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Microparticles and Pre-eclampsia

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Abstract

Preeclampsia is a leading cause of maternal and fetal/neonatal mortality and morbidity worldwide. The early identification of patients with an increased risk for preeclampsia is therefore one of the most important goals in obstetrics. The availability of highly sensitive and specific physiologic and biochemical markers would allow not only the detection of patients at risk but also permit a close surveillance, an exact diagnosis, timely intervention (e.g. fetal-lung maturation), as well as simplified recruitment for future studies looking at therapeutic medications and additional prospective markers. Today, several markers may offer the potential to be used, most likely in a combinatory analysis, as predictors or diagnostic tools. Microparticles constitute a cellular marker of a pro inflammatory and procoagulant responses in normal pregnancy. In pre-eclamptic situations circulating MP with procoagulant potential may be part of the exacerbation of these responses.

Keywords: Microparticles; Exosomes; Endothelium; Endothelial-derived; Platelets; Platelet-derived; Syncytiotrophoblast-derived; Diseases; Tissue factor; Extracellular matrix; Preeclampsia

Introduction

Eukaryotic cells release vesicles in their environment. This occurs by membrane shedding resulting in presence in the microenvironment and in circulation of Microparticles. Another mechanism consists in secretion of membranes;

The event originates exosomes both in physiological and in pathological conditions [1,2]. Release occurs from the cell surface as a budding process involving local rearrangement of the cytoskeleton [3]. MPs-mediated binding to other cells occurs by integration into the membrane, by adhesion to the cell surface or by ligand-receptor interaction [4]. MPs and exosomes occur commonly *in vitro* and *in vivo*; therefore they can be present in low concentrations in normal plasma [1,2]. Cells can release MPs during activation or death, apoptosis or necrosis as well, and their generation seems to be a well regulated process, although these vesicles are highly variable in size, composition and function [5,6]. Apoptosis normally occurs in the human placenta. As a consequence, cell blebs, post-apoptotic debris (also referred to as syncytial knots) and membrane MPs are released into the blood of pregnant women. These events become prominent during Preeclampsia (PE) [7]. A pregnancy-related disorder of pregnancy with the highest rate of both maternal and neonatal morbidity and mortality [8]. An excessive or deregulated cell death, which results in the generation of an overwhelming burden of apoptotic material, alarms the immune system. This plays a role in the pathogenesis of systemic connective tissue diseases and possibly of small vessels vasculitis. Infiltration of leukocytes and activation of endothelial cells and platelets are hallmarks of normal pregnancy, indicating that physiologic pregnancy is a condition characterized by an activation of the innate immune system. Conversely, a failure in the physiologic termination of inflammatory events is probably a requirement for PE to develop [7].

Pre-eclampsia

Preeclampsia (PE) is a multi-factorial and multi-system disorder of pregnancy, which is characterized by appearance of hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mm Hg) accompanied by proteinuria (>=300 mg/24 hour) after twenty weeks of gestational age in previously normotensive women [9]. The most severe and sometimes life threatening maternal complications are: HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome, eclamptic seizures and disseminated intravascular coagulation. Furthermore in 20% to 30% of cases PE is complicated by Fetal Growth Restriction (FGR) [10,11]. PE can have an early onset (PE starting before 34 weeks of gestation) or late onset (PE starting after 34 weeks of gestation), and symptoms can remain mild or become severe (when one or more of the following were present: systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mmHg,

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proteinuria >5 g/24 hour, oliguria, cerebral visual disturbances, epigastric pain, nausea and vomiting, pulmonary edema, impaired liver function of unclear etiology, thrombocytopenia) [9,12]. These multiform clinical presentations strongly suggest that PE actually includes different diseases.

PE affects 5% to 8% of all pregnancies and remains one of the major causes of maternal and fetal mortality and morbidity. In developed countries, where the diagnosis and management of the disease is a major aim of prenatal care, maternal mortality attributable to PE has been reduced. However, prenatal mortality, prenatal and long term morbidity and neurological sequelae due to FGR and/or preterm delivery, are still an important problem [9,13]. Despite extensive clinical trials, nowadays there is no effective way to prevent PE, and delivery is the only effective therapy. This is partly due to the fact that the etiology and the pathogenesis of the disease are poorly understood. All form of PE are characterized by an excessive inflammation and endothelial injury with clotting dysfunction, among then there is a big part of PE pregnancies where maternal problems are accompanied by a placental dysfunction with a consequent FGR. For these reason, PE could be classified as placental (with feto-placental involvement) or maternal (without feto-placental compromise) [14].

In PE cases with placental involvement, oxidative stress and activation of the maternal vascular endothelium may originate from placental release of lipid peroxidation products, cytokines, and MPs leading to an acute inflammatory response [8].

Microparticles and preeclampsia

Cellular MPs are ubiquitously shed from cell membranes or secreted as endocytic vesicles called exosomes. Shed MPs are >=100 nm in size and are generated during apoptosis or necrosis. In contrast, exosomes are smaller (<100 nm), express more limited protein content and are released from late endosomes. Both membrane particles and exosomes can be detected in the circulation in non-pregnant and pregnant women. During normal pregnancy MPs are increased and they increase further with PE [15,16]. MPs constitute a cellular marker of pro inflammatory and pro coagulant responses in normal pregnancy. In pregnancies with vascular complications, circulating MP with pro coagulant potential may be part of the exacerbation of these responses. In PE pregnancies, significant reduction in platelet MP number was found. The pro coagulant activity generated by the total annexin V MP was unchanged, suggesting that the MPs remaining in the circulation were pro coagulant [17]. PE is associated with an increased release of factors from the placental syncytium into maternal blood, including the antiangiogenic factors soluble fms-like tyrosine kinase-1 and soluble endoglin, the antifibrinolytic factor plasminogen activator inhibitor-1, prostanoids, lipoperoxides, cytokines, and MPs. These factors are suggested to promote maternal endothelium dysfunction and are associated with placental damage in pregnancies also complicated by FGR [18].

Preeclamptic MPs, but not healthy pregnant MPs cause endothelial dysfunction in isolated myometrial arteries from healthy pregnant women after overnight incubation, whereas other preeclamptic plasma constituents protect the endothelium from this effect [19,20].

MP release is controlled likely independently from metabolic energy [21-23]. In contrast, exosomes are released from late endosomes; therefore contain a limited amount of protein [23]. MPs are a heterogeneous population and their numbers, cellular origin, composition and functional characteristics, both *in vitro* and *in vivo*, depend on the circumstances under which they were generated [24]. MPs are as a rule phospholipids microvesicles containing membrane proteins of their parental cells; they circulate in the peripheral blood and play active roles in the pathogenesis of several illnesses [5,23]. They demonstrate procoagulant properties, possibly linked to phosphatidylserine exposed at their surface [4]. MPs can be released from nearly every cell type, and bear at least some characteristics of the parent cell [25]. MPs were considered inert debris without specific function, but recent data demonstrated pathophysiologic mechanisms orchestrated by MPs in vascular diseases associated with endothelial dysfunction. This role of MPs and exosomes indicates that they may represent novel pathways in short or long-distance paracrine transcellular signaling in vascular environment [6]. Rare hereditary syndromes with disturbances in membrane vesiculation leading to a decreased numbers of MPs clinically present with a bleeding tendency [6].

DNA-associated MPs in maternal plasma express significantly increased placental-derived Human Leukocyte Antigen-G (HLA-G) and Placental Alkaline Phosphatase (PLAP). Preeclamptic women had higher levels of DNA-associated MPs than control pregnant women. HLA-G MPs from the plasma of preeclamptic women had more DNA per MP than HLA-G MPs from the plasma of normal pregnant women. DNA amounts per HLA-G MP increase in preeclamptic women which might indicate dysfunctional extra villous cytotrophoblasts [26]. MPs that circulate in blood may be a source of DNA for molecular analyses, including prenatal genetic diagnoses. However, since MPs are heterogeneous in nature, further characterization is important before use in clinical settings. Quantification of maternal MPs using characteristics defined by MPs generated *in vitro* revealed a significant increase of DNA (+) MPs in the plasma of women with PE compared with plasma from women with normal pregnancies. Apoptotic MPs are therefore a likely source of stable DNA that could be enriched for both early genetic diagnosis and monitoring of pathological pregnancies [27].

MPs are pro-coagulant vesicles derived from various cells. Evidence is accumulating that MPs are of pathophysiological relevance in autoimmune, cardiovascular, and thromboembolic diseases and inflammatory disorders. Therefore, their role in the development of PE was investigated and MP from preeclamptic patients influenced endothelial-dependent vasodilatation. Placenta derived MP increase during pregnancy, possibly because of placental growth. In PE, reduced numbers of PDMPs are due to decreased platelet counts. Increased numbers of monocyte-derived MP reflect monocyte activation, which may be an expression of the systemic inflammation in PE. Women with a history of PE have an increased risk for cardiovascular disease in later life. Women with a history of PE show signs of hypercoagulability as indicated by higher thrombin generation and higher platelet derived MP levels [28,29]. An excessive or deregulated cell death, which results in the generation of an overwhelming burden of apoptotic material, alarms the immune system. This plays a role in the pathogenesis of systemic connective tissue diseases and possibly of small vessels vasculitis. Infiltration of leukocytes and activation of endothelial cells and platelets are hallmarks of normal pregnancy, indicating that physiologic pregnancy is a condition characterized by an activation of the innate immune system. Conversely, a failure in the physiologic termination of inflammatory events is probably a requirement for PE to develop [30].

Syncytiotrophoblast MPs

PE shows characteristics of an inflammatory disease including leukocyte activation. Increased levels of particular subsets of leukocyte-derived MP reflect activation of their parental cells in PE [20]. During this kind of event there are not only particles derived from platelets, endothelium and various leukocytes but also Syncytiotrophoblast-derived MPs (STBMPs) [21]. The higher amounts of STBMPs circulating in maternal blood in PE might lead to the excessive maternal inflammatory reactions, interacting with both immune and endothelial cells [21,22]. They may contribute to the systemic inflammatory response of both normal and pre-eclamptic pregnancies, although inhibitory activity has also been described. Moreover, trophoblast-derived exosomes may contribute to or cause the down regulation of T cell activity that has been repeatedly observed during pregnancy. Deletion of activated T cells which express Fas ligand by Fas-expressing exosomes derived from trophoblast may contribute to immune regulation necessary for normal pregnancy [21]. PE involves an overt activation of the maternal innate immune system, proposed to result from the elevated release of inflammatory STBMPs and cytokines from underlying placental anomaly involving abnormal trophoblast differentiation [31]. The syncytiotrophoblast is the outer layer of placenta which is in direct contact with maternal blood. As such it is uniquely positioned to alter maternal hemostasis and endothelial function. The syncytium is known to release anti-angiogenic factors including fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), as well as the anti-fibrinolytic factor plasminogen activator inhibitor-1 (PAI-1). Its release of MPs has also been suggested to play a role in regulating maternal endothelial and immune cell function. It is of note that syncytial release of the above-mentioned factors increases in PE, a major cause of maternal mortality and morbidity. In PE, hypoxia and reperfusion injury in the placenta is associated with activation of the maternal endothelium [32,33]. Normal pregnancy is associated with a systemic maternal inflammatory reaction, including the activation of peripheral blood monocytes. This reaction is exaggerated in PE, a severe placenta-dependent disorder of pregnancy specific to humans. It has been suggested that placental STBMPs, which are released into the peripheral blood, may contribute to the maternal response. STBMP washed from the maternal side of a placental cotyledon and STBMP shed by explants cultured in air up-regulated cell surface expression of the adhesion molecule CD54 and induced the production of Interleukin (IL)-8, IL-6 and IL-1beta. Cytokine production was time-and dose-dependent. It is suggested that monocyte activation in normal pregnancy and PE may be induced by STBMP released by the placenta. The higher amounts of STBMP circulating in maternal blood in PE might lead to the excessive maternal inflammatory reaction [22,23].

The excess shedding of STBMP may be caused by hypoxia as a result of poor placentation, which is often a feature of PE. Similar placental pathology occurs in some cases of normotensive FGR (nFGR), but in the absence of maternal disease. Increased STBMP levels were found in early-onset PE but not in nFGR providing further evidence for their role in the pathogenesis of the maternal syndrome [34]. Manifest PE is associated with activation of peripheral neutrophils as well as elevations in maternal cell-free DNA. Activated circulatory neutrophils secrete nuclear DNA to generate extracellular DNA lattices, termed NETs (Neutrophil Extracellular Traps). Placental STBMs, which are released in elevated amounts in PE, can induce NETs in isolated neutrophils. Furthermore, there is evidence for the increased presence of NETs directly in the intervillous space of pre-eclamptic placentae [35].

Endothelial-derived MPs (EDMPs)

There are established markers of Extracellular Matrix (ECM) injury, commonly soluble markers such as Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), E-selectin, von Willebrand Factor (vWF), etc., pointing out that many of these are in fact mixtures of true soluble molecules with membrane-bound forms, for example, Endothelial-Derived MPs (EDMPs). EDMPs are heterogeneous: those released in activation vs. apoptosis are distinctive in phenotypic markers and procoagulant properties. Application of EDMP phenotype analysis can distinguish endothelial state of activation from apoptosis. Some EDMPs carry functional vWF with properties different from soluble vWF. Certain EDMPs bind to and activate monocytes; EDMP-monocyte conjugates were found to be a marker of inflammatory disease. Clinical studies have revealed elevated plasma levels of EDMP in PE. Further refinement of EDMP assay could open new windows for evaluating and monitoring endothelial injury in thrombotic and inflammatory disorders, such as PE [36]. The complex role of MPs in vascular diseases is an area of immense interest. That promises to yield important advances into diagnosis and therapy [2].

PE and procoagulant properties of MPs

Pregnancy is characterized by haemostasis activation, and in PE endothelial dysfunction, platelet and leukocyte activation are further characteristic features. Changes from the non-pregnant to the pregnant state are associated with hemostasis activation as an integrated part of an inflammatory reaction that is even more pronounced when pregnancy is complicated with PE [37]. Platelet activation is increased in PE but not in other hypertensive disorders or in normal pregnancy. This may be part of the pathophysiologic factors of PE complications but is not predictable by the platelet count and is not apparent in all women with PE [38]. In PE, T-cell (T-suppressor and T-helper cell) and granulocyte MP numbers are increased. Elastase concentrations are also increased in PE and correlated with granulocyte MP numbers [39]. Inflammation and endothelial dysfunction are prominent in PE. MPs may link these processes, as MPs induce the production of pro-inflammatory cytokines by endothelial cells and cause endothelial dysfunction. MPs from preeclamptic patients induce endothelial dysfunction by directly affecting the expression of inflammation-related genes in this cell [40]. Endothelial MP levels are higher in women with PE than in women with gestational hypertension and control subjects. The measurement of endothelial MPs may be useful as a diagnostic tool for PE in pregnant women [41,42]. The clinical features of the maternal syndrome of PE can be explained by generalized maternal endothelial cell dysfunction, which is a part of a more global maternal systemic inflammatory response. There is growing evidence that these effects are associated with the shedding of cellular debris, including STBMP, cell-free DNA and mRNA, from the surface of the placenta (syncytiotrophoblast) into the maternal circulation. The increased shedding of this debris seen in PE is believed to be caused by placental ischaemia, reperfusion and oxidative stress. The enhanced shedding of STBMP and Corticotrophin-Releasing Hormone (CRH) mRNA in PE labour may have a role in cases of postpartum worsening of PE [43]. Both inflammation and thrombosis can be orchestrated by the interactions between circulating cells, such as leukocytes and platelets, with vascular, endothelial and smooth muscle cells, which, during activation or apoptosis, can release circulating MPs.

Indeed, MPs are membrane vesicles with procoagulant and pro inflammatory properties. Circulating MPs or those generated *in vitro* from apoptotic T cells display deleterious effects on endothelial and/or vasomotor function. In contrast, MPs might be protective to endothelial cells. MPs induce NO release, decrease production of reactive oxygen species and induce angiogenesis from endothelial cells. This protective role for the endothelium was confirmed also by their *in vivo* injection in mice in which they were also able to reverse endothelial dysfunction in a model of heart ischemia/reperfusion. On the contrary, MPs from preeclamptic women compared to those from normal pregnant women showed pro-inflammatory properties in the vascular wall inducing vascular hypo reactivity in vessels from humans and mice. These effects were associated with complex interactions between NO and cyclooxygenase systems *via* endothelial cell activation. Altogether, these findings suggest that MPs can be considered as vectors of biological messages for vascular homeostasis, during immunity and inflammation [44]. There is growing evidence implicating congenital and acquired thrombophilias in PE. Pregnancy itself is notably a hypercoagulable state, at least in part, due to the physiological changes in the coagulation and fibrinolytic systems; this has the potential for interaction with an acquired or heritable thrombophilia to cause adverse experiences. Recurrent fetal loss is associated with antiphospholipid antibody syndrome, procoagulant platelet MPs and some inherited thrombophilias such as Factor V Leiden. There have been reports of both heritable and acquired thrombophilias being associated with PE. However, these associations are not consistently reported with hereditary thrombophilias. The presence of thrombophilia might influence the severity of a condition such as PE, rather than cause it. The risk of fetal loss related to antiphospholipid syndrome can be reduced with antithrombotic therapy with heparin and low dose aspirin [45]. Platelets and the coagulation system may be involved in the pathogenesis of PE. The percentage of CD62P+ platelets, CD62P+ platelet MPs and platelet-monocyte aggregates were significantly higher in women with PE than the pregnant controls. In the most comprehensive laboratory analysis to date, it was found evidence of both platelet and coagulation activation in women with PE [46].

MPs and nitric-oxide production in PE

MPs in PE could act as vectors to stimulate intracellular cascades in vascular cells; leading to an enhanced Nitric-Oxide (NO) production to counteract increased COX-2 vasoconstrictor metabolites by taking into account pregnancy [47]. Preeclamptic women displayed increased circulating levels of leukocyte- and platelet- derived MPs compared with healthy pregnant individuals. MPs from preeclamptic, but not healthy, pregnant women induced *ex vivo* vascular hyporeactivity to serotonin in human omental arteries and mouse aortas. Hyporeactivity was reversed by a NO synthase inhibitor and associated with increased NO production. In the presence of a Cyclooxygenase (COX)-2 inhibitor, serotonin-mediated contraction was partially reduced in arteries treated with healthy MPs but was abolished after treatment with preeclamptic MPs. This was associated with increased 8-isoprostane production. Preeclamptic MPs induced up-regulation of inducible nitric-oxide synthase and COX-2 expression, evoked nuclear factor-kappa B activation, and enhanced oxidative and nitrosative stress. Interestingly, the MPs originating most probably from leukocytes were responsible for the COX-2 vasoconstrictor component of preeclamptic MPs, whereas those of platelet origin were mainly involved in NO release. Moreover, vascular hyporeactivity was observed in arteries taken from mice treated *in vivo* with preeclamptic MPs [48].

PE and pro inflammatory properties of MPs

Compared with non-pregnancy, monocytes were primed to produce more TNF-alpha throughout normal pregnancy, more IL-12p70 in the first and second trimesters, and more IL-18 in the first trimester only. Intracellular cytokine measurements (TNF-alpha and IL12p70) showed little change by comparison. IFN-gamma production was suppressed in all three trimesters. In pre-eclampsia, IL-18 secretion was increased. Secreted but not intracellular measures of TNF-alpha and IL-12p70 were also further enhanced compared with normal pregnancy. Inhibition of IFN-gamma production was lost and involved both CD56 (+) NK and CD56 (-) lymphocyte subsets. Circulating STBMPs could contribute to inflammatory changes. Unbound STBMP could be detected in normal pregnancy by the second trimester and increased significantly in the third. They were also bound *in vivo* to circulating monocytes. Women with PE had significantly more circulating free but not cell-bound STBMPs. Inflammatory priming of PBMCs during pregnancy is confirmed and is established by the first trimester. It is associated with early inhibition of IFN-gamma production. The inflammatory response is enhanced in PE with loss of the IFN-gamma suppression. Circulating STBMs bind to monocytes and stimulate the production of inflammatory cytokines [49]. PE is associated with increased placental debris circulating in maternal plasma. Fetal Corticotrophin-Releasing Hormone (CRH) mRNA levels were higher in PE than in control pregnancies. Women with PE had higher levels of Tissue Factor Pathway Inhibitor (TFPI), prothrombin F(1+2) fragment [F(1+2)], factor XIIa, soluble vascular cell adhesion molecule 1, von Willebrand factor and Plasminogen Activator inhibitor 1 (PAi1) than controls. Placental debris, assessed by fetal circulating CRH mRNA levels in maternal blood, is related to coagulation potential, i.e. FVII activity, but not to markers of coagulation or endothelial activation in pre-eclampsia [50]. Fetal DNA and fetal CRH mRNA are associated with *in vitro* generated STBMPs, and that the ratio of fetal DNA to mRNA (CRH) varied according to whether the particles were derived by predominantly apoptotic, apo-necrotic or necrotic pathways. Circulatory fetal mRNA and fetal DNA levels were significantly elevated in the PE than in normotensive controls. Alterations in the fetal mRNA to DNA ratio between the study and control groups were minimal, even when stratified into early (<34 weeks of gestation) and late (>34 weeks of gestation) onset PE. Although circulatory fetal DNA and mRNA levels are significantly elevated in PE, the ratios in maternal plasma are not dramatically altered [51]. PE shows characteristics of an inflammatory disease including leukocyte activation, altered concentrations of sL-selectin and elastase, up-regulation of Nuclear Factor of Kappa light chain gene enhancer in B cells inhibitor (NFkappaB-1A) and Cyclin-Dependent Kinase Inhibitor (CDKN)-1A compared with normotensive pregnant women. Interleukin-1 Receptor Antagonist (IL-1RA), Tumor Necrosis Factor (TNF)-R1, Monocyte-derived MPs, cytotoxic T-cell-derived and granulocyte-derived MPs were elevated in preeclamptic patients compared with pregnant women [52].

Conclusion

Preeclampsia remains a major cause of maternofetal disease and mortality. The analysis if circulating microparticles might help in the early diagnosis and therapeutic intervention.

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