vesicles in maternal blood? Prospects for diagnostic biomarker discovery. *J Mol Med*. 2023;101(1):65–81. doi: 10.1007/s00109-022-02278-0 EDN: CQBYWH
45. Marell PS, Blohowiak SE, Evans MD, et al. Cord blood-derived exosomal CNTN2 and BDNF: potential molecular markers for brain health of neonates at risk for iron deficiency. *Nutrients*. 2019;11(10):1–11. doi: 10.3390/nu11102478
46. Goetzl L, Darbinian N, Merabova N. Noninvasive assessment of fetal central nervous system insult: potential application to prenatal diagnosis. *Prenat Diagn*. 2019;39(8):609–615. doi: 10.1002/pd.5474

AUTHORS' INFO

*** Zarina R. Mukhametzyanova**, Postgraduate Student,
Depart. of Biochemistry and Clinical Laboratory Diagnostics;
address: 49 Butlerova st, Kazan, Russia, 420012;
eLibrary SPIN: 1117-8860;
ORCID: 0000-0002-7525-7455;
e-mail: zarinam75@gmail.com

Ilshat G. Mustafin, Dr. Sci. (Medicine), Professor, Head of Depart.
of Biochemistry and Clinical Laboratory Diagnostics;
eLibrary SPIN: 1588-6988;
ORCID: 0000-0001-9683-3012;
e-mail: ilshat64@mail.ru

Timur E. Kurmanbaev, Cand. Sci. (Medicine), Senior Lecturer,
Depart. of Obstetrics and Gynecology;
eLibrary SPIN: 7818-6181;
ORCID: 0000-0003-0644-5767;
e-mail: timka_rus@inbox.ru

Evgenii Y. Yupatov, Dr. Sci. (Medicine), Assistant Professor,
Head of Depart., Depart. of Obstetrics and Gynecology;
eLibrary SPIN: 3094-6491;
ORCID: 0000-0001-8945-8912;
e-mail: e.yupatov@mcclinics.ru

Rosa M. Nabiullina, Cand. Sci. (Medicine), Assistant Professor,
Depart. of Biochemistry and Clinical Laboratory Diagnostics;
eLibrary SPIN: 9596-0831;
ORCID: 0000-0001-5942-5335;
e-mail: nabiullina.rosa@yandex.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Мухаметзянова Зарина Рамисовна**, аспирант,
каф. биохимии и клинической лабораторной диагностики;
адрес: Россия, 420012, Казань, ул. Бутлерова, д. 49;
eLibrary SPIN: 1117-8860;
ORCID: 0000-0002-7525-7455;
e-mail: zarinam75@gmail.com

Мустафин Ильшат Ганиевич, д-р мед. наук, профессор,
зав. каф. биохимии и клинической лабораторной диагностики;
eLibrary SPIN: 1588-6988;
ORCID: 0000-0001-9683-3012;
e-mail: ilshat64@mail.ru

Курманбаев Тимур Ерланович, канд. мед. наук,
старший преподаватель, каф. акушерства и гинекологии;
eLibrary SPIN: 7818-6181;
ORCID: 0000-0003-0644-5767;
e-mail: timka_rus@inbox.ru

Юпатов Евгений Юрьевич, д-р мед. наук, доцент, зав. каф.
акушерства и гинекологии;
eLibrary SPIN: 3094-6491;
ORCID: 0000-0001-8945-8912;
e-mail: e.yupatov@mcclinics.ru

Набиуллина Роза Муллаяновна, канд. мед. наук, доцент,
каф. биохимии и клинической лабораторной диагностики;
eLibrary SPIN: 9596-0831;
ORCID: 0000-0001-5942-5335;
e-mail: nabiullina.rosa@yandex.ru