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Review Article

The theranostic roles of extracellular vesicles in pregnancy disorders

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ABSTRACT Extracellular vesicles (EVs) are nanovesicles that carry bioactive cargoes of proteins, lipids, mRNAs, and miRNAs between living cells. Their role in cellular communication has gained the attention of several research reports globally in the last decade. EVs are critically involved in sperm functions, oocyte functions, fertilization, embryonic development, and pregnancy. The review summarizes the state-of-the-art of EVs research in the diagnostic and therapeutic (theranostic) potentials of the EVs during the pregnancy that might provide a solution for gestational disturbances such as implantation failure, maternal health problems, gestational diabetes, and preeclampsia. EVs can be found in all biological fluids of the fetus and the mother and would provide a non-invasive and excellent tool for diagnostic purposes. Moreover, we provide the current efforts in manufacturing and designing targeted therapeutics using synthetic and semi-synthetic nanovesicles mimicking the natural EVs for efficient drug delivery during pregnancy.

Keywords: diagnosis, extracellular vesicles, placenta, pregnancy, therapy

INTRODUCTION

Extracellular vesicles (EVs) are group of nanovesicles secreted by living cells and their diameter range from 30 nm up to 1 μm. They include exosomes, microvesicles, ectosomes, and apoptotic bodies (Zhang et al., 2019b). EVs carry nucleic acid and protein cargo, are secreted by many types of cells to help in cell-to-cell communication and play an important crucial role in reproduction physiology (Qamar et al., 2020; Fang et al., 2021; Qamar et al., 2021; Saadeldin, 2021).

The generic term EVs is used to describe all secreted membrane vesicles. The International Society for Extracellular Vesicles (ISEV) has defined and categorized EVs into three main groups: apoptotic bodies; microvesicles; and nanosized EVs called exosomes (Crescitelli et al., 2013; Théry et al., 2018; Willms et al., 2018). EVs can transfer messenger RNA, micro-RNA (miRNA), proteins, and lipids cargoes in between different cells, alter gene expression, and modulate the target cells behaviors (Deregibus et al., 2007; Crescitelli et al., 2013; Raposo and Stoorvogel, 2013; Colombo et al., 2014; Kowal et al.,

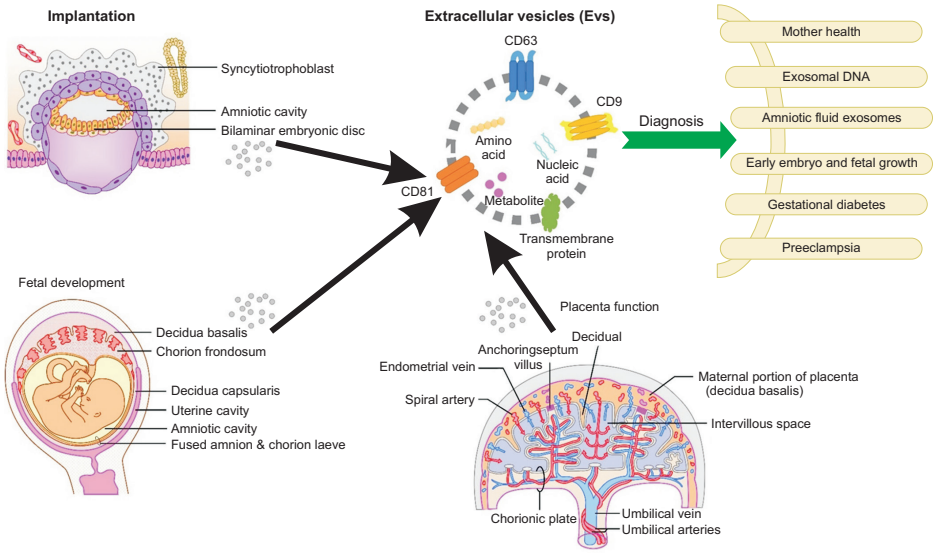

Fig. 1. The diagnostic roles of extracellular vesicles (EVs) derived from different stages of pregnancy. EVs express tetraspanins such as CD9, CD63, and CD81. EVs interplay during embryo implantation, secreted in all biological fluids (amniotic fluid and blood) of the fetus and maternal circulation, and can be a marker for placental functions. Isolating and charactering EVs would be a helpful tool to diagnose and monitor gestational pathophysiology such as maternal health, embryo growth, gestational diabetes, and preeclampsia.

2014; Lo Cicero et al., 2015; Théry et al., 2018). EVs can be defined by specific tetraspanins or surface markers such as CD9, CD63, and CD81 (Fig. 1) (Colombo et al., 2014).

Exosomes (30-180 nm diameter) are biosynthesized in the multivesicular bodies (MVBs) and require sorting of contents before exosomes secretion via endocytic pathway (van Niel et al., 2018). Their shapes are rounded or cup-shaped vesicles and can carry proteins, ribonucleic acids (RNAs), and lipids (Zhang et al., 2019b). Microvesicles (100-1000 nm diameter) are resulted from cell membrane budding and fissions, and of different shapes. Unlike the exosomes and microvesicles, apoptotic bodies are ranging from 500-2000 nm and resulted from endoplasmic reticulum and cell membrane, and contain nuclear factions and deoxyribonucleic acid (DNA) (Alharbi et al., 2021).

Theranostics is a term integrating the translational research of diagnosis, prognosis, and therapeutics, and provides a transition from conventional way of medicine to a targeted and personalized medicine. The involvement of EVs in all stages of mammalian reproduction including males, females, fertilization, embryonic development, and pregnancy has attracted many researchers to unveil the potential roles in diagnosis and therapy of several reproductive disorders (Saadeldin et al., 2014; Saadeldin et al., 2015; Mahiddine et al., 2020; Abdelaal et al., 2021; Qamar et al., 2021). Moreover, easiness in retrieval allows scientist to use EVs as a non-invasive tool to judge on the embryo quality and pregnancy in contrary to the invasive tools (Ali et al., 2020; Cho et al., 2020). In this review, we highlighted the important theranostic roles of EVs during the entire stages of pregnancy started from implantation, placentation, and fetal growth.

Role of EVs in implantation and pregnancy

1) EVs and embryo adhesion to endmoetrium

The roles of EVs and exosomes are claimed to be the markers in reproduction but it is beyond the marker; they paly pivotal role, particularly evidenced in pig for establishing successful pregnancy (Jankovičová et al., 2020). The efficiency of *in vivo* as compared to that of the *in vitro* in claimed to be due to the lack of maternal and embryo communication, mainly through cargo's transferred between embryo and mother (Betteridge, 2003; De Bem et al., 2017; Jankovičová et al., 2020).

Some reports indicate that EVs, particular exosome-like vesicles, found to express putative endometrial markers, such as glycodelin A and receptors for estrogen and progesterone, thus confirming their endometrial origin (Luddi et al., 2019). The flushing of uterine has yielded EVs, found to be the richest source of endometrial transcripts and showed endometrial gene profiles (Luddi et al., 2019). EVs can cross the physiological barriers, and essential roles in cell-to-cell communication (Nair and Salomon, 2018).

EVs showed role in embryo attachment to the endometrium during maternal recognition of pregnancy, evidenced in most of domestic animals where serum EVs contain specific miRNAs that target the focal adhesion

(FA) signals, mainly through decreasing the prostaglandin F secretion (Klohonatz et al., 2019). The source of the EVs leads to the variation in the functions, for instance macrophage derived EVs were found to induce placental pro-inflammatory responses, but those originated from monocytes did not affect pro-inflammatory responses (Rice et al., 2018). Similarly, the macrophage originated exosomes were found to induce placental inflammatory cytokines, as a means of mode of the control of the maternal embryo communication (Holder et al., 2016).

The serum EVs in mares contain miRNAs that change upon pregnancy status and may modulate mRNA expression related to embryo adhesion to the endometrium. This data indicates that the exosomes is playing roles in having different cargoes for various physiological state (Klohonatz et al., 2016), which may an indication of a potential role in maternal recognition of pregnancy. Moreover, plasma miRNA has been used also to early monitor the pregnancy in cattle (Lim et al., 2021). Furthermore, the endometrial derived exosomes previously described were identified from uterine flushing, found to modulate endometrial response, which suggest that EVs secreted from embryos and endometrium are involved in embryonic-maternal interactions for successful conceptus implantation (Nakamura et al., 2016).

In humans also, exosomes were internalized by trophoblast cells and showed to enhance the adhesive capacity, a response mediated partially through active focal adhesion kinase signaling. Thus, exosomes found to contribute to the endometrial-embryo interactions within the human uterine microenvironment essential for successful implantation (Greening et al., 2016). The analysis of endometrial fluid has also revealed there were cytokines, chemokines, proteases, antiproteases and other factors, which could have capacity to modulate blastocyst and functions for the implantation (Salamonsen et al., 2016). EVs released from the early developing embryos and the endometrium are found in the uterine fluid and function to transfer mRNAs, miRNAs, proteins, and lipids between cells during the peri-implantation period (Salamonsen et al., 2016; Nakamura et al., 2020).

2) EVs and endometrium immunomodulation

EVs are a critical modulator of immunological response in the physiological and pathological conditions, and pregnancy is a complicated interaction of immune system protects the early embryo and fetus from immunological rejection to maintain successful pregnancy till full-term and delivery (Nair and Salomon, 2018). As placenta play a vital role in performing a multitude of functions to support the pregnancy, and it found to contain EVs that regulating the maternal immune response for successful pregnancy establishment and outcome (Tannetta et al., 2014; Nair and Salomon, 2018). Placenta-derived EVs show several functions such as suppressing immune reactions to the developing embryos, establishing and maintaining a regulatory inflammatory response to combat microbial and pathogenic attacks (Tannetta et al., 2014). Adjustment of these mechanisms is crucial for successful gestation and healthy progeny. Alterations in these mechanisms will ultimately lead to pregnancy complications and disorders (Nair and Salomon, 2018).

Furthermore, the preimplantation embryo-derived EVs carry certain cargoes potentially capable of modulating the endometrial immune response (Giacomini et al., 2019), which is believed to be basic functional change expected on embryo maternal immune scape mechanism (Trowsdale and Betz, 2006). In other ways, EVs exert a paradoxical and temporal immunotolerance and proinflammatory effects during fertilization, and subsequent implantation, respectively (Trowsdale and Betz, 2006).

EVs from amniotic fluid also showed the immunomodulation function and able to affect the essential molecules in immunity like transforming growth factor beta and hepatic growth factors (Beretti et al., 2018). The EVs effect was also observed on peripheral blood mononuclear cells, which indicates that it can modify the inflammatory response (Admyre et al., 2007).

The roles of exosomes are also extended to contain bioactive Fas-L and TRAIL, which are able to induce apoptosis, are secreted by the placenta and tie up the immunomodulatory and protective role of human placenta to its EVs secretions (Stenqvist et al., 2013). And its immunoregulatory roles extend to the late pregnancy stage, observed on a third trimester normal pregnant women, producing TNFα and IL-6, confirming that maternal immune cells are primed by pregnancy, which functions regulated by exosome communication in paternal-paternal crosstalk (Southcombe et al., 2011).

Diagnostic roles for female infertility and pregnancy disorders

Interestingly, placental cells such as trophoblasts and syncytiotrophoblasts release EVs as early as the pregnancy established and the release is modulated by the health condition of the pregnancy and the placenta, such as the oxygen tension, circulation, and glucose (Ouyang et al., 2014; Albrecht et al., 2016; Mobarak et al., 2019a; Mobarak et al., 2019b). Importantly, the amniotic fluid represents an enriched source of diagnostic biomarkers of abundant maternal and fetal nucleic acid and proteins carried on the EVs cargo and reflect the maternal and fetal health status (Ebert and Rai, 2019). We summarize the diagnostic potentials of EVs during pregnancy to monitor both maternal and fetal pathophysiology (Fig. 1).

1) Mother health

Analysis of exosomal contents could provide a non-invasive tool for detecting the maternal health during pregnancy. For instance, the relative concentration and numbers of exosomes are increased in the maternal circulation of obese pregnant women that is mostly related to the increased lipid levels, inflammatory reactions, hyperglycemia and oxidative stress, as indicated by increase in the levels of interleukins (IL-6 and IL-8) and tumor necrosis factor (TNF-α) (Salomon et al., 2013; Rice et al., 2015; Elfeky et al., 2017; Delhaes et al., 2018). Notably, the placental EVs miRNA signature (particularly mir-517A and mir-518B) is markedly correlated with the conditions of the placenta (Luo et al., 2009). These miRNAs showed dramatic decrease after the delivery that clearly indicated about the placental functionality during pregnancy (Luo et al., 2009). Interestingly, amniotic fluid EVs reflect the oxidative stress status of the embryonic cells. Additionally, the high-mobility group box 1 (HMGB1) and cell-free fetal telomere fragments (cffTF) contents in the amniotic fluid EVs were all increased in the damaged and senescence-induced oxidative stressed amniotic epithelial cells (Sheller-Miller et al., 2017). Amnion epithelial cells EVs characteristics, heat shock protein (HSP) 70 contents, and the activated form of pro-senescence and term parturition associated marker p38 mitogen activated protein kinase (MAPK) (P-p38 MAPK) were all elevated after exposure to oxidative stress (Sheller et al., 2016). Furthermore, maternal exposure to alcohol alters the amniotic fluid EVs miRNA contents (upregulated let-7g, 25-3p, 199a-3p and 214-3p and downregulated 206-3p and 22-3p) and showed significant molecular effects on stem cell regulation and differentiation (Tavanasefat et al., 2020).

2) Genetic diseases

In the last few years, studies have explained that large sized EVs contain packaged DNA molecules and could be released from fetal origins (Hahn et al., 2014; Repiská et al., 2018; Konečná et al., 2019). Therefore, plasma cell-free or exosomal DNA can be a marker for the genetic diseases and follow up of the pregnancy complications till term and delivery (Konečná et al., 2019). Interestingly, the DNA-associated micro-particles (MPs) in maternal plasma express fetal-derived human leukocyte antigen-G (HLA-G) or placental alkaline phosphatase (PLAP) are increased in the second trimester of pregnant women and further increased in pre-eclampsia patients (Orozco et al., 2009). Another form of the EVs, the apoptotic nanoparticles enriched with stable DNA strands, was significantly increased in the pregnancy complications such as pre-eclampsia (Orozco et al., 2008).

3) Early embryo and Fetal growth

EVs could play an important marker for the monitoring of embryonic growth and health status (Yang et al., 2020). The concentrations of placental EVs (positive for placental alkaline phosphatase/CD63) were significantly reduced in case of fetal growth restriction (FGR) (Miranda et al., 2018).

Furthermore, the EVs contents of miR-20b-5p, miR-942-5p, miR-324-3p, miR-223-5p, and miR-127-3p were increased in the maternal serum of small-for-gestational ages infants, while miR-661, miR-212-3p, and miR-197-3p were elevated in the maternal serum of large-for-gestational age infants (Rodosthenous et al., 2017). Moreover, there was a correlation between the levels of miRNAs (miR-483-5p, miR-10a-5p, miR-204-5p, miR-202-3p, miR-345-5p, miR-885-5p, miR-127-3p, miR-148b-3p, miR-324-3p, miR-1290, miR-597-5p, miR-139-5p, miR-215-5p, and miR-99b-5p) and the birth weight-for-gestational age z-score as non-invasive biomarkers of monitoring the fetal growth during pregnancy (Rodosthenous et al., 2017).

Interestingly, deep sequencing studies revealed that the EVs contents of miR-25, miR-16b, and miR-3596 were significantly increased in case of early embryonic-mortal-

ity on day-17 and day-24 of pregnancy in cattle (Pohler et al., 2017).

The numbers of placenta derived-EVs in the maternal plasma were dramatically increased with the gestational age (i.e., third trimester vs. second trimester vs. first trimester) and these EVs were able to improve the endothelial cell migration as a step forward to healthy circulation during placentation (Salomon et al., 2014).

Proteomic contents of amniotic fluid EVs of placental alkaline phosphatase/CD63 markers are increased in the normal term labor (TL), spontaneous preterm birth (PTB), and preterm premature rupture of membranes (pPROM) when compared with term not in labor (TNIL). The amniotic fluid EVs were also increased in PTB compared with pPROM (Dixon et al., 2018). Amniotic fluid EVs concentrations were also positively correlated with the number of pregnancies and the HSP contents were increased by the mid-trimester and may contribute to immune regulation within the amniotic cavity (Asea et al., 2008).

4) Gestational diabetes

One of the problems associated with pregnant women in the last trimester is the insulin resistance and gestational diabetes mellitus (GDM) and its complications such as foetoplacental endothelial dysfunction (Sáez et al., 2018a). Using the EVs is a promising tool for GDM diagnosis, follow up, and appropriate interference with the affected pregnant women. The concentration of circulating EVs is proportionally correlated with the gestational age and physical condition of the pregnant women and the concentration was increased more significantly in case of GDM (Salomon et al., 2016; Liu et al., 2018). Sequencing data of EVs from GDM affected women showed variable expression of certain miRNAs, such as hsa-miR-125a-3p, hsa334 miR-99b-5p, hsa-miR-197-3p, hsa-miR-22-3p and hsa-miR-224-5p that are linked to PI3/AKT signaling and glucose metabolism/insulin resistance (Nair et al., 2018). Interestingly, EVs were isolated from the human umbilical vein endothelium of normal and GDM-affected women and supplemented to the endothelium. EVs from GDM showed delayed wound healing for the endothelium when compared with the normal EVs. Moreover, EVs of GDM increased L-arginine transport, hCAT-1 and eNOS expression and activity, reactive oxygen species, and p44/42mapk activation in the endothelium (Sáez et al., 2018b).

5) Preeclampsia and placenta dysfunction (preterm labor)

Preeclampsia is a pregnancy disorder clinically recognized by increased systolic blood pressure and symptoms of liver and kidney damages. Preeclampsia often appears on the 20th weeks of pregnant women whose blood pressure had been normal (Roberts and Cooper, 2001). Several research groups unraveled the essential diagnostic roles of the EVs as well as the mediation of preeclampsia pathogenesis and other placental disorders (van der Post et al., 2011; Mitchell et al., 2015; Tsochandaridis et al., 2015; Gilani et al., 2016; Cuffe et al., 2017; Ermini et al., 2017; Pillay et al., 2017; Salomon and Rice, 2017; Tannetta et al., 2017a; Tannetta et al., 2017b; Jin and Menon, 2018; Morgan, 2018; Salomon et al., 2018).

It has been found that the relative concentration of placental-derived EVs increased in early onset preeclampsia but decreased in late onset preeclampsia compared to the normal pregnancy. The ratio of PLAP+ EVs/total number of EVs was reduced in early onset preeclampsia and late onset preeclampsia (Pillay et al., 2016). It has been reported that the placental protein 13 (PP13) was reduced in placental derived syncytiotrophoblast extracellular vesicles in preeclampsia suggesting its pathophysiological role in the maternal circulation (Sammar et al., 2018).

Syncytiotrophoblast EVs were increased in numbers and showed altered molecular loads and modulated the exaggerated inflammatory state during preeclampsia (Göhner et al., 2017). Furthermore, higher levels of neprilysin have been identified in preeclampsia EVs that possesses a pathological role in preeclampsia-associated hypertension, heart failure, and amyloid deposition (Gill et al., 2019).

Interestingly, miR-141 expression was increased in the placentae from preeclampsia patients and its inhibition in trophoblasts decreased cellular viability and invasion capabilities (Ospina-Prieto et al., 2016). Additionally, the level of circulating exosomal hsa-miR-210 was increased in preeclampsia placentas (Biró et al., 2019). It is known that hsa-miR-210 significantly impacts the cellular viability, metabolic activity, and invasion capability of trophoblasts (Muralimanoharan et al., 2012; Luo et al., 2016; Hayder et al., 2021). Moreover, syncytin-2 was found to be reduced in serum-derived EVs from women with preeclampsia when compared to the normal pregnancy (Vargas et al., 2014).

The concentration of EVs was increased in extravillous trophoblast cultured under 1% compared to 8% O_2. Moreover, hundreds of miRNAs were identified in extravillous trophoblast EVs and were associated with cellular migration and cytokine generation. Furthermore, EVs from extravillous trophoblast cultured at 8% O_2 increased the endothelial cells migration when compared with those cultured at 1% O_2 (Truong et al., 2017).

Pre-term birth is another problem associated with placental dysfunctions and can lead to lifelong complications of the pre-term born babies. Several miRNAs have been identified in the EVs of the preterm births that could be a useful biomarker for predicting the pre-term birth. Results revealed that hsa-miR-100-5p, hsa-miR-141-3p, hsa-miR-194-5p, hsa-miR-515-5p, hsa-miR-517a-3p, hsa-miR518e-5p, hsa-miR-525-5p, hsa-miR-377-3p, and hsa-miR-483-5p are good candidates for predicting pre-term birth when analyzed in the EVs isolated from the maternal plasma (Fallen et al., 2018).

Therapeutic roles of synthetic and semi-synthetic exosomes for female infertility and pregnancy

Based on the previously mentioned roles of EVs for pathogenesis and diagnosis of pregnancy disorders, the necessity for therapeutic interventions is needed. The EVs as a drug delivery option showed several advantages. First, EVs is extracted from the patient's own cells, and hence they are less immunogenic. Second, EVs contain lipid bilayers where they increase the cellular internalization of loaded drugs. Third, the minute size of EVs avoids the phagocytosis by immune cells. In addition, EVs showed specificity for fusion with the target cells and therefore would reduce off-target effects (Zhang et al., 2019b). Nanotechnology and nanomedicine have introduced encouraging results for the development of novel targeted delivery of drugs during the pregnancy (Zhang et al., 2019a; Hashem and Gonzalez-Bulnes, 2020; Pereira et al., 2020). Surface-functionalized plCSA binding peptide (plCSA-BP)-decorated nanoparticles could be successfully designed to target placental chondroitin sulfate A that uniquely expressed in the placenta (Zhang et al., 2019a). Similar surface-functionalized nanoparticles, liposomes, immunoliposomes, or the lipid-polymer nanoparticles and their target drug delivery for uterus and placenta to treat pre-term birth, ectopic pregnancy, and fetal growth restriction are reviewed in (Zhang et al., 2019a).

Peptide-bound liposomes are mimicking the functions of EVs and also have been used for the targeted drug delivery for pregnancy complications (Pepe and Albrecht, 2021). For instance, intravenous injection of liposomes containing the peptide CRGDKGPDC bound to insulin-like growth factor (IGF-2) enhanced placental weight in wild type animals (King et al., 2016). Similarly, miRNA can be loaded in the liposomes and used for therapeutics during pregnancy. Liposomes were decorated with the peptide CCGKRK and bound with miR-145 or miR-675 inhibitor peptide nucleic acid conjugate to suppress miR-145 or miR-675, respectively. These liposomes were injected in the pregnant mice and increased the fetal and placental weights and enhanced the human cytotrophoblast proliferation *in vitro* (Beards et al., 2017).

Overall, re-engineering placenta-specific EVs is a very promising approach for the development of bio-inspired and targeted drug delivery systems to treat pregnancy complications (Du et al., 2017; Arrighetti et al., 2019).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

There is a trending and encouraging data that support the potential diagnostic and therapeutic roles of EVs during the early stages of embryonic development, fetal development, and maternal health. Investigating the molecular cargo of the EVs provides a non-invasive tool for diagnostics of critical illness of the fetus and mother, and guides for natural and synthetic targeted EVs-like therapeutics.

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REFERENCES

Abdelaal NE, Tanga BM, Abdelgawad M, Allam S, Fathi M, Saadeldin IM, Bang S, Cho J. 2021. Cellular therapy via spermatogonial stem cells for treating impaired spermatogenesis, non-obstructive azoospermia. Cells 10:1779.

Admyre C, Johansson SM, Qazi KR, Filén JJ, Lahesmaa R, Norman M, Neve EP, Scheynius A, Gabrielsson S. 2007. Exosomes with immune modulatory features are present in human breast milk. J. Immunol. 179:1969-1978.

Albrecht C, Caniggia I, Clifton V, Göhner C, Harris L, Hemmings D, Jawerbaum A, Johnstone E, Jones H, Keelan J, Lewis R, Mitchell M, Murthi P, Powell T, Saffery R, Smith R, Vaillancourt C, Wadsack C, Salomon C. 2016. IFPA meeting 2015 workshop report III: nanomedicine applications and exosome biology, xenobiotics and endocrine disruptors and pregnancy, and lipid. Placenta 48 Suppl 1:S12-S16.

Alharbi MG, Lee SH, Abdelazim AM, Saadeldin IM, Abomughaid MM. 2021. Role of extracellular vesicles in compromising cellular resilience to environmental stressors. Biomed Res. Int. 2021:9912281.

Ali MA, Islam MF, Rahman SML, Zohara BF. 2020. Pregnancy diagnosis in goat by using vaginal cytology and transabdominal ultrasonography. J. Anim. Reprod. Biotechnol. 35:338-346.

Arrighetti N, Corbo C, Evangelopoulos M, Pastò A, Zuco V, Tasciotti E. 2019. Exosome-like nanovectors for drug delivery in cancer. Curr. Med. Chem. 26:6132-6148.

Asea A, Jean-Pierre C, Kaur P, Rao P, Linhares IM, Skupski D, Witkin SS. 2008. Heat shock protein-containing exosomes in mid-trimester amniotic fluids. J. Reprod. Immunol. 79:12-17.

Beards F, Jones LE, Charnock J, Forbes K, Harris LK. 2017. Placental homing peptide-microRNA inhibitor conjugates for targeted enhancement of intrinsic placental growth signaling. Theranostics 7:2940-2955.

Beretti F, Zavatti M, Casciaro F, Comitini G, Franchi F, Barbieri V, La Sala GB, Maraldi T. 2018. Amniotic fluid stem cell exosomes: therapeutic perspective. Biofactors 44:158-167.

Betteridge KJ. 2003. A history of farm animal embryo transfer and some associated techniques. Anim. Reprod. Sci. 79:203-244.

Biró O, Fóthi Á, Alasztics B, Nagy B, Orbán TI, Rigó J Jr. 2019. Circulating exosomal and Argonaute-bound microRNAs in preeclampsia. Gene 692:138-144.

Cho J, Uh K, Ryu J, Fang X, Bang S, Lee K. 2020. Development of PCR based approach to detect potential mosaicism in porcine embryos. J. Anim. Reprod. Biotechnol. 35:323-328.

Colombo M, Raposo G, Théry C. 2014. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu. Rev. Cell Dev. Biol. 30:255-289.

Crescitelli R, Lässer C, Szabó TG, Kittel A, Eldh M, Dianzani I, Buzás EI, Lötvall J. 2013. Distinct RNA profiles in subpopulations of extracellular vesicles: apoptotic bodies, microvesicles and exosomes. J. Extracell. Vesicles 2:20677.

Cuffe JSM, Holland O, Salomon C, Rice GE, Perkins AV. 2017. Review: placental derived biomarkers of pregnancy disorders. Placenta 54:104-110.

De Bem THC, da Silveira JC, Sampaio RV, Sangalli JR, Oliveira MLF, Ferreira RM, Silva LA, Perecin F, King WA, Meirelles FV, Ramos ES. 2017. Low levels of exosomal-miRNAs in maternal blood are associated with early pregnancy loss in cloned cattle. Sci. Rep. 7:14319.

Delhaes F, Giza SA, Koreman T, Eastabrook G, McKenzie CA, Bedell S, Regnault TRH, de Vrijer B. 2018. Altered maternal and placental lipid metabolism and fetal fat development in obesity: current knowledge and advances in non-invasive assessment. Placenta 69:118-124.

Deregibus MC, Cantaluppi V, Calogero R, Lo Iacono M, Tetta C, Biancone L, Bruno S, Bussolati B, Camussi G. 2007. Endothelial progenitor cell–derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood 110:2440-2448.

Dixon CL, Sheller-Miller S, Saade GR, Fortunato SJ, Lai A, Palma C, Guanzon D, Salomon C, Menon R. 2018. Amniotic fluid exosome proteomic profile exhibits unique pathways of term and preterm labor. Endocrinology 159:2229-2240.

Du W, Zhang K, Zhang S, Wang R, Nie Y, Tao H, Han Z, Liang L, Wang D, Liu J, Liu N, Han Z, Kong D, Zhao Q, Li Z. 2017. Enhanced proangiogenic potential of mesenchymal stem cell-derived exosomes stimulated by a nitric oxide releasing polymer. Biomaterials 133:70-81.

Ebert B and Rai AJ. 2019. Isolation and characterization of amniotic fluid-derived extracellular vesicles for biomarker discovery. Methods Mol. Biol. 1885:287-294.

Elfeky O, Longo S, Lai A, Rice GE, Salomon C. 2017. Influence of maternal BMI on the exosomal profile during gestation and their role on maternal systemic inflammation. Placenta 50:60-69.

Ermini L, Ausman J, Melland-Smith M, Yeganeh B, Rolfo A, Litvack ML, Todros T, Letarte M, Post M, Caniggia I. 2017. A single sphingomyelin species promotes exosomal release of endoglin into the maternal circulation in preeclampsia. Sci. Rep. 7:12172.

Fallen S, Baxter D, Wu X, Kim TK, Shynlova O, Lee MY, Scherler K, Lye S, Hood L, Wang K. 2018. Extracellular vesicle RNAs

reflect placenta dysfunction and are a biomarker source for preterm labour. J. Cell. Mol. Med. 22:2760-2773.

Fang X, Tanga BM, Bang S, Seong G, Saadeldin IM, Lee S, Cho J. 2022. Oviduct epithelial cells-derived extracellular vesicles improve preimplantation developmental competence of in vitro produced porcine parthenogenetic and cloned embryos. Mol. Reprod. Dev. 89:54-65.

Giacomini E, Alleva E, Fornelli G, Quartucci A, Privitera L, Vanni VS, Viganò P. 2019. Embryonic extracellular vesicles as informers to the immune cells at the maternal-fetal interface. Clin. Exp. Immunol. 198:15-23.

Gilani SI, Weissgerber TL, Garovic VD, Jayachandran M. 2016. Preeclampsia and extracellular vesicles. Curr. Hypertens. Rep. 18:68.

Gill M, Motta-Mejia C, Kandzija N, Cooke W, Zhang W, Cerdeira AS, Bastie C, Redman C, Vatish M. 2019. Placental syncytiotrophoblast-derived extracellular vesicles carry active NEP (neprilysin) and are increased in preeclampsia. Hypertension 73:1112-1119.

Göhner C, Plösch T, Faas MM. 2017. Immune-modulatory effects of syncytiotrophoblast extracellular vesicles in pregnancy and preeclampsia. Placenta 60 Suppl 1:S41-S51.

Greening DW, Nguyen HP, Elgass K, Simpson RJ, Salamonsen LA. 2016. Human endometrial exosomes contain hormone-specific cargo modulating trophoblast adhesive capacity: insights into endometrial-embryo interactions. Biol. Reprod. 94:38.

Hahn S, Giaglis S, Buser A, Hoesli I, Lapaire O, Hasler P. 2014. Cell-free nucleic acids in (maternal) blood: any relevance to (reproductive) immunologists? J. Reprod, Immunol. 104-105:26-31.

Hashem NM and Gonzalez-Bulnes A. 2020. State-of-the-art and prospective of nanotechnologies for smart reproductive management of farm animals. Animals (Basel) 10:840.

Hayder H, Fu G, Nadeem L, O'Brien JA, Lye SJ, Peng C. 2021. Overexpression of miR-210-3p impairs extravillous trophoblast functions associated with uterine spiral artery remodeling. Int. J. Mol. Sci. 22:3961.

Holder B, Jones T, Sancho Shimizu V, Rice TF, Donaldson B, Bouqueau M, Forbes K, Kampmann B. 2016. Macrophage exosomes induce placental inflammatory cytokines: a novel mode of maternal-placental messaging. Traffic 17:168-178.

Jankovičová J, Sečová P, Michalková K, Antalíková J. 2020. Tetraspanins, more than markers of extracellular vesicles in reproduction. Int. J. Mol. Sci. 21:7568.

Jin J and Menon R. 2018. Placental exosomes: a proxy to understand pregnancy complications. Am. J. Reprod. Immunol. 79:e12788.

King A, Ndifon C, Lui S, Widdows K, Kotamraju VR, Agemy L, Teesalu T, Glazier JD, Cellesi F, Tirelli N, Aplin JD, Ruoslahti E, Harris LK. 2016. Tumor-homing peptides as tools for targeted delivery of payloads to the placenta. Sci. Adv. 2:e1600349.

Klohonatz KM, Cameron AD, Hergenreder JR, da Silveira JC, Belk AD, Veeramachaneni DN, Bouma GJ, Bruemmer JE. 2016. Circulating miRNAs as potential alternative cell signaling associated with maternal recognition of pregnancy in the mare. Biol. Reprod. 95:124.

Klohonatz KM, Nulton LC, Hess AM, Bouma GJ, Bruemmer JE. 2019. The role of embryo contact and focal adhesions during maternal recognition of pregnancy. PLoS One 14:e0213322.

Konečná B, Tóthová Ľ, Repiská G. 2019. Exosomes-associated DNA-new marker in pregnancy complications? Int. J. Mol. Sci. 20:2890.

Kowal J, Tkach M, Théry C. 2014. Biogenesis and secretion of exosomes. Curr. Opin. Cell Biol. 29:116-125.

Lim HJ, Kim HJ, Lee JH, Lim DH, Son JK, Kim ET, Jang G, Kim DH. 2021. Identification of plasma miRNA biomarkers for pregnancy detection in dairy cattle. J. Anim. Reprod. Biotechnol. 36:35-44.

Liu J, Wang SZ, Wang QL, Du JG, Wang BB. 2018. Gestational diabetes mellitus is associated with changes in the concentration and bioactivity of placental exosomes in the maternal circulation across gestation. Eur. Rev. Med. Pharmacol. Sci. 22:2036-2043.

Lo Cicero A, Stahl PD, Raposo G. 2015. Extracellular vesicles shuffling intercellular messages: for good or for bad. Curr. Opin. Cell Biol. 35:69-77.

Luddi A, Zarovni N, Maltinti E, Governini L, Leo V, Cappelli V, Quintero L, Paccagnini E, Loria F, Piomboni P. 2019. Clues to non-invasive implantation window monitoring: isolation and characterisation of endometrial exosomes. Cells 8:811.

Luo R, Wang Y, Xu P, Cao G, Zhao Y, Shao X, Li YX, Chang C, Peng C, Wang YL. 2016. Hypoxia-inducible miR-210 contributes to preeclampsia via targeting thrombospondin type I domain containing 7A. Sci. Rep. 6:19588.

Luo SS, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, Mishima T, Takizawa T, Shigihara T, Goto T, Izumi A, Ohkuchi A, Matsubara S, Takeshita T, Takizawa T. 2009. Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. Biol. Reprod. 81:717-729.

Mahiddine FY, Qamar AY, Kim MJ. 2020. Canine amniotic membrane derived mesenchymal stem cells exosomes addition in canine sperm freezing medium. J. Anim. Reprod. Biotechnol. 35:268-272.

Miranda J, Paules C, Nair S, Lai A, Palma C, Scholz-Romero K, Rice GE, Gratacos E, Crispi F, Salomon C. 2018. Placental exosomes profile in maternal and fetal circulation in intrauterine growth restriction - liquid biopsies to monitoring fetal growth. Placenta 64:34-43.

Mitchell MD, Peiris HN, Kobayashi M, Koh YQ, Duncombe G, Illanes SE, Rice GE, Salomon C. 2015. Placental exosomes in normal and complicated pregnancy. Am. J. Obstet. Gynecol. 213(4 Suppl):S173-S181.

Mobarak H, Heidarpour M, Lolicato F, Nouri M, Rahbarghazi R, Mahdipour M. 2019a. Physiological impact of extracellular vesicles on female reproductive system; highlights to possible restorative effects on female age-related fertility. Biofactors 45:293-303.

Mobarak H, Rahbarghazi R, Lolicato F, Heidarpour M, Pashazadeh F, Nouri M, Mahdipour M. 2019b. Evaluation of the association between exosomal levels and female reproductive system and fertility outcome during aging: a systematic review protocol. Syst. Rev. 8:293.

Morgan TK. 2018. Cell- and size-specific analysis of placental extracellular vesicles in maternal plasma and pre-eclampsia. Transl. Res. 201:40-48.

Muralimanoharan S, Maloyan A, Mele J, Guo C, Myatt LG, Myatt L. 2012. MIR-210 modulates mitochondrial respiration in placenta with preeclampsia. Placenta 33:816-823.

Nair S, Jayabalan N, Guanzon D, Palma C, Scholz-Romero K, Elfeky O, Zuñiga F, Ormazabal V, Diaz E, Rice GE, Duncombe G, Jansson T, McIntyre HD, Lappas M, Salomon C. 2018. Human placental exosomes in gestational diabetes mellitus carry a specific set of miRNAs associated with skeletal muscle insulin sensitivity. Clin. Sci. (Lond.) 132:2451-2467.

Nair S and Salomon C. 2018. Extracellular vesicles and their immunomodulatory functions in pregnancy. Semin. Immunopathol. 40:425-437.

Nakamura K, Kusama K, Bai R, Sakurai T, Isuzugawa K, Godkin JD, Suda Y, Imakawa K. 2016. Induction of IFNT-stimulated genes by conceptus-derived exosomes during the attachment period. PLoS One 11:e0158278.

Nakamura K, Kusama K, Suda Y, Fujiwara H, Hori M, Imakawa K. 2020. Emerging role of extracellular vesicles in embryo-maternal communication throughout implantation processes. Int. J. Mol. Sci. 21:5523.

Orozco AF, Jorgez CJ, Horne C, Marquez-Do DA, Chapman MR, Rodgers JR, Bischoff FZ, Lewis DE. 2008. Membrane protected apoptotic trophoblast microparticles contain nucleic acids: relevance to preeclampsia. Am. J. Pathol. 173:1595-1608.

Orozco AF, Jorgez CJ, Ramos-Perez WD, Popek EJ, Yu X, Kozinetz CA, Bischoff FZ, Lewis DE. 2009. Placental release of distinct DNA-associated micro-particles into maternal circulation: reflective of gestation time and preeclampsia. Placenta 30:891-897.

Ospina-Prieto S, Chaiwangyen W, Herrmann J, Groten T, Schleussner E, Markert UR, Morales-Prieto DM. 2016. MicroRNA-141 is upregulated in preeclamptic placentae and regulates trophoblast invasion and intercellular communication. Transl. Res. 172:61-72.

Ouyang Y, Mouillet JF, Coyne CB, Sadovsky Y. 2014. Review: placenta-specific microRNAs in exosomes - good things come in nano-packages. Placenta 35 Suppl:S69-S73.

Pepe GJ and Albrecht ED. 2021. Novel technologies for target delivery of therapeutics to the placenta during pregnancy: a review. Genes (Basel) 12:1255.

Pereira KV, Giacomeli R, Gomes de Gomes M, Haas SE. 2020. The challenge of using nanotherapy during pregnancy: technological aspects and biomedical implications. Placenta 100:75-80.

Pillay P, Maharaj N, Moodley J, Mackraj I. 2016. Placental exosomes and pre-eclampsia: maternal circulating levels in normal pregnancies and, early and late onset pre-eclamptic pregnancies. Placenta 46:18-25.

Pillay P, Moodley K, Moodley J, Mackraj I. 2017. Placenta-derived exosomes: potential biomarkers of preeclampsia. Int. J. Nanomedicine 12:8009-8023.

Pohler KG, Green JA, Moley LA, Gunewardena S, Hung WT, Payton RR, Hong X, Christenson LK, Geary TW, Smith MF. 2017. Circulating microRNA as candidates for early embryonic viability in cattle. Mol. Reprod. Dev. 84:731-743.

Qamar AY, Hussain T, Rafique MK, Bang S, Tanga BM, Seong G, Fang X, Saadeldin IM, Cho J. 2021. The role of stem cells and their derived extracellular vesicles in restoring female and male fertility. Cells 10:2460.

Qamar AY, Mahiddine FY, Bang S, Fang X, Shin ST, Kim MJ, Cho J. 2020. Extracellular vesicle mediated crosstalk between the gametes, conceptus, and female reproductive tract. Front. Vet. Sci. 7:589117.

Raposo G and Stoorvogel W. 2013. Extracellular vesicles: exosomes, microvesicles, and friends. J. Cell Biol. 200:373-383.

Repiská G, Konečná B, Shelke GV, Lässer C, Vlková BI, Minárik G. 2018. Is the DNA of placental origin packaged in exosomes isolated from plasma and serum of pregnant women? Clin. Chem. Lab. Med. 56:e150-e153.

Rice GE, Scholz-Romero K, Sweeney E, Peiris H, Kobayashi M, Duncombe G, Mitchell MD, Salomon C. 2015. The effect of glucose on the release and bioactivity of exosomes from first trimester trophoblast cells. J. Clin. Endocrinol. Metab. 100:E1280-E1288.

Rice TF, Donaldson B, Bouqueau M, Kampmann B, Holder B. 2018. Macrophage- but not monocyte-derived extracellular vesicles induce placental pro-inflammatory responses. Placenta 69:92-95.

Roberts JM and Cooper DW. 2001. Pathogenesis and genetics of pre-eclampsia. Lancet 357:53-56.

Rodosthenous RS, Burris HH, Sanders AP, Just AC, Dereix AE, Svensson K, Solano M, Téllez-Rojo MM, Wright RO, Baccarelli AA. 2017. Second trimester extracellular microRNAs in maternal blood and fetal growth: an exploratory study. Epigenetics 12:804-810.

Saadeldin IM. 2021. Extracellular vesicles mediate the embryonic-maternal paracrine communication. In: Alzahrani FA, Saadeldin IM (Eds.), Role of Exosomes in Biological Communication Systems, Springer, Singapore, pp. 77-97.

Saadeldin IM, Kim SJ, Choi YB, Lee BC. 2014. Improvement of cloned embryos development by co-culturing with parthenotes: a possible role of exosomes/microvesicles for embryos paracrine communication. Cell. Reprogram. 16:223-234.

Saadeldin IM, Oh HJ, Lee BC. 2015. Embryonic-maternal crosstalk via exosomes: potential implications. Stem Cells Cloning 8:103-107.

Sáez T, de Vos P, Sobrevia L, Faas MM. 2018a. Is there a role for exosomes in foetoplacental endothelial dysfunction in gestational diabetes mellitus? Placenta 61:48-54.

Sáez T, Salsoso R, Leiva A, Toledo F, de Vos P, Faas M, Sobrevia

L. 2018b. Human umbilical vein endothelium-derived exosomes play a role in foetoplacental endothelial dysfunction in gestational diabetes mellitus. Biochim. Biophys. Acta Mol. Basis Dis. 1864:499-508.

Salamonsen LA, Evans J, Nguyen HP, Edgell TA. 2016. The microenvironment of human implantation: determinant of reproductive success. Am. J. Reprod. Immunol. 75:218-225.

Salomon C, Kobayashi M, Ashman K, Sobrevia L, Mitchell MD, Rice GE. 2013. Hypoxia-induced changes in the bioactivity of cytotrophoblast-derived exosomes. PLoS One 8:e79636.

Salomon C, Nuzhat Z, Dixon CL, Menon R. 2018. Placental exosomes during gestation: liquid biopsies carrying signals for the regulation of human parturition. Curr. Pharm. Des. 24:974-982.

Salomon C and Rice GE. 2017. Role of exosomes in placental homeostasis and pregnancy disorders. Prog. Mol. Biol. Transl. Sci. 145:163-179.

Salomon C, Scholz-Romero K, Sarker S, Sweeney E, Kobayashi M, Correa P, Longo S, Duncombe G, Mitchell MD, Rice GE, Illanes SE. 2016. Gestational diabetes mellitus is associated with changes in the concentration and bioactivity of placenta-derived exosomes in maternal circulation across gestation. Diabetes 65:598-609.

Salomon C, Torres MJ, Kobayashi M, Scholz-Romero K, Sobrevia L, Dobierzewska A, Illanes SE, Mitchell MD, Rice GE. 2014. A gestational profile of placental exosomes in maternal plasma and their effects on endothelial cell migration. PLoS One 9:e98667.

Sammar M, Dragovic R, Meiri H, Vatish M, Sharabi-Nov A, Sargent I, Redman C, Tannetta D. 2018. Reduced placental protein 13 (PP13) in placental derived syncytiotrophoblast extracellular vesicles in preeclampsia - a novel tool to study the impaired cargo transmission of the placenta to the maternal organs. Placenta 66:17-25.

Sheller S, Papaconstantinou J, Urrabaz-Garza R, Richardson L, Saade G, Salomon C, Menon R. 2016. Amnion-epithelial-cell-derived exosomes demonstrate physiologic state of cell under oxidative stress. PLoS One 11:e0157614.

Sheller-Miller S, Urrabaz-Garza R, Saade G, Menon R. 2017. Damage-associated molecular pattern markers HMGB1 and cell-Free fetal telomere fragments in oxidative-Stressed amnion epithelial cell-derived exosomes. J. Reprod. Immunol. 123:3-11.

Southcombe J, Tannetta D, Redman C, Sargent I. 2011. The immunomodulatory role of syncytiotrophoblast microvesicles. PLoS One 6:e20245.

Stenqvist AC, Nagaeva O, Baranov V, Mincheva-Nilsson L. 2013. Exosomes secreted by human placenta carry functional Fas ligand and TRAIL molecules and convey apoptosis in activated immune cells, suggesting exosome-mediated immune privilege of the fetus. J. Immunol. 191:5515-5523.

Tannetta D, Collett G, Vatish M, Redman C, Sargent I. 2017a. Syncytiotrophoblast extracellular vesicles - circulating biopsies reflecting placental health. Placenta 52:134-138.

Tannetta D, Dragovic R, Alyahyaei Z, Southcombe J. 2014. Extracellular vesicles and reproduction-promotion of successful pregnancy. Cell. Mol. Immunol. 11:548-563.

Tannetta D, Masliukaite I, Vatish M, Redman C, Sargent I. 2017b. Update of syncytiotrophoblast derived extracellular vesicles in normal pregnancy and preeclampsia. J. Reprod. Immunol. 119:98-106.

Tavanasefat H, Li F, Koyano K, Gourtani BK, Marty V, Mulpuri Y, Lee SH, Shin KH, Wong DTW, Xiao X, Spigelman I, Kim Y. 2020. Molecular consequences of fetal alcohol exposure on amniotic exosomal miRNAs with functional implications for stem cell potency and differentiation. PLoS One 15:e0242276.

Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, Antoniou A, Arab T, Archer F, Atkin-Smith GK, Ayre DC, Bach JM, Bachurski D, Baharvand H, Balaj L, Baldacchino S, Bauer NN, Baxter AA, Bebawy M, Beckham C, Bedina Zavec A, Benmoussa A, Berardi AC, Bergese P, Bielska E, Blenkiron C, Bobis-Wozowicz S, Boilard E, Boireau W, Bongiovanni A, Borràs FE, Bosch S, Boulanger CM, Breakefield X, Breglio AM, Brennan MÁ, Brigstock DR, Brisson A, Broekman ML, Bromberg JF, Bryl-Górecka P, Buch S, Buck AH, Burger D, Busatto S, Buschmann D, Bussolati B, Buzás EI, Byrd JB, Camussi G, Carter DR, Caruso S, Chamley LW, Chang YT, Chen C, Chen S, Cheng L, Chin AR, Clayton A, Clerici SP, Cocks A, Cocucci E, Coffey RJ, Cordeiro-da-Silva A, Couch Y, Coumans FA, Coyle B, Crescitelli R, Criado MF, D'Souza-Schorey C, Das S, Datta Chaudhuri A, de Candia P, De Santana EF, De Wever O, Del Portillo HA, Demaret T, Deville S, Devitt A, Dhondt B, Di Vizio D, Dieterich LC, Dolo V, Dominguez Rubio AP, Dominici M, Dourado MR, Driedonks TA, Duarte FV, Duncan HM, Eichenberger RM, Ekström K, El Andaloussi S, Elie-Caille C, Erdbrügger U, Falcón-Pérez JM, Fatima F, Fish JE, Flores-Bellver M, Försönits A, Frelet-Barrand A, Fricke F, Fuhrmann G, Gabrielsson S, Gámez-Valero A, Gardiner C, Gärtner K, Gaudin R, Gho YS, Giebel B, Gilbert C, Gimona M, Giusti I, Goberdhan DC, Görgens A, Gorski SM, Greening DW, Gross JC, Gualerzi A, Gupta GN, Gustafson D, Handberg A, Haraszti RA, Harrison P, Hegyesi H, Hendrix A, Hill AF, Hochberg FH, Hoffmann KF, Holder B, Holthofer H, Hosseinkhani B, Hu G, Huang Y, Huber V, Hunt S, Ibrahim AG, Ikezu T, Inal JM, Isin M, Ivanova A, Jackson HK, Jacobsen S, Jay SM, Jayachandran M, Jenster G, Jiang L, Johnson SM, Jones JC, Jong A, Jovanovic-Talisman T, Jung S, Kalluri R, Kano SI, Kaur S, Kawamura Y, Keller ET, Khamari D, Khomyakova E, Khvorova A, Kierulf P, Kim KP, Kislinger T, Klingeborn M, Klinke DJ 2nd, Kornek M, Kosanović MM, Kovács ÁF, Krämer-Albers EM, Krasemann S, Krause M, Kurochkin IV, Kusuma GD, Kuypers S, Laitinen S, Langevin SM, Languino LR, Lannigan J, Lässer C, Laurent LC, Lavieu G, Lázaro-Ibáñez E, Le Lay S, Lee MS, Lee YXF, Lemos DS, Lenassi M, Leszczynska A, Li IT, Liao K, Libregts SF, Ligeti E, Lim R, Lim SK, Linē A, Linnemannstöns K, Llorente A, Lombard CA, Lorenowicz MJ, Lörincz ÁM, Lötvall J, Lovett J, Lowry MC, Loyer X, Lu Q, Lukomska B, Lunavat TR, Maas SL, Malhi H, Marcilla A, Mariani J, Mariscal J, Mar-

tens-Uzunova ES, Martin-Jaular L, Martinez MC, Martins VR, Mathieu M, Mathivanan S, Maugeri M, McGinnis LK, McVey MJ, Meckes DG Jr, Meehan KL, Mertens I, Minciacchi VR, Möller A, Møller Jørgensen M, Morales-Kastresana A, Morhayim J, Mullier F, Muraca M, Musante L, Mussack V, Muth DC, Myburgh KH, Najrana T, Nawaz M, Nazarenko I, Nejsum P, Neri C, Neri T, Nieuwland R, Nimrichter L, Nolan JP, Nolte-'t Hoen EN, Noren Hooten N, O'Driscoll L, O'Grady T, O'Loghlen A, Ochiya T, Olivier M, Ortiz A, Ortiz LA, Osteikoetxea X, Østergaard O, Ostrowski M, Park J, Pegtel DM, Peinado H, Perut F, Pfaffl MW, Phinney DG, Pieters BC, Pink RC, Pisetsky DS, Pogge von Strandmann E, Polakovicova I, Poon IK, Powell BH, Prada I, Pulliam L, Quesenberry P, Radeghieri A, Raffai RL, Raimondo S, Rak J, Ramirez MI, Raposo G, Rayyan MS, Regev-Rudzki N, Ricklefs FL, Robbins PD, Roberts DD, Rodrigues SC, Rohde E, Rome S, Rouschop KM, Rughetti A, Russell AE, Saá P, Sahoo S, Salas-Huenuleo E, Sánchez C, Saugstad JA, Saul MJ, Schiffelers RM, Schneider R, Schøyen TH, Scott A, Shahaj E, Sharma S, Shatnyeva O, Shekari F, Shelke GV, Shetty AK, Shiba K, Siljander PR, Silva AM, Skowronek A, Snyder OL 2nd, Soares RP, Sódar BW, Soekmadji C, Sotillo J, Stahl PD, Stoorvogel W, Stott SL, Strasser EF, Swift S, Tahara H, Tewari M, Timms K, Tiwari S, Tixeira R, Tkach M, Toh WS, Tomasini R, Torrecilhas AC, Tosar JP, Toxavidis V, Urbanelli L, Vader P, van Balkom BW, van der Grein SG, Van Deun J, van Herwijnen MJ, Van Keuren-Jensen K, van Niel G, van Royen ME, van Wijnen AJ, Vasconcelos MH, Vechetti IJ Jr, Veit TD, Vella LJ, Velot É, Verweij FJ, Vestad B, Viñas JL, Visnovitz T, Vukman KV, Wahlgren J, Watson DC, Wauben MH, Weaver A, Webber JP, Weber V, Wehman AM, Weiss DJ, Welsh JA, Wendt S, Wheelock AM, Wiener Z, Witte L, Wolfram J, Xagorari A, Xander P, Xu J, Yan X, Yáñez-Mó M, Yin H, Yuana Y, Zappulli V, Zarubova J, Žėkas V, Zhang JY, Zhao Z, Zheng L, Zheutlin AR, Zickler AM, Zimmermann P, Zivkovic AM, Zocco D, Zuba-Surma EK. 2018. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J. Extracell. Vesicles 7:1535750.

Trowsdale J and Betz AG. 2006. Mother's little helpers: mechanisms of maternal-fetal tolerance. Nat. Immunol. 7:241-246.

Truong G, Guanzon D, Kinhal V, Elfeky O, Lai A, Longo S, Nuzhat Z, Palma C, Scholz-Romero K, Menon R, Mol BW, Rice GE, Salomon C. 2017. Oxygen tension regulates the miRNA profile and bioactivity of exosomes released from extravillous trophoblast cells - liquid biopsies for monitoring complications of pregnancy. PLoS One 12:e0174514.

Tsochandaridis M, Nasca L, Toga C, Levy-Mozziconacci A. 2015. Circulating microRNAs as clinical biomarkers in the predictions of pregnancy complications. Biomed. Res. Int. 2015:294954.

van der Post JA, Lok CA, Boer K, Sturk A, Sargent IL, Nieuwland R. 2011. The functions of microparticles in pre-eclampsia. Semin. Thromb. Hemost. 37:146-152.

van Niel G, D'Angelo G, Raposo G. 2018. Shedding light on the cell biology of extracellular vesicles. Nat. Rev. Mol. Cell Biol. 19:213-228.

Vargas A, Zhou S, Éthier-Chiasson M, Flipo D, Lafond J, Gilbert C, Barbeau B. 2014. 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. 28:3703-3719.

Willms E, Cabañas C, Mäger I, Wood MJA, Vader P. 2018. Extracellular vesicle heterogeneity: subpopulations, isolation techniques, and diverse functions in cancer progression. Front. Immunol. 9:738.

Yang H, Ma Q, Wang Y, Tang Z. 2020. Clinical application of exosomes and circulating microRNAs in the diagnosis of pregnancy complications and foetal abnormalities. J. Transl. Med. 18:32.

Zhang B, Liang R, Zheng M, Cai L, Fan X. 2019a. Surface-functionalized nanoparticles as efficient tools in targeted therapy of pregnancy complications. Int. J. Mol. Sci. 20:3642.

Zhang Y, Liu Y, Liu H, Tang WH. 2019b. Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci. 9:19.