Microparticles and Exosomes: Impact on Normal and Complicated Pregnancy

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Eukaryotic cells release vesicles into their environment by membrane shedding (ectosomes or microparticles) and secretion (exosomes). Microparticles and exosomes occur commonly *in vitro* and *in vivo*. The occurrence, composition and function(s) of these vesicles change during disease (progression). During the last decade, the scientific and clinical interest increased tremendously. Evidence is accumulating that microparticles and exosomes may be of pathophysiological relevance in autoimmune, cardiovascular and thromboembolic diseases, as well as inflammatory and infectious disorders. In this review, we will summarize the discovery, biology, structure and function of microparticles and exosomes, and discuss their (patho-) physiological role during normal and complicated pregnancy.

Introduction

Microparticles

During 1940s, human blood and plasma were shown to contain a subcellular clotting-promoting factor.[1] More than 25 years later, it was demonstrated that this fraction consists of small platelet-derived particles.[2] Their clinical relevance became apparent in 1979, when a case report of a young woman with an unexplained congenital bleeding disorder was presented. She suffered from a disease, later termed Scott syndrome, characterized by reduced prothrombin consumption because of impaired release of microparticles (MP) and phospholipid scrambling.[3,4]

Microparticles are released from cells by 'shedding' and, according to most investigators, range in size between 0.1 and 1 μm. In contrast to MP, exosomes are secreted from intracellular multi-vesicular bodies (MVB) and range in size from 30 to 90 nm (Fig. 1). MP are widely distributed and commonly occur in cell cultures *in vitro* and in body fluids *in vivo*. For instance, human blood contains MP as well as exosomes originating from various types of cells.[5] Many studies on MP showed that their numbers, cellular origin, composition, and function(s) are disease (state) dependent, but whether or not these changes are related to disease development or are a consequence of the disease process itself is still debated. Proteomes of MP, isolated from human platelets, endothelial cells, malignant cells, lymphocytes, and

plasma, have been published.[6–9] These studies identified a myriad of proteins, including structural proteins, metabolic enzymes, integrins, and membrane fusion proteins.

Exosomes

Exosomes were described in the early 1980s as 5′-nucleotidase activity-containing vesicles.[10] Subsequently, exosomes were shown to be involved in the removal of the transferrin receptor from maturing reticulocytes. This surface receptor internalizes by 'inward' blebbing. These blebs (endosomes) pinch off very small (30–90 nm) 'intraluminal' vesicles. Endosomes containing 'intraluminal vesicles' are called MVB. Finally, once 'intraluminal' vesicles become secreted, i.e. after membrane fusion of MVB and the surrounding plasma membrane, they are called exosomes.[11–13]

Similar to MP, exosomes are also widely distributed and commonly occur in cell cultures *in vitro* and in body fluids *in vivo*.[5] Exosomes are smaller than (most) MP and their proteomes differ.[14] Exosomes contain cytosolic proteins or proteins from the endocytic compartment or plasma membrane, whereas proteins of nuclear, mitochondrial, endoplasmic-reticulum or Golgi-apparatus origin are absent.[15] About 80% of exosomal proteins are conserved among species, and characteristic (but not distinctive) protein families include tetraspannins, heat shock proteins and major histocompatibility complex (MHC) class I and II molecules.[15] Also proteomes of exosomes from various human body fluids have been determined.[16,17]

It should be mentioned, that isolation procedures of MP and exosomes often differ between investigators.[18] To exclude contamination of small cells (e.g. platelets), loss of vesicles and functional changes, isolation procedures of MP and exosomes need to be taken into account when data from different research groups are compared. For instance, the *in vitro* methods to isolate syncytiotrophoblast-derived MP (STBM) strongly affect their effects on T lymphocytes.[19] Also the use of different CD markers for identification,[18,20–22] age[23] and food consumption[24,25] may affect circulating numbers of MP and, possibly, also exosomes.

Fig. 2 illustrates the increasing scientific and clinical interest in MP and exosomes. This increase may be explained by the long and ever increasing list of biologically relevant functions that have been attributed to these vesicles, and their association with disease (progression).

Functions of microparticles and exosomes

Microparticles are best known for their coagulant properties, especially platelet-derived MP (PMP), which expose (per surface area, compared to platelets) high numbers of binding sites for (activated) coagulation factors, thereby enabling formation of tenase- and prothrombinase complexes. According to most investigators, PMP are by far the most common MP occurring in human blood. MP of various cellular origin, including PMP, may expose tissue factor (TF), the initiator of coagulation *in vivo*,[26–29] and this TF may be transferred to other cells.[30,31] Alternatively, by binding to cells, MP also trigger expression

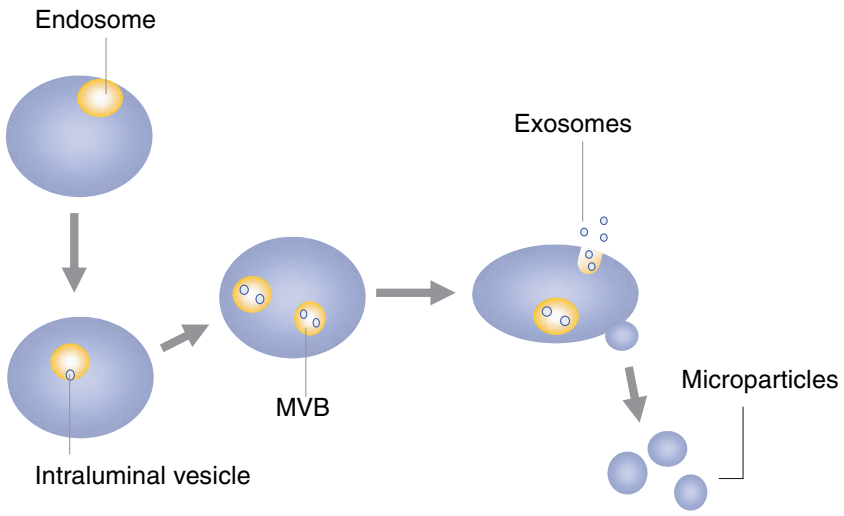

Fig. 1 Microparticles and exosomes. This figure shows the formation of an endosome by invagination. By inward blebbing of the endosomal membrane, intraluminal vesicles are formed. Endosomes containing intraluminal vesicles are called multivesicular body (MVB). Cells release the contents of their MVB when the membrane of the MVB fuses with the plasma membrane. In contrast to exosomes, microparticles are formed by major structural rearrangements of the cytoskeleton and are 'budded' off from the outer cell membrane.

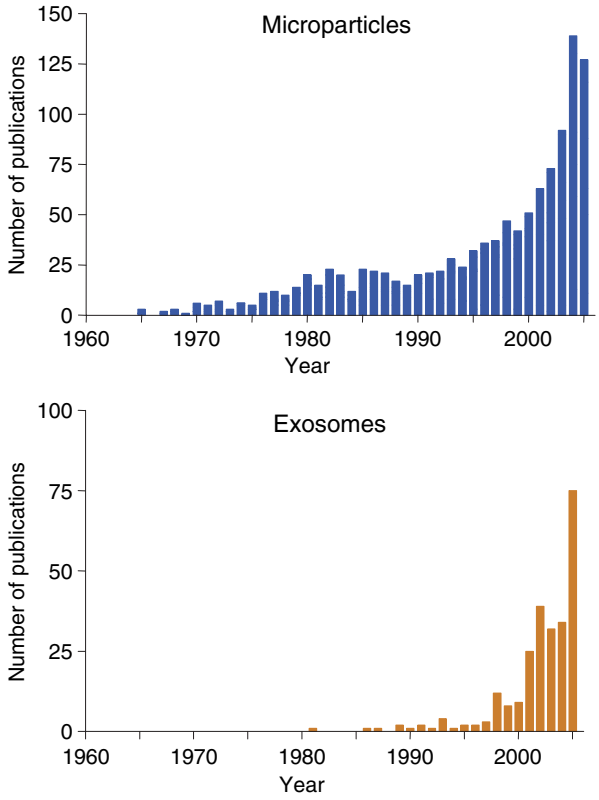

Fig. 2 Scientific interest in microparticles and exosomes (1965–2005). This overview shows the growing scientific interest in extracellular vesicles. (a) Scientific publications on microparticles from platelets, erythrocytes, leukocytes, endothelial cells, tumor cells, and other cells. (b) Exosomes. This figure was produced from PubMed, using as search string in *All indexed fields* [microparticle*] OR [vesicle*] OR [bleb*] OR [particle*] AND *All indexed fields* [erythrocyte*] OR [platelet*] OR [thrombocyte*] OR [granulocyte*] OR [monocyte*] OR [endothelial*]. For tumor-derived vesicles, a different search string was used: *Title* [particle*] OR [vesicle*] OR [bleb*] OR [microparticle*] OR [microvesicle*] OR [shed*] AND *Title* [tumour*] OR [tumor*] OR [cancer*]. For exosomes, the search string *All fields* [Exosome*] was used. This figure was prepared by R. J. Berckmans, PhD (AMC, the Netherlands).

Table I Cellular Origin of Circulating Microparticles in Prothrombotic Diseases

Disease	Cellular origin of MP	Reference(s)
Anti-phospholipid syndrome	Monocytes	104
	Endothelial cells	105
Atherosclerosis	Leukocytes	106
Coronary artery disease	Platelets	107
	Endothelial cells	108
	Monocytes	109
Cancer	Platelets	110
Diabetes mellitus	Platelets	111
	Granulocytes	112
	Monocytes	113
Heparine-induced thrombocytopenia	Platelets	114
Hypertension	Platelets	115
	Monocytes	116
Idiopathic thrombocytopenia	Platelets	117
Paroxysmal nocturnal hemoglobinuria	Platelets	118
Sepsis	Platelets, granulocytes	28
	Leukocytes	119
Systemic lupus erythematosus	Platelet	120
Thrombotic thrombocytopenic purpura	Endothelium	121
Uraemia	Platelets	122
Vasculitis	Endotheliual cells	22
	Neutrophils, platelets	123
Sickle cell disease	Erythrocytes	124
	Endothelial cells, monocytes	125

Overview on the so far published data on the cellular origin of circulating microparticles in prothrombotic diseases.

and production of TF. At least *in vitro*, PMP facilitate inactivation of coagulation factors Va and VIIIa by activated protein C. Thus, (P)MP may also possess anti-coagulant properties.[32] MP support coagulation *in vitro* as well as *in vivo*, and increased numbers of MP from various cell types have been reported to occur in diseases associated with a procoagulant state (summarized in Table I).

The list of MP functions is growing rapidly and includes not only coagulation but also inflammation,[33] leukocyte adhesion and aggregation,[34] angiogenesis,[35] vasoconstriction,[36] immune modulation,[37–39] and endothelial dysfunction.[36,40] As most functions were established only *in vitro* by using isolated vesicle preparations in model systems, we (still) do not know to which extent MP also exhibit such functions *in vivo*. With regard to coagulation, however, there is direct evidence that MP promote coagulation and thrombus formation *in vivo*.[26,41]

Initially, exosomes were considered to be 'dustbins' used by cells to remove redundant molecules, e.g. the transferrin receptors. Recent findings that caspase 3, heat-shock proteins and cytostatic drugs may accumulate in exosomes (and MP), are in line

with this function.[42–46] Exosomes may also contribute to a change in haemostatic balance towards a procoagulant state. *In vitro*-prepared exosomes from mast cells support thrombin generation and induce endothelial expression of plasminogen activator inhibitor-1.[47] In general, cell-derived vesicles may transmit infectious agents or receptors that facilitate the uptake of infectious agents into (target) cells. Exosomes facilitate spreading of prion proteins,[48] and MP may transfer various receptors that facilitate cellular uptake of human immunodeficiency virus-1.[49,50] Gould and coworkers proposed the 'Trojan exosome' hypothesis, in which they postulated that retroviruses may use exosomes as vehicles for extracellular traffic and infection.

The most important function of cell-derived vesicles, however, seems to be intercellular communication. By exposing cell-type specific adhesion receptors or ligands, vesicles can bind to particular cells and deliver their 'message' (e.g. bioactive lipids, cytokines, and growth factors).[51] It has become firmly established that exosomes modulate the immune response.[15] On one hand they can facilitate antigen presentation, and on the other hand suppress the immune response e.g. by exposing FasL.[52,53] Exosomes from antigen-presenting (dendritic) cells, 'dexosomes', expose MHC class I and II molecules.[15] Dexosomes have been tested in clinical trials as adjuvant anti-cancer therapy; they suppress graft-versus-host disease in various animal models and protect against Toxoplasma gondii infection.[54–57] Although the functions of MP and exosomes are many, their true (patho) physiological functions *in vivo* are still unknown.

Microparticles and exosomes in normal pregnancy

The success of human pregnancy depends on various physiologic processes. First, pregnancy is an immunological phenomenon as the semiallogeneic fetus is not rejected and second, the maternal haemostatic balance shifts towards a procoagulatory state. Therefore, immunologic disorders and coagulation abnormalities can lead to adverse pregnancy outcomes.[58] Paternal genes are expressed preferentially in the syncytiotrophoblasts (ST) and immune tolerance towards the fetus requires specific suppression of the maternal immune system.[59] How fetal trophoblast cells escape the maternal immune response remains unknown, but clonal deletion of immune cells recognizing paternal antigens in the placenta is thought to play a role.[59–64] T lymphocytes that recognize fetal antigens decrease during pregnancy and remain low post-partum to protect the fetus against the maternal immune system. Placental FasL triggers local depletion of activated maternal (Fas-exposing) T lymphocytes that recognize placental paternal antigens,[65–68] and FasL-exposing trophoblasts induce Fas-dependent apoptosis of activated T lymphocytes.[66,68,69]

Exosomes, often supposed to originate at least in part from the placenta, have been implicated in the establishment of an immune privilege for the developing fetus.[39,60,70–73] Compared to non-pregnant women, increased levels of exosomes occur in pregnant women. Incubation of T lymphocytes (Jurkat cells) with such exosomes resulted in down-regulation of the expression of both CD3-ξ and Janus kinase 3 (JAK 3), as well as in caspase 3 activation. These responses correlated to exposed FasL of the exosomal fractions.[39,71,73] CD3-ξ affects the clonal selection of T lymphocytes, which leads to decreased T-lymphocyte-mediated responses and an increased rate of antibody production protective in human pregnancy (elevated Th2/Th1 immune response). Expression and activation of JAK3 is a key regulatory link between CD3-ξ expression and apoptosis, thus contributing to establishment of immune privilege at the feto-maternal interface.[73]

Although exosomes from human first trimester trophoblast cells do not expose (membrane-associated) FasL, they contain a biologically active (37 kDa) form of 'encapsulated' (intravesicular) FasL that triggers (Fas-mediated) T-cell apoptosis following disruption of exosomes (Figs 3 and 4).[60,70] Mincheva-Nilsson et al. investigated the effect of soluble MHC class I chain-related proteins A and B (MIC) on the expression of natural killer cell receptors (NKG2D) in peripheral blood mononuclear cells (PBMC).[72] They showed that MIC expression in placenta was restricted to apical and basal cell membranes of ST and to 'cytoplasmic vacuoles as MIC-loaded microvesicles/exosomes' of these cells.[72] As soluble MIC molecules were present at elevated levels in maternal blood throughout normal pregnancy and were released by placental explants *in vitro*, MIC-containing exosomes may be released from placental villi into the maternal blood. The human placenta also expresses several matrix metalloproteases, however, it cannot be ruled out that soluble MIC is a cleavage product in the circulation of pregnant women (Fig. 4).[70,72] Evidently, by transporting

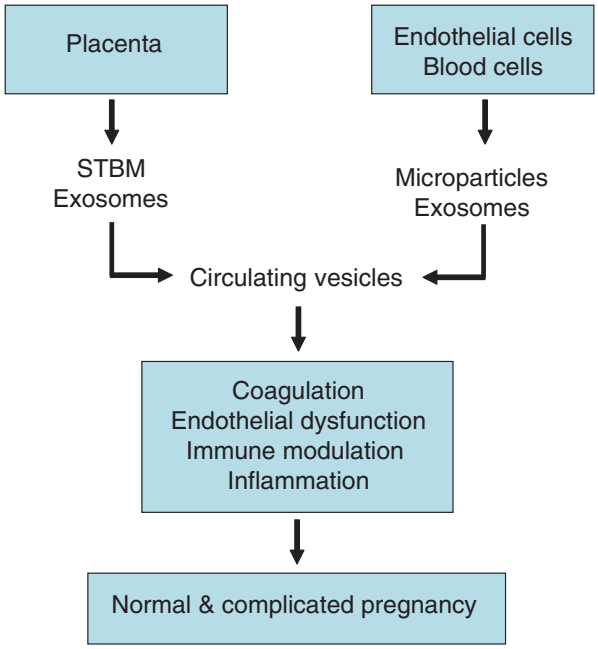

Fig. 3 Microparticles and exosomes in pregnancy. A flow-chart showing the different populations of circulating vesicles from placenta (STBM, exosomes) and from other cells (endothelial cells, platelets, leukocytes, erythrocytes) and the processes thought to be affected by these vesicles related to normal or complicated pregnancies.

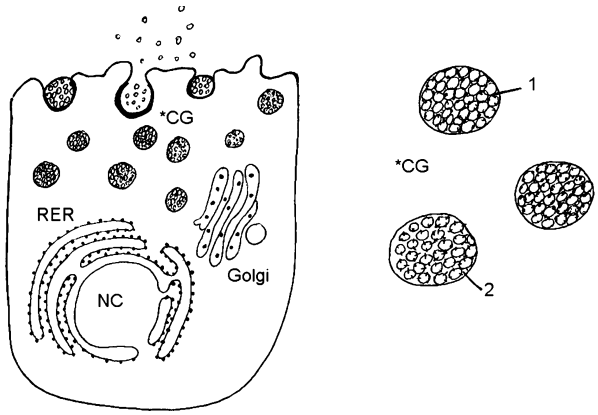

Fig. 4 Syncytiotrophoblast-derived microvesicles. According to the studies of Fränsmyr and Abrahams[60] as well as Mincheva-Nilsson[72], FasL (1)- and MIC-loaded (2) microvesicles are synthesized in the RER and Golgi-apparatus of syncytiotrophoblasts, transported to cytoplasmic granules and stored or secreted via exocytosis. Nc, nucleus; CG, cytoplasmic granules.

bio-molecules that modulate the immune response, like FasL or MIC, placental-derived vesicles may be considered as a 'new physiological mechanism of silencing the maternal immune system', thereby promoting 'fetal allograft immune escape'. As many adverse pregnancy outcomes can result from the failure to suppress adequately T-lymphocyte activation pathways, defining the mechanism through which circulating placenta-derived vesicles modulate activation components, such as CD3-ξ, JAK3, and MIC/NKG2D, may possibly provide new therapeutic targets.

MP and exosomes in complicated pregnancy

Early pregnancy loss

Between 25 and 50% of reproductive-aged women experience one or more miscarriages, often due to fetal chromosomal abnormalities, especially with increasing maternal age.[58,74] The WHO classification defines the occurrence of three or more consecutive spontaneous miscarriages regardless of previous live births as recurrent fetal abortion (RSA).[75] RSA affects about 1–3% of women during child-bearing years.[76] Known risk factors are genetic abnormalities, uterine pathologies, endocrine dysfunctions, autoimmune diseases, acquired and inherited thrombophilic disorders, and environmental factors.[77] In nearly 50% of affected women, the cause of RSA remains unknown.[78]

Trophoblast invasion into the uterine spiral arteries and development and maintenance of adequate utero-placental circulation are pre-requisites for successful pregnancy.[79] This invasion may be promoted by (trophoblast-released) soluble FasL-induced apoptosis of smooth muscle cells in the spiral arteries, thus contributing to utero-placental circulation.[80]

During normal pregnancy, the haemostatic balance shifts towards a procoagulatory state with an increase in clotting factors and fibrinogen as well as a decrease in anticoagulant factors and fibrinolytic activity.[58,81] In RSA, fibrin deposits are present in the intervillous space of the placenta, raising the question whether RSA may be secondary to an exaggerated haemostatic response during pregnancy.[79,82,83] This 'hypercoagulability' may involve other procoagulant factors, including MP and exosomes.[47,84] In 2001, Laude et al. used a prothrombinase assay to study the coagulation-promoting capacity of circulating MP in 74 non-pregnant women with idiopathic RSA and 50 non-pregnant controls. RSA patients were divided into two groups: 49 women with more than three RSA and less than 10 weeks gestational age, and 25 women with more than one late pregnancy loss

(gestational age > 10 weeks).[85] Isolated MP fractions from RSA women (55%) showed an increased coagulation-promoting capacity, 29 (59%) in the early and 12 (48%) in the late pregnancy loss group.

Carp et al. evaluated the numbers of $CD51^+/CD31^+$ MP, i.e. MP presumably of endothelial cell origin, in non-pregnant women with RSA ($n = 96$; ≥3 RSA) *versus* non-pregnant women without a history of miscarriage ($n = 90$).[86] They reported increased numbers of endothelial MP in 12 patients (12.5%) and in two controls (2%; $P < 0.008$). Furthermore, injection of artificially prepared procoagulant phospholipid vesicles, i.e. vesicles containing phosphatidylserine, into pregnant mice induced thrombosis in the placental bed and led to reduced birth weight.[87] Taken together, the presence of circulating (procoagulant) MP in women with RSA seems to be an acquired thrombophilia, becoming clinically manifest during pregnancy.[79,83,85,86] The mechanisms underlying the presence and contribution of these MP to the pathophysiology of miscarriage, however, remain unclear and additional studies are essential to specify their precise role in the development of RSA.

Premature labour

Preterm labour is a major obstetric problem occurring in 5–7% of pregnant women. The premature fetus can develop neurological, gastrointestinal, infectious, and other disorders. One of the most important causes for preterm labour is (subclinical) infection. Recently, a role for exosomes in immune suppression during premature labour has been suggested. Levels of exosomes in sera from pregnant women were shown to be almost twofold higher in those delivering at term compared to women delivering preterm. Concurrently, exosomes of women delivering at term contained higher levels of FasL and HLA-DR and elicited greater suppression of CD3-ξ and JAK3.[39]Although the underlying pathophysiology remains unknown, these data implicate that exosomes may be involved in suppressing T-lymphocyte activation during pregnancy, thereby contributing to an immune privilege for the developing fetus, necessary to achieve a term pregnancy.

Preeclampsia

Preeclampsia is a heterogenic multisystem disorder characterized by hypertension and proteinuria and develops in the second-half of pregnancy. The incidence is 2–5%, and preeclampsia is a major cause of maternal and fetal morbidity and mortality. Although the exact etiology remains unknown, a generally accepted hypothesis is following the two-stage model. Insufficient trophoblast invasion into spiral arteries of the uterus early in pregnancy results in abnormal placentation with subsequent placental hypoperfusion. In the second stage, placental factors are released into the maternal circulation, leading to a systemic inflammatory response and endothelial dysfunction.[88]

Microparticles may modulate or reflect several of the key-processes in preeclampsia, including inflammation, coagulation, platelet activation, and endothelial dysfunction. The first scientific papers reporting on the occurrence of MP in preeclampsia, focused on total numbers of MP in preeclampsia compared with normotensive pregnant and non-pregnant women. A summary of these articles can be found in Table II. Obviously, circulating MP originate from various types of cells and their composition depends on the status of the parental cells. Data from different studies on circulating MP in preeclampsia are inconsistent. Several studies reported a decrease in circulating numbers of PMP and an increase in endothelial cell-derived MP (EMP). Decreased numbers of PMP may be related to decreased platelet numbers in the maternal circulation, and/or (increased) attachment of MP to the endothelium or other cells in the maternal circulation. Despite the overall decrease of PMP, however, subpopulations of PMP exposing a well-established platelet activation marker (P-selectin) were found to be increased (15.4%) compared to normotensive pregnant and non-pregnant controls (10.9% and 8.0%, respectively).[89] The observed increase of EMP in preeclampsia may reflect endothelial-cell activation,[90] and increases in (numbers of) leukocyte-derived MP may reflect inflammation.[91,92]

Complement activation may be part of the systemic inflammatory response in preeclampsia. MP activate complement via the classical pathway *in vitro*. Isolated MP from preeclamptic patients, however, exposed no increased levels of bound C1q, C3, and C4. Interestingly, increased numbers of MP were present exposing C-reactive protein (CRP), a well-known complement activator molecule, suggesting that circulating MP may be involved in complement activation.[93]

Circulating MP are known to affect endothelial function. Incubation of myometrial arteries with MP

Table II Numbers of Circulating Microparticles in Normal and Disturbed Pregnancy

Cellular origin	Marker	Control	PR	PE	IUGR	PIH	Units	References
Total	*Annexin V*	122	429	260	182		MP/μL	126
Platelets	CD41	39	193	37.5*	90			
Endothelial cells	CD51	7	13	9	12			
Endothelial cells	CD62e		712	1930*		822	Counts/μL	127
Endothelial cells	CD31		6119	10 497*		6768	Counts/μL	90
Endothelial cells	$CD31^+/CD41^-$		8	14*				
Platelets	$CD31^+/CD42^+$		7.9	10 751				
Platelets	CD61		49	33		39	10^9/L	128
Platelets	CD61		6.6%	3.7%*			% of platelets	129
Total	*Annexin V*		7.5	11.68*			Nmol/L Eq PS	91
Platelets	CD31		4.2	5.83*				
Lymphocytes	CD11a		2.9	5.85*				
Total	*Annexin V*	2357	1960	2256			10^6/L	92
Platelets	CD61	2014	1618	1818				
T cells	CD4	13	ND	29*				
T cells	CD8	12	ND	15*				
Granulocytes	CD66	7	8	79*				
B cells	CD20	3	10	5				
Monocytes	D14	ND	ND	ND				
Erythrocytes	CD234	150	122	234				
Endothelial cells	CD62e	11	ND	23				
Total	*Annexin V*	6.7	5.1	2.6*			10^9/L	89
Platelets	CD61	6.6	4.9	2.2*				

Overview of studies measuring circulating numbers of MP in normal and complicated pregnancy.
Eq PS, equivalents of phosphatidylserine; control, not pregnant; PR, pregnant; PE, preeclampsia; IUGR, intra-uterine growth retardation; PIH, pregnancy-induced hypertension; Ref, references, ND, not detectable.
*Significantly different from pregnant controls.

from preeclamptic patients impaired bradykinin-mediated relaxation.[40,94]

Microparticles from preeclamptic women also induced vascular hyporeactivity to serotonin in human omental arteries and aortas from pregnant and non-pregnant mice, and these effects were associated with increased nitric oxide production.[91]

Microparticles may contribute to preeclampsia by enhancing coagulation activation that already occurs during normal pregnancy. As the capacity of MP from preeclamptic patients to promote coagulation (thrombin generation assay) was not increased, it seemed unlikely that circulating MP were directly involved in coagulation activation.[95] In addition, MP from preeclamptic patients also failed to affect RNA expression of inflammation-related genes and genes encoding adhesion receptors in endothelial cells.[96] Thus, MP seem to modulate some but not all (patho)physiological processes, at least *in vitro*, that may play a role in (the development of) preeclampsia. As mice infused with *in vitro* prepared (artificial) phosphatidylserine/phosphatidylcholine vesicles developed symptoms characteristic of preeclampsia, a role for MP in the pathophysiological development of preeclampsia seems likely.[97]

Despite the fact that STBM constitute only a small fraction of the total number of circulating MP in the maternal blood, significantly elevated numbers of STBM have been reported in preeclamptic women compared to normal pregnancy.[98] In contrast, STBM were not increased in late onset preeclampsia or IUGR.[99] Perfusion of subcutaneous fat arteries with *in vitro* prepared STBM altered the relaxation response to acetylcholine,[100] but *in vivo* concentrations of STBM did not have such an effect. STBM inhibited endothelial cell proliferation,[101] activated neutrophils and influenced proliferation and activation of T lymphocytes[19,102] Similar to the before mentioned MP from preeclamptic patients, STBM hardly affected endothelial gene expression: the

expression of 28 genes changed twofold or more out of 10 000 genes examined by microarray. The observed changes were related to inhibition of endothelial cell proliferation.[103] Taken together, the exact contribution of STBM to the etiology of preeclampsia needs further investigation.

The role of exosomes in preeclampsia has not been investigated yet. As immunologic factors certainly contribute to the development of preeclampsia and immunologic maladaptation may be one of the underlying phenomena in preeclampsia, this would be very interesting.

Conclusions

Cell-derived vesicles like MP and exosomes have been investigated in many different diseases. So far, their pathophysiologic relevance in cardiovascular, thromboembolic as well as inflammatory and immunologic disorders has been proven mainly *in vitro*. To which extent MP and exosomes contribute, affect and/or reflect disease development, however, is to be determined. Because of lack of standardized protocols to isolate MP and exosomes from human body fluids such as blood, additional studies are required to determine precisely the role of these different types of vesicles in normal and complicated pregnancy.

In normal pregnancy, placenta-derived exosomes expressing or containing FasL (and possibly MIC) may promote a state of immune privilege for the semiallogeneic fetus by silencing the maternal immune response. As complicated pregnancies can result from an inadequate suppression of maternal T-lymphocyte activation, this mechanism may constitute a new therapeutic target. Circulating MP with increased procoagulant potential in women with RSA may be a chronic phenomenon, comparable to acquired thrombophilia, possibly becoming clinically manifested during pregnancy. Whether these MP are secondary to RSA or were already existent before pregnancy, however, is still unknown. Recent data indicate that women with premature labour have decreased numbers of circulating placenta-derived exosomes and possibly indicate inappropriate down-regulation of the maternal immune system. Although data are lacking on the presence of exosomes in preeclampsia, there is growing evidence that MP are somehow associated with the pathophysiology underlying disease acquisition and progression. Nevertheless, there is no clear correlation between circulating numbers of MP and the disease state in different women suffering from preeclampsia.

Taken together, ongoing research is essential to elucidate further the impact of circulating MP and exosomes in normal and complicated pregnancy.

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