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Research Article

Role IVF in Preeclampsia Pathogenesis: impact of extracellular vesicles

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Abstract

Preeclampsia (PE) is a complex and life-threatening pregnancy complication affecting both mother and fetus. Recent studies have shown a possible link between PE and in Vitro Fertilization (IVF) treatments, suggesting that Extracellular Vesicles (EVs) play a crucial role in the pathophysiology of PE [1,2]. This review aims to provide a comprehensive understanding of the involvement of EVs in the development of PE, as well as their potential role in IVF-related PE. We also explore the potential use of EVs as diagnostic biomarkers and therapeutic targets for PE in the context of Assisted Reproductive Technologies (ART).

Key words: Preeclampsia; Extracellular Vesicles; Vitro Fertilization; Reproductive Technologies; Female Reproductive System

Introduction

Preeclampsia is a multifactorial pregnancy complication affecting 3-8% of pregnancies worldwide [3], characterized by the onset of hypertension and proteinuria after 20 weeks of gestation. This disorder severely affects maternal and fetal health, leading to preterm birth, Intrauterine Growth Restriction (IUGR), and even maternal and fetal death [4]. Despite advances in obstetric care, the etiology and pathophysiology of PE remain elusive, making early diagnosis and effective treatments challenging. In recent years, Assisted Reproductive Technologies (ART), Including in Vitro Fertilization (IVF), have increased dramatically. Several studies have reported a higher incidence of PE among women who underwent IVF treatments [5]. This association suggests a potential role of Extracellular Vesicles (EVs) in developing PE, as they have been identified as crucial mediators of cell-to-cell communication in various physiological and pathological processes, including pregnancy [6]. Recent advances in Assisted Reproductive Technologies (ART), such as in Vitro Fertilization (IVF), have increased success rates for infertile couples. However, these technologies have also been associated with a higher risk of pregnancy complications, including Preeclampsia (PE) [7]. The involvement of Extracellular Vesicles (EVs) in the Pathogenesis of PE, particularly in the context of IVF, warrants further investigation to better understand this relationship and identify potential diagnostic and therapeutic strategies for PE. This review provides a comprehensive overview of the current knowledge on the role of EVs in PE, with a particular focus on their potential involvement in IVF-related PE, and discusses future perspectives and challenges in the field. This review will focus on the role of EVs in the development of PE, particularly in the context of IVF, and discuss the potential use of EVs as diagnostic biomarkers and therapeutic targets for PE.

Preeclampsia: An Overview

Pathophysiology and Risk Factors

The Pathophysiology of PE is complex and multifactorial, involving genetic, immunological, and environmental factors [8]. The most widely accepted theory involves abnormal placentation, leading to placental ischemia and the subsequent release of soluble factors into the maternal circulation, promoting

endothelial dysfunction, inflammation, and, ultimately, the clinical manifestations of PE [9]. Key risk factors for PE include nulliparity, advanced maternal age, obesity, pre-existing medical conditions (e.g., hypertension, diabetes, renal disease), and history of PE in previous pregnancies [10]. Additionally, IVF treatments have emerged as a potential risk factor for developing PE [11].

Clinical Presentation and Diagnosis

PE is a heterogeneous disorder with a wide range of clinical presentations, from mild to severe [12]. The main clinical features include new-onset hypertension and proteinuria after 20 weeks of gestation [13]. Other symptoms include edema, headache, visual disturbances, and epigastric pain [14]. The diagnosis of PE is primarily based on clinical and laboratory findings [15]. However, due to the lack of specific biomarkers, early diagnosis and differentiation from other hypertensive disorders of pregnancy remain challenging [16].

Management and Treatment

The management of PE primarily focuses on controlling maternal blood pressure, preventing seizures (eclampsia), and monitoring fetal well-being [17]. Antihypertensive medications are commonly used to manage blood pressure, while magnesium sulfate is administered to prevent seizures [18]. Fetal surveillance, including ultrasound and non-stress tests, is essential for monitoring fetal well-being and guiding delivery timing [19]. In severe cases, early delivery may be necessary to protect the health of the mother and the fetus [20]. However, this can lead to complications associated with preterm birth, such as respiratory distress syndrome and neonatal intensive care unit admission [2].

Prevention Strategies

Current preventive strategies for PE include the administration of low-dose aspirin for women at high risk of developing the disorder [21]. Aspirin has been shown to reduce the risk of PE by 10-20% when initiated before 16 weeks of gestation [22]. Identifying specific risk factors, such as those related to IVF, could help tailor prevention strategies for individual patients and improve outcomes.

Extracellular Vesicles: Biogenesis, Classification, and Functions

Biogenesis and Classification

Extracellular vesicles are lipid bilayer-enclosed particles released by cells into the extracellular environment [23]. They are formed by the inward budding of the endosomal membrane (exosomes) or the outward budding of the plasma membrane (microvesicles) [24]. EVs can be classified into three main categories based on their size, biogenesis, and molecular markers: exosomes (30-150 nm), microvesicles (100-1000 nm), and apoptotic bodies (500-2000 nm) [25].

Functions of Extracellular Vesicles

EVs have diverse functions in intercellular communication, immune modulation, and tissue homeostasis [26]. They can carry various bioactive molecules, including proteins, lipids, and nucleic acids, which can be transferred to recipient cells, influencing their function [27]. In the context of pregnancy, EVs have been implicated in processes such as placental development, maternal-fetal immune tolerance, and the maintenance of pregnancy [28].

Extracellular Vesicle Cargo

The cargo of EVs consists of various bioactive molecules, including proteins, lipids, and nucleic acids, which can be transferred to recipient cells and modulate their function [29]. The cargo composition is determined by the cell of origin, the cellular state, and the physiological or pathological context [30]. In pregnancy, EV cargo can include placental proteins, hormones, and regulatory RNAs, which may contribute to pregnancy-related processes and complications, such as PE [31].

Isolation and Characterization of Extracellular Vesicles

The isolation and characterization of EVs from biological fluids, such as blood and urine, have been challenging due to their small size and heterogeneous nature [32]. Several techniques have been developed for EV isolation, including ultracentrifugation, size-exclusion chromatography, and immunoaffinity capture [33]. Each method has advantages and limitations, and the choice of technique depends on the specific research question and the intended downstream analysis [34]. Following isolation, EVs can be characterized by their size, morphology, and molecular markers using nanoparticle tracking analysis, transmission electron microscopy, and flow cytometry [6].

Extracellular Vesicles in Female Reproductive System: Origin of Releases

In the Vagina

These vesicles, known as vaginosomes, have been demonstrated to affect sperm capacitation and acrosome response in mice, similar to EVs reported in other female biofluids [35]. There is some evidence that extracellular RNAs present in the vagina, notably miR-186-5p, can guard against HIV-1 infection [36].

In the Uterus

Uterosomes are extracellular vesicles that can be found in the uterus' luminal fluid [37]. Uterosome-related proteins, which are secreted by endometrial epithelial cells, appear to be engaged in crucial embryo-implantation pathways, indicating that these vesicles are vital in early pregnancy [38]. In addition to being secreted by endometrial cells, uterosomes have been demonstrated to be taken up by endometrial epithelial cells and profoundly change their transcriptome[39].

In the Ovaries

The fluid surrounding an expanding oocyte, the cell in an ovary that can develop into an ovum, is known as Follicular Fluid (FF). Blood plasma components that penetrate the "blood-follicle barrier" and the secretory activity of granulosa and thecal cells contribute to producing follicular fluid [40]. The Cumulus-Oocyte Complex

(COC) grows just before ovulation, enabling the egg to complete meiotic maturation. This is likely the result of communication between granulosa cells and the COC. Many studies show that the EVs released from the FF can mediate several mechanisms, such as the transforming growth factor-β (TGF-β) pathway [41]. COC expansion mechanism can be mediated by the miRNAs released within these EVs; human-derived EVs contain miRNAs that target genes involved in follicular maturation inhibition and meiosis resume [42, 43]. On the other hand, other studies suggest that differences in the impact of EVs may be allocated to variations in their molecular cargo at different periods of the menstrual cycle [44, 45]. EVs have also been demonstrated to be taken up by and modify the transcriptome of epithelial cells that line the fallopian tubes, resulting in the expression of genes that increase the chance of fertilization and embryo development [46].

Role of Extracellular Vesicles in Normal Pregnancies

Fertilization and EVs

The female reproductive system undergoes sperm capacitation, also called sperm activation, which starts the signaling pathways required for the sperm to penetrate the several layers of the female egg. Sperm cells receive plasma membrane Ca2+-ATPase 4a (PMCA4a) and PMCA1 from oviductosomes, uterosomes, and vagisomes during the sperm capacitation process [47,48]. EVs released from the oviduct and uterus have also been demonstrated to transmit tyrosine phosphorylated proteins to sperm, which may alter capacitation [37,47]. In Vitro Fertilization (IVF) relies on adding sperm to a collected egg; however, the oocyte must be completely developed before fertilization. It has been demonstrated that incubating retrieved oocytes with follicular fluid-derived EVs and/or oviductosomes enhances oocyte maturation and embryonic development [49,50].

Implantation, Maternal-Fetal Crosstalk and EVs

Following fertilization, the conceptus trophectoderm releases EVs into the uterine fluid, and these vesicles are thought to help facilitate communication between the endometrial lining and the fertilized egg before implantation [51,52]. EVs are a crucial mediator of the bidirectional connection between the endometrial and trophoblast cells, allowing for the transfer of vital cargo to promote embryo implantation, such as angiogenic and proliferative factors [53]. Recent data reveals that lower-grade embryos produce more EVs than higher-quality embryos, and these EVs are often smaller in diameter, suggesting that the amount and size of EVs released from IVF embryos may be a sign of embryo quality [54-56]. Co-culturing IVF embryos generates a microenvironment that utilizes paracrine communication, resulting in better embryonic development than independently cultured embryos [57]. These EVs, which enhance the developmental competence of co-cultured embryos and include the pluripotency genes Nanog, Klf4, Oct4, Sox2, and c-Myc, may be partially responsible for this phenomenon [58]. Early gestation is a critical time for cellular communication at the maternal-fetal interface, which controls pregnancy outcomes. The endometrium and growing conceptus may rapidly exchange biomolecules when placentation is successful. Besides, previous data indicate that EVs are essential in modifying maternal immunity and enabling immunological tolerance to fetal antigens, which lowers the chance of rejection/abortion [59]. When EVs are floating freely in the mother's bloodstream, the proteins carried by trophoblastic EVs may perform a dual function by inhibiting complement activation and controlling the activity of maternal T cells, which could otherwise result in unfavorable immune reactions to paternally derived antigens expressed by the placenta [60].

Placentation And Evs

In humans, between weeks 10 and 12, the placenta, which sustains the fetus for several months and serves as the primary transporter of oxygen and nutrients for the developing fetus, connects to the mother's uterus by remodeling the spiral arteries along the uterine wall. This remodeling is facilitated by extravillous cytotrophoblasts [61]. Within this context, extravillous trophoblasts have been demonstrated to migrate into the decidua of the uterus using EVs produced from cytotrophoblasts [62]. It has been shown that EVs generated from the placenta express the immunomodulatory proteins GLA-G5, B7-H1, and B7-H3, which can influence T cell responses and may be related to maternal-fetal tolerance [63]. Recent research reveals that placental-derived EVs interact with maternal lung and liver immune cells through surface integrins [64]. Bioengineered EVs were injected into pregnant mice, and the results revealed EV trafficking to fetal cells, indicating that maternal EVs may cross the placenta and affect the baby [65] (Table 1).

Table 1: EVs In Normal Pregnancies and EVs In Complicated Pregnancies (Preeclampsia).

EVs In Normal Pregnancies		
EV Type - Source	**Effect**	**Reference**
Placental Exoxomes	Carry active TNF superfamily members as immune suppressive	Stenqvist et al., 2013
Trophoblastic EVs	Players in immune tolerance	Kovacs et al., 2019
Macrophage Derived Exosomes	Increasing the release of pro-inflammatory cytokines	Holder et al. 2016
Placental Trophoblasts Derived Exoxomes	Shielding against viral infection during pregnancy	Delorme-Axford et al.,2013
Maternal and Umbilical Serum Exosomes	Enhance tube formation abilities	Jia et al., 2018
Placental Exoxomes	Engage in the changes of insulin sensitivity in normal pregnancies	Nair et al., 2018

Exosomes from Amnion Epithelial Cells	Response to oxidative stress in delivery	Sheller et al., 2016
Exosomes from Foetal Cord Arterial Blood	Plays a role in birth timing determination	Ithier et al., 2019
Exoxomes from Endometrial Epithelium	Successful embryo implantation during pregnancy	Nair et al., 2021
Human Endometrial Epithelial Cells-derived Exosomes	Enhanced focal adhesion kinase signaling	Greening et al., 2016
Placental Exoxomes	Reflects fetal growth and it may be a useful indicator of placental function	Miranda et al.,2018
Fetal-derived Exosomes	Travel to the maternal side to potentially transmit signals to the uterus and cervix	Menon et al., 2017
EVs In Complicated Pregnancies (Preeclampsia)		
EV Type - Source	**Effect**	**Reference**
EVs Derived from Injured Placenta	Induce PE-like symptoms like hypertension and proteinuria in mice by inducing endothelial injury	Han et al., 2019
Plasma Exosomes	Was 1.47-fold and 1.45-fold higher, respectively, compared with healthy controls	Li et al., 2020
Exosome Isolated from Women Pre-eclampsia	Implicated in endothelial cell dysfunction in obese children	Choi et al., 2013
Total Exosomes and Placental Exosomes	Concentration of exosomes was higher in PE than normal pregnancies matched by gestational age	Salomon et al., 2017
Exosomes From Preeclampsia	Contribute to the dissemination of endothelial damage by sequestering the free vascular endothelial growth factor (VEGF) in the maternal circulation	Patton et al., 2015
EVs Released by Placental Syncytiotrophoblasts	Carry neprilysin, which cleaves vasopeptides, thus contributing to the establishment of hypertension, a hallmark of PE	Gill et al, 2019
EVs Released by Placental Syncytiotrophoblasts	Endothelial dysfunction underlying the maternal complications that lead to vascular constriction in PE	Knight et al., 1998
PE-derived Exosomes	Involved in vascular dysfunction due to their abundant sFlt-1 and sEng contents.	Ermini et al., 2017

Role of Extracellular Vesicles in Preeclampsia

Altered Extracellular Vesicle Profile in Preeclampsia

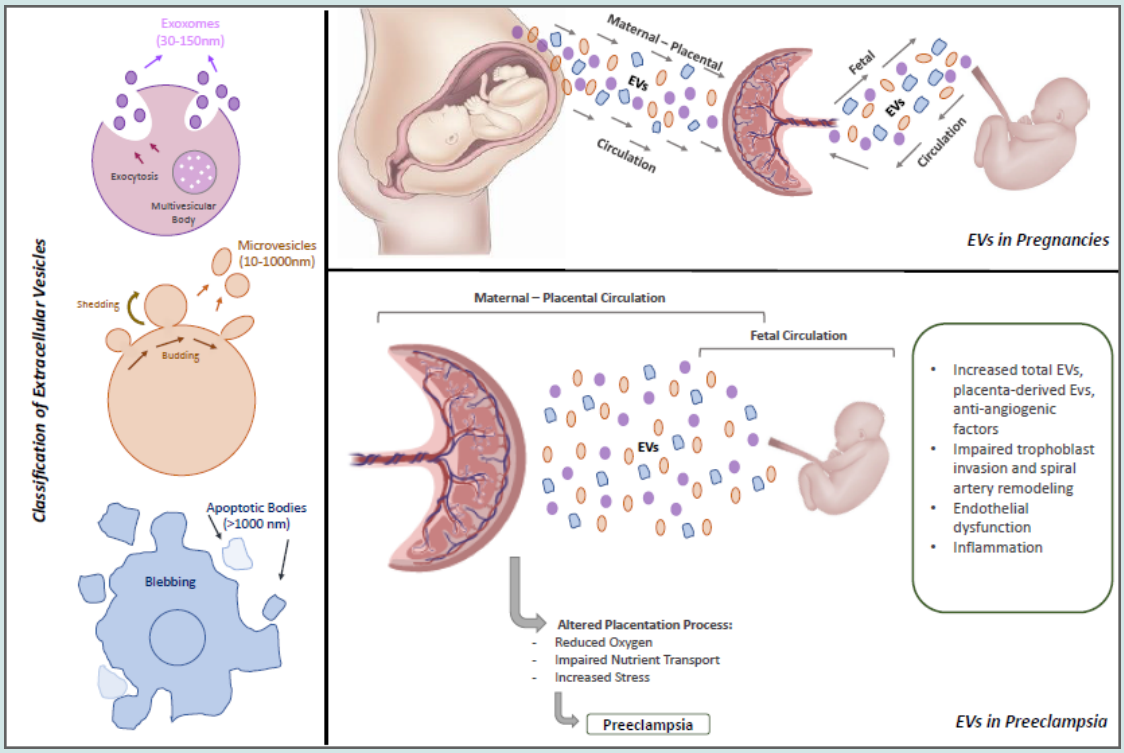

Figure 1: Extracellular Vesicles_Preeclampsia.

Several studies have reported an altered EV profile in the maternal circulation of women with PE compared to normotensive pregnant women [31]. Specifically, women with PE have increased total EVs, placenta-derived EVs, and EVs containing pro-inflammatory and anti-angiogenic factors [66] (Figure 1).

Placental Extracellular Vesicles in Preeclampsia

Placenta-derived EVs play a crucial role in the pathophysiology of PE [67]. They carry various bioactive molecules that can contribute to endothelial dysfunction and systemic inflammation [2]. In PE, the placenta releases more EVs, containing factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which are known to induce maternal vascular dysfunction [18].

Potential Mechanisms Linking Extracellular Vesicles to Preeclampsia Pathogenesis

EVs have been implicated in several pathways related to the pathogenesis of PE, including:

a. Impaired trophoblast invasion and spiral artery remodeling: Placental EVs can modulate the invasion of Extravillous Trophoblasts (EVTs) into the maternal decidua and spiral arteries [68]. In PE, EVs may carry factors that inhibit trophoblast invasion and impair spiral artery remodeling, leading to placental ischemia [69].

b. Endothelial dysfunction: EVs containing anti-angiogenic factors, such as sFlt-1 and sEng, can disrupt the balance of angiogenic and anti-angiogenic factors, contributing to endothelial dysfunction in PE [30].

c. Inflammation: Pro-inflammatory factors carried by EVs can promote systemic inflammation, which further exacerbates endothelial dysfunction and contributes to the clinical manifestations of PE [22].

Extracellular Vesicles in the Maternal-Fetal Interface

The maternal-fetal interface is critical for maintaining pregnancy and ensuring proper fetal development [26]. EVs have been implicated in regulating maternal-fetal communication and immune tolerance at this interface [70]. In PE, the altered EV profile at the maternal-fetal interface may contribute to the breakdown of immune tolerance and the subsequent development of the disorder [6].

Long-term Consequences of Preeclampsia and Extracellular Vesicles

Preeclampsia has been associated with long-term health consequences for both the mother and the offspring [27]. Women who have experienced PE are at an increased risk of developing cardiovascular diseases later in life, such as hypertension, ischemic heart disease, and stroke [71]. Offspring born to mothers with PE are at a higher risk of developing metabolic and cardiovascular disorders, including hypertension, diabetes, and obesity [72]. The role of EVs in mediating these long-term consequences is not yet fully understood, but the altered EV profile during pregnancy may have lasting effects on maternal and offspring health [73].

Extracellular Vesicles in IVF and Preeclampsia

Increased Incidence of Preeclampsia in IVF Pregnancies

Several studies have reported an increased risk of PE among women who conceived through IVF [74]. The reasons for this increased risk are partially clear. However, it has been suggested that IVF-related factors may contribute to the development of PE [17].

Potential Role of Extracellular Vesicles in IVF-Related Preeclampsia

The altered EV profile observed in PE may also be present in IVF pregnancies, suggesting a potential role of EVs in the development of IVF-related PE [75]. Further research is needed to determine this association's specific factors and mechanisms.

Extracellular Vesicles in Ovarian Stimulation and Embryo Culture

Ovarian stimulation and embryo culture are essential components of IVF treatments that may influence the EV profile in maternal circulation [76]. Ovarian stimulation with exogenous hormones can alter the local EV profile in the follicular fluid, which may affect oocyte quality and embryo development [77]. Additionally, embryo culture conditions, including specific growth factors and cytokines, can influence the EVs released by the developing embryo and the surrounding environment [78]. The potential impact of these IVF-related factors on the EV profile and the subsequent risk of PE warrants further investigation.

Diagnostic and Therapeutic Potential of Extracellular Vesicles in Preeclampsia

Extracellular Vesicles as Diagnostic Biomarkers

Given the altered EV profile in PE, EVs have been proposed as potential diagnostic biomarkers for early disorder detection [79]. Studies have shown that specific placenta-derived EVs and EV-associated factors such as sFl t-1 and sEng can be detected in maternal circulation before clinical symptoms, suggesting their potential use in early diagnosis and risk stratification of PE [80]. However, further research is needed to validate these findings and establish standardized EV isolation and analysis methods in a clinical setting.

Extracellular Vesicles as Therapeutic Targets

The involvement of EVs in the pathophysiology of PE also presents opportunities for therapeutic intervention. Potential strategies include:

a. Modulation of EV release: Targeting the molecular mechanisms responsible for the release of placenta-derived EVs could help to reduce the number of harmful EVs in maternal circulation [80].

b. Inhibition of EV uptake: Blocking the uptake of placenta-derived EVs by maternal cells may prevent the deleterious effects of their bioactive cargo on maternal vascular function [31].

c. Neutralization of EV cargo: Therapeutic agents, such as antibodies or small molecules, could be developed to neutralize the pro-inflammatory and anti-angiogenic factors carried by placenta-derived EVs in PE [81].

d. Replacement of defective EVs: Administration of exogenous EVs with a "healthy" cargo may help to restore the balance of angiogenic and anti-angiogenic factors and promote proper placental function [82].

Challenges and Limitations of Extracellular Vesicle-Based Diagnostics and Therapeutics

Despite the promising potential of EVs as diagnostic biomarkers and therapeutic targets for PE, several challenges and limitations must be addressed. One major challenge is EV population heterogeneity, making it difficult to identify specific EV subpopulations and their molecular signatures associated with PE [83]. Additionally, the need for standardized EV isolation, characterization, and quantification methods presents a significant obstacle to the reproducibility and comparability of findings across different studies [84]. Furthermore, the safety and efficacy of EV-based therapeutics must be carefully evaluated in preclinical and clinical studies before their implementation in clinical practice [85].

Future Perspectives and Challenges

The study of extracellular vesicles in the context of preeclampsia and IVF has opened new avenues for understanding the pathophysiology of this complex disorder and the potential links between assisted reproductive technologies and adverse pregnancy outcomes. However, several challenges remain to overcome before EVs can be fully harnessed for diagnostic and therapeutic purposes. Firstly, standardization of EV isolation, characterization, and quantification methods is crucial to ensure the reproducibility and comparability of findings across different studies [86]. Secondly, identifying specific EV subpopulations and their molecular signatures in preeclampsia will be essential for developing targeted diagnostic and therapeutic strategies [87]. Translating EV-based interventions into clinical practice will require extensive preclinical and clinical evaluation to ensure their safety and efficacy [86]. Advances in EV research will be crucial for overcoming the current challenges associated with the study of EVs in PE and IVF [88]. Moreover, interdisciplinary collaborations between reproductive medicine specialists, EV researchers, and bioengineers will be essential for translating emerging insights into clinically relevant diagnostic and therapeutic applications [89]. Finally, further research is needed to determine the long-term consequences of altered EV profiles in PE and IVF on maternal and offspring health and the potential benefits of early intervention strategies based on EV biology [90].

Conclusion

Extracellular vesicles have emerged as essential players in the pathophysiology of preeclampsia, particularly in IVF. The altered EV profile observed in women with PE and their roles in placental development, endothelial dysfunction, and inflammation suggests that EVs may serve as promising diagnostic biomarkers and therapeutic targets for this complex disorder. Further research is needed to elucidate the specific mechanisms linking EVs to preeclampsia and to overcome the challenges associated with their clinical application [7]. Extracellular vesicles have emerged as critical players in the pathophysiology of preeclampsia, particularly in IVF. The altered EV profile observed in women with PE and their roles in placental development, endothelial dysfunction, and inflammation suggests that EVs may serve as promising diagnostic biomarkers and therapeutic targets for this complex disorder. Further research is needed to elucidate the specific mechanisms linking EVs to preeclampsia, to identify the factors and pathways involved in IVF-related PE, and to overcome the challenges associated with the clinical application of EVs in the diagnosis and treatment of PE [91].

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