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Umbilical Cord Blood Changes in Neonates from a Preeclamptic Pregnancy

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1. Introduction

During pregnancy, mother's well-being affects directly the newborn development. Some maternal and placental complications, such as gestational diabetes, preeclampsia (PE), preterm delivery and intrauterine growth restriction (IUGR), may contribute to fetal growth deviations or fetal development modifications. Usually the newborn weight correlates positively with placenta weight, showing the interaction between the development of placenta and fetal growth.

Normal human pregnancy is associated with physiological blood changes, namely, neutrophilic leukocytosis, hyperlipidemia and procoagulant, hypofibrinolytic and inflammatory conditions. PE has been associated with an enhancement in these changes and with placental abnormalities, that may condition its perfusion and, therefore, feto-maternal transfer. The placental dysfunction, characterized by a disturbance in the angiogenic/anti-angiogenic factors and in the hypoxia/placental reoxygenation process, seems to trigger a maternal endothelial dysfunction. To this maternal endothelial dysfunction may also contribute the oxidative stress, dyslipidemia and the inflammatory process which are present in maternal circulation.

PE is a maternal pathology involving placental modifications, which is also associated with fetal complications. Prematurity and IUGR, are the most representative complications. In this chapter we will address the impact of the maternal disturbances in the newborns from a normal and a preeclamptic (PEc) gestation. Indeed, there are several studies in literature about changes in maternal circulation, but few studies about fetal blood changes in the presence of PE. Moreover, these studies have shown controversial results. We intend to focus on neonatal consequences of PE, by assessing different biochemical and hematologic parameters in the umbilical cord blood. In this way, we will address the effect of some modifications usually observed in PEc women, such as, in lipid profile, in hematologic profile, inflammatory and antioxidant markers, angiogenic/anti-angiogenic factors and hemostatic disturbances, in umbilical cord blood.

Disturbances in angiogenic/anti-angiogenic factors, in the lipid profile and an enhanced inflammatory response, in the fetal circulation, may cause a short-term effect, such as endothelial dysfunction. However, the impact of these modifications, that are known cardiovascular risk changes, in the future life of these newborn are still unknown and should be clarified. These neonates and their mothers should deserve, therefore, a closer clinical follow-up later in life. This issue will be also addressed in this chapter.

2. Preeclampsia

Hypertensive diseases in pregnancy are the most common causes of mortality and maternal and fetal morbidity (WHO, 2005). PE is a frequent cause for hospitalization, labour induction and dystocic labour, reasons that justify the study of this disease.

Some controversy exists concerning the terminology and the classification of hypertensive disorders; indeed, several reported studies used different classifications. The more consensual, is the classification proposed by the "International Society for the Study of Hypertension in Pregnancy" (ISSHP). The diagnosis of hypertension in pregnancy, according to this classification (Brown et al., 2001) is performed in accordance with the following criteria: an occasional measurement of diastolic blood pressure greater than 110 mmHg, or two or more consecutive measurements equal to or greater than 90 mmHg, with 6 hours or longer intervals between measurements. PE is defined as the onset of hypertension associated with proteinuria after 20 weeks of gestation, in previously normotensive pregnant women (Table 1). Typically, PE is asymptomatic, but in its most severe form it may also present with headache, epigastric pain, visual disturbances and changes in consciousness.

Preeclampsia ISSHP classification:
Hypertension - diastolic blood pressure ≥ 110 mmHg (an occasional measurement), or ≥ 90 mmHg (two or more consecutive measurements)
Proteinuria (≥ 300 mg/day)
Both present, after 20 weeks of gestation, returning to normal postpartum

Table 1. Preeclampsia ISSHP classification

Eclampsia is the most severe form of pregnancy-induced hypertension. It is characterized by the appearance of seizures, which may occur before, during or within 48 hrs after birth. Eclampsia may appear in pregnant women with moderate increases in blood pressure and mild proteinuria.

2.1 Epidemiology of preeclampsia /risk factors and complications

PE is a pregnancy specific disorder, characterized by an impaired blood perfusion of vital organs, including the fetal-placental unit. The prevalence of PE, although usually reported as 5 to 8%, presents some variations in the literature (Sibai et al., 2005; Maynard et al., 2008), particularly for different populations.

The risk of developing PE seems to be associated with some factors, such as nulliparity (about 2/3 of cases occur in the first pregnancy), multiple pregnancy, change of paternity, age over 40 years, family history of PE and eclampsia, body mass index (BMI) greater than 35 kg/m², diabetes, disease prior to pregnancy (e.g., diabetes mellitus, hypertension, renal disease and thrombophilia) and hydatidiform mole (Duckitt & Harrington, 2005; Magnussen et al., 2007; Jim et al., 2010). According to Magnussen et al. (2007), there is an enhanced risk to develop PE, when cardiovascular risk factors, such as increased triglycerides (TG), total cholesterol and LDLc, are present before pregnancy.

Several studies associate smoking habits with a lower risk of developing PE (Magnussen et al., 2007; Wikström et al., 2010). However, maternal smoking is associated with various maternal and fetal complications (Kalle, 2001; Steyn et al., 2006), including placenta previa, low birth weight, preterm birth, miscarriage and neonatal death.

PE is the main maternal risk factor associated with low birth weight newborns and/or IUGR (Table 2). Intrauterine growth restriction and/or fetal death can occur in about 30% of PEc cases as a direct result of placental insufficiency (Jim et al., 2010). The neonatal complications risk is higher in cases of severe PE and eclampsia (Duley, 2009). IUGR is associated with a high rate of perinatal morbidity and mortality (Rizzo & Arduini, 2009).

Several studies indicate that PE is associated with a higher incidence of newborns with low birth weight (Groom et al., 2007; Duley, 2009; Wu et al., 2009). In addition, there's an increased incidence of newborns with low birth weight in pregnant women who developed PE at an earlier stage of pregnancy, compared with those who later developed PE (Xiong & Fraser, 2004; Groom et al., 2007). Prematurity is the leading cause of perinatal morbidity and mortality (Goldenberg et al., 2008) and PE is often associated with preterm delivery (Sibai et al., 2005; Goldenberg et al., 2008; Duley, 2009; Wu et al., 2009). Some neonatal complications resulting from PEc pregnancy are described, and are associated with prematurity, including jaundice, respiratory distress, apnea, seizures, hypoglycaemia and prolonged hospitalization (Duley, 2009; Wu et al., 2009).

Newborn complications:
Intrauterine growth restriction (IUGR)
Prematurity
Neurologic lesions
Neonatal death
Long term chronic diseases ("fetal programming" or "fetal origins of disease in adult life")

Table 2. Newborn complications in preeclampsia

According to Barker's theory, the origin of some adulthood chronic diseases such as cardiovascular diseases, hypertension and diabetes have their origin in intrauterine life (Barker & Bagby, 2005). This hypothesis, called "fetal programming" or "fetal origins of disease," suggests that the intrauterine environment in which the fetus develops may be the origin of diseases in adult life. Changes that may occur in intrauterine environment and that somehow could disrupt normal development of the fetus can trigger metabolic changes, which may result in the development of long-term disorders (Barker, 2004).

There are studies revealing that children of PEc women present in adolescence, higher blood pressure levels with increased risk of developing hypertension, compared to children of normotensive pregnant women (Vatten et al., 2003; Tenhola et al., 2006, Kajantie et al., 2009). In another study, adolescents with low birth weight also presented blood pressure values higher than adolescents who were born with adequate weight (Covelli et al., 2007).

Low birth weight appears to be associated with an increased risk of developing type 2 Diabetes mellitus(Whincup et al., 2008), cardiovascular disease (Barker & Bagby, 2005) and hypertension (Lenfant, 2008) in adult life. This risk appears to be even greater if, in addition to low birth weight, further develop a marked increase in BMI (Eriksson et al., 2007; Barker et al., 2009). In a recent study, Raghupathy et al. (2010) mentioned that individuals who were underweight at birth and during infancy, followed by a sharp increase in BMI during adolescence, were associated with a reduction in glucose tolerance and development of type 2 Diabetes mellitus.

2.2 Etiology and pathophysiology of preeclampsia

PE is considered a multisystem disorder, affecting several organs and maternal systems, including the vascular system, liver, kidney and brain. Despite the intensive research in this area, the etiology of PE remains unknown. PE seems to have a multifactorial cause and is also known as the "disease of theories". In fact, there are several hypotheses raised to explain its etiology. Some those theories propose modifications in the trophoblastic invasion, immunologic intolerance between maternal and fetoplacental tissue, inflammatory changes in pregnancy and genetic modifications, underlying PE development.

Although its unknown cause, it is consensual that there are modifications occurring at different levels, like changes in placental perfusion, increased inflammatory response with changes in leukocyte activation, activation of the coagulation system, endothelial dysfunction and changes in lipid metabolism. The most accepted theory describes two stages for PE (Roberts & Gammil, 2005; Steegers et al., 2010): stage 1 - reduced placental perfusion; stage 2 - multisystem maternal syndrome.

According to this theory, the first pathological change in PE occurs in the uteroplacental circulation, resulting in an inadequate vascular remodelling and/or placental ischemia. In the second phase, the damaged placenta (ischemic placenta) secretes factors that cause endothelial dysfunction, followed by the appearance of maternal clinical symptoms.

The event(s) that trigger(s) the change in the trophoblastic invasion remains unknown; however, genetic, immunological and environmental factors (nutritional deficiencies and hypoxia environment) seem to have some contribution.

The remodelling of spiral arteries takes place at the end of the 1st trimester of pregnancy, and is very important, because it allows an increasing blood flow, in response to higher feto-maternal exchanges. A failure in this process may result in reduced placental blood flow, causing the formation of a hypoxic environment that may trigger PE, which might be associated or not with IUGR. In this case, the spiral arteries have a reduction in its lumen and may be linked to inadequate placentation and acute atherosis, or both.

The placenta seems to play a key role in the pathogenesis of PE, since the clinical symptoms disappear only after placental expulsion. PE seems to develop after a partial failure in the process of placentation, a process that occurs between 6-18 weeks of gestation. In this condition, only some of the spiral arteries of the placental circulation are invaded by trophoblasts. In the myometrial spiral arteries the muscular-elastic layer is not replaced; therefore, vascular resistance is higher and uteroplacental flow is reduced, as compared to what occurs in a normal pregnancy. This decrease in placental perfusion may significantly affect oxygenation, nutrition and fetal development. The reduction in placental perfusion in PE is usually accompanied by a reduction in fetal weight for gestational age (Catarino et al., 2008a).

The first observations on this phenomenon have been published for over three decades (Brosens et al., 1972), but several authors have confirmed these observations and attempted to clarify the mechanisms involved (Chaddha et al., 2004; Burton et al., 2009). Doppler fluxometry applied to the uterine arteries allowed the confirmation of the hemodynamic disturbances underlying placental insufficiency, and demonstrated that in PE occurs an increased (circulatory) resistance of placental vascular territory (Papageorghiou & Leslie, 2007; Boukerrou et al., 2009). As changes in placental blood flow are observed in PE before the onset of symptoms (Papageorghiou & Leslie, 2007), uterine artery Doppler, is performed early in the second trimester of pregnancy, in order to predict PE.

In PE an acute atherosis in the myometrial spiral arteries may also develop. The acute atherosis is an injury similar to the atherosclerotic lesion, characterized by the presence of fibrin deposits, accumulation of foam cells and infiltration of mononuclear leukocytes. This type of injury leads to a reduction of the arteries lumen, and, thus, to a decrease in placental perfusion, even in the absence of an inadequate placentation (Pijnenborg et al., 2006). The atherosis may progress to acute vascular obstruction of the spiral arteries, reducing blood flow to the placenta and causing placental infarction. In a study involving 400 placentas from PEc women, the vascular lesions in the placenta correlated with the severity of this pathology (Ghidini et al., 1997).

2.2.1 Maternal syndrome of preeclampsia

Placenta has the ability to synthesize several molecules, including mediators of inflammation and angiogenic factors, whose expression appears to be regulated by oxygen pressure and by the presence of oxidative stress (Rusterholz et al., 2007; Redman & Sargent, 2009). The expression of these molecules appears to be affected in PE; placental hypoxia/reperfusion and placental oxidative stress seems to be involved in this regulation, however, other modulators may contribute to that expression, such as genetic and immunological factors.

Some studies state that PE induces changes in the placental expression of tumor necrosis factor (TNF)-α, increasing this and other pro-inflammatory cytokines (Hung et al., 2004), and interleukin (IL)-6 (Bowen et al., 2005); however, there are conflicting results (Rusterholz et al., 2007).

Placenta seems to be the main source of placental growth factor (PlGF) and soluble vascular endothelial growth factor receptor (sVEGFR)-1, during pregnancy. A change in placental function may, therefore, interfere with the synthesis of these angiogenic/anti-angiogenic

factors. It has been shown that PEc placentas present an increased expression of sFlt1 (Gu et al., 2008), and a decreased expression of PlGF (Gu et al., 2008). These placental factors and cytokines appear to be released in maternal circulation, resulting in a generalized endothelial dysfunction, causing the multisystem complications of a PEc pregnancy (Rusterholz et al., 2007; Maynard et al., 2008) (Fig. 1).

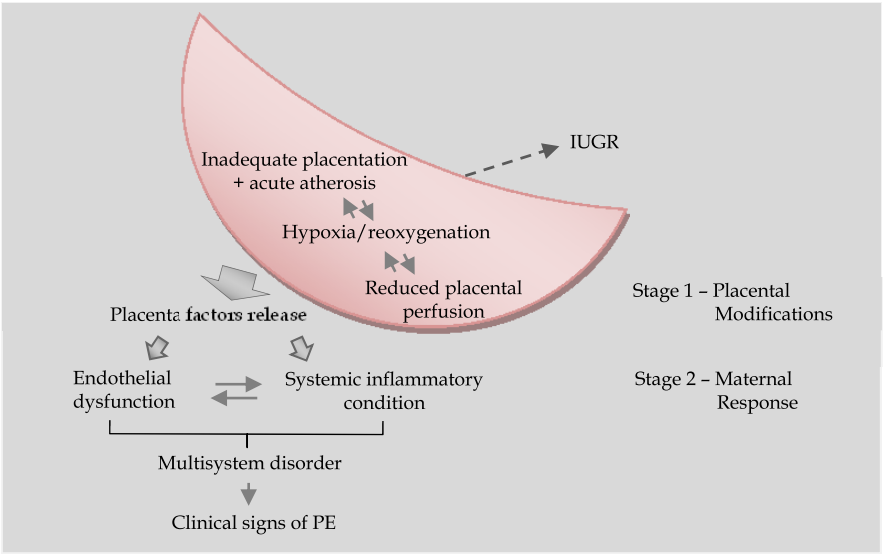

Fig. 1. Possible mechanisms involved in the pathogenesis of preeclampsia

3. Maternal and umbilical cord blood modifications

PE is a disorder involving maternal and placental changes. It involves fetal complications, such as, prematurity and IUGR, which are the most representative. Newborns, whose mothers develop PE, usually present a lower birth weight than infants born from mothers with a normal pregnancy (Catarino et al., 2008a). Moreover, newborns small for gestational age, as well as newborns with Apgar score below 7, are frequently observed in PE (Catarino et al., 2008a).

There are several studies concerning maternal modifications in PE, but there are few studies carried out in umbilical cord blood. We will address the effect of some modifications usually observed in PEc women, such as, in lipid profile, in hematologic profile, inflammatory and antioxidant markers, angiogenic/anti-angiogenic factors and hemostatic disturbances, in umbilical cord blood.

3.1 Angiogenic/anti-angiogenic factors

A normal placental development is essential for adequate feto-maternal nutrients and gas exchanges. In addition, placenta is an important endocrine organ that synthesizes various hormones, cytokines and angiogenic growth factors. These factors are released into the maternal circulation, and may contribute to changes in endothelial function. It is

recognized that placenta has an important role in the protection and development of the fetus, promoting feto-maternal exchanges which are essential to a normal pregnancy. On the other hand, it is also recognized that in PE there are changes in placental development (Pijnenborg et al., 2006; Young et al., 2010), which can compromise the feto-maternal exchange, limiting fetal development, and trigger a maternal and fetal response to adapt to these changes.

Angiogenic factors have been subject of intensive research in recent years, as they appear to be involved in the aetiology of PE. Several studies show a decrease in the concentration of PlGF (Polliotti et al., 2003; Levine et al., 2004) and an increase in circulating levels of sVEGFR-1 (McKeeman et al., 2004; Levine et al., 2004) in PEc women. Nevertheless, there is some controversy regarding the concentration of VEGF in pregnant women with PE (Simmons et al., 2000; McKeeman et al., 2004). Since sVEGFR-1 is an antagonist of PlGF and VEGF, there is a reduction of the effects of these factors, i.e., a change in angiogenesis and in endothelial function (Luttun & Carmeliet, 2003). The anti-angiogenic effect in pregnant women with PE seems to disappear after delivery (Maynard et al., 2008; Myatt & Webster, 2009), strengthening the involvement of placental factors in PE. VEGF plays an important role in vascular development, especially at placenta level, but also induces NO and prostaglandins synthesis, which are mediators of vasodilation (Myatt & Webster, 2009).

The processes of vasculogenesis/angiogenesis are crucial for the development of uteroplacental circulation and placenta. In a study performed by our group (Catarino et al., 2009a), we observed a disturbance of the angiogenic/anti-angiogenic factors in the maternal circulation in PE. PEc women had significantly higher levels of sVEGFR-1 (Fig. 2B) and VEGF values and significantly lower PlGF levels (Fig. 2A). This disruption in angiogenesis factors seems to be associated with placental dysfunction, since these factors are mainly produced by the placenta (Kaufmann et al., 2004), during pregnancy.

We also observed a positive correlation between levels of PlGF and maternal placental weight, in PEc pregnancy, which highlights the importance of PlGF in placental development (Catarino et al., 2009a). It is worthy to note that sVEGFR-1, an inhibitor of PlGF and VEGF, was significantly correlated with the amount of proteinuria, a marker of PE severity, suggesting an important role of sVEGFR-1 in the pathogenesis of PE (Catarino et al., 2009a). The abnormal development of the placenta in PE, reduces the placenta perfusion and may also contribute to the observed increase in the amounts of sVEGFR-1 and VEGF, since the tissue hypoxia regulates its production, stimulating it.

In cord blood samples of PEc cases, we observed a significant decrease in PlGF (Fig. 2C) and VEGF concentrations and a significant increase in the levels of sVEGFR-1 (Fig. 2D) (Catarino et al., 2009a). This disruption, particularly at values of PlGF and sVEGFR-1, seems to be an indirect indicator of the involvement of placental dysfunction in PE, since both are produced primarily in the placenta.

The observed correlation between mother and child for sVEGFR-1 seems to indicate that the release of these factors by placenta, occurs both for the maternal and fetal circulation. However, the levels of sVEGFR-1 are higher in the blood of mothers, when compared with cord blood levels, which allows us to suppose that decidua, since it is able to secrete sVEGFR-1 (Lockwood et al., 2007), may also contribute for maternal levels of sVEGFR-1.

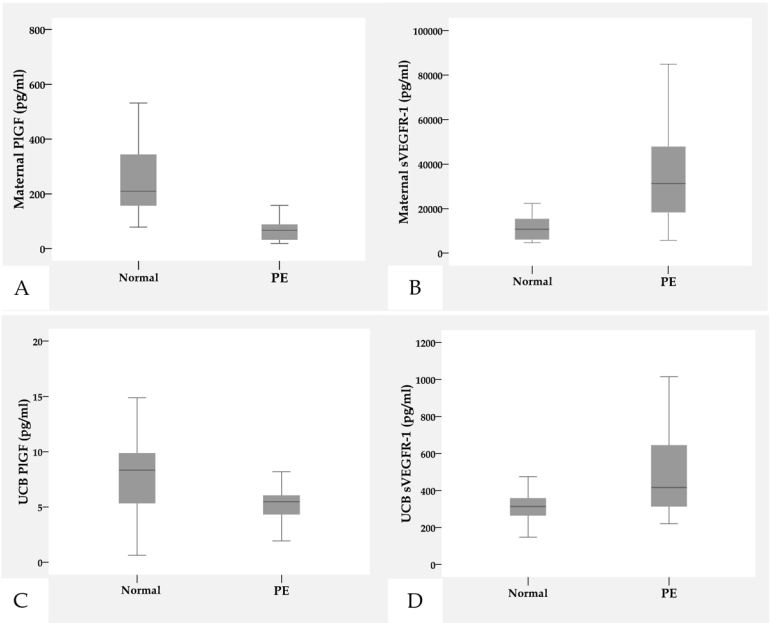

Fig. 2. Concentrations of PlGF in maternal blood (A) and cord blood (C), and sVEGFR-1 levels in maternal blood (B) and cord blood (D) from women with preeclampsia (PE) or with normal pregnancy (N). (Adapted from Catarino et al., 2009a)

3.2 Endothelial dysfunction

Several investigators support the hypothesis that in PE endothelial dysfunction occurs, what contributes to the onset of maternal clinical manifestations. Furthermore, this dysfunction seems to be the link between changes in placental and multisystem complications (Roberts & Gammil, 2005; Young et al., 2010).

In literature, a large number of studies describing changes in endothelial function markers in PE can be found, in particular, an increase of plasma endothelin-1 (Baksu et al., 2005a; Bernardi et al., 2008a), soluble vascular cell adhesion molecule (sVCAM), plasma fibronectin (Aydin et al., 2006; Dane et al., 2009) and tissue fibronectin (Powers et al., 2008), a decrease of plasma and urinary nitric oxide (NO) levels (Baksu et al., 2005a; Mao et al., 2009).

PE is thus associated with a decrease in vasodilatory mediators such as NO and prostacyclin, and an increase in vasoconstrictive mediators such as endothelin-1, angiotensin II and thromboxane A2 (Myatt & Webster, 2009). There are also markers related with hemostasis that are altered in PE and can also be considered as markers of endothelial dysfunction (see Hemostasis section).

In PE, there are several entities that may induce or contribute to injury and/or endothelial dysfunction. These include changes at the level of angiogenic factors/anti-angiogenic, the presence of oxidative stress, exacerbation of the inflammatory process, changes in lipid profile and also a hypoxic environment (Myatt & Webster, 2009).

3.3 Hemostasis

The hemostatic system is altered in PE, which may increase the incidence of maternal and fetal complications. In PEc women, a decrease in the number of platelets compared with normal pregnancy is frequently described (Howarth et al., 1999; Osmanağaoğlu et al., 2005), and thrombocytopenia may occur. Maternal thrombocytopenia is usually associated with more severe pathology, including the HELLP syndrome. Harlow et al. (2002) stated that the decrease in the platelets value is the result of an increase in consumption, as they observed intense platelet activation in patients with PE compared with other pregnancy hypertensive diseases and normal pregnancy. On the other hand, the increase in the mean platelet volume (increased younger platelets, with larger size) (Howarth et al., 1999) and the higher thrombopoietin circulating levels (specific growth factor that promotes thrombocytopoiesis) in women with PE (Johnson et al., 2001), reflect an increase in platelet production. Thus, the reduction of platelet count in PE seems to be due to a higher consumption.

The fibrinolytic system is usually disturbed in PE, due to increased plasminogen activator inhibitor (PAI)-1 and PAI-2. Several studies describe a significant increase in plasma levels of PAI-1 in cases of PE compared to normal pregnancy (Belo et al., 2002a; Tanjung et al., 2005; Sartori et al., 2008; Hunt et al., 2009). The expression of PAI-1 is also elevated in placentas from PEc pregnant women, and PAI-1 plasma levels seem to be positively correlated with the severity of placental damage (Estelles et al., 1998). PAI-2 can be considered a marker of placental function, as it is mainly synthesized at trophoblastic tissue. In PE a decrease in plasma PAI-2 seems to occur (Roes et al., 2002; Tanjung et al., 2005; Sartori et al., 2008), suggesting a modification of placental function. Considering the increased PAI-1 and the decrease of PAI-2, some authors suggest that the rise in the ratio PAI-1/PAI-2 in maternal plasma may be considered a marker of PE (Chappell et al., 2002; Hunt et al., 2009). Several authors report that tissue plasminogen activator (tPA), one of the physiological plasminogen activators, is increased in PE (Belo et al., 2002a; Tanjung et al., 2005; Hunt et al., 2009). Increased levels of D-dimers (fragments of fibrin degradation products) were also reported in PE (Belo et al., 2002a; Hunt et al., 2009), reflecting an increase in the activation process of coagulation and fibrinolysis. The production of D-dimer depends on the formation of thrombin, resulting from activation of the coagulation and fibrinolytic systems. At hemostatic level changes in other parameters, such as a decrease in antithrombin III (Osmanağaoğlu et al., 2005; Tanjung et al., 2005) and an increase in thrombin-antithrombin complex (TAT) in PE (Hunt et al., 2009) were described.

In order to clarify the involvement of hemostatic abnormalities in PE, we assessed fibrinolytic markers, in particular, tPA and PAI antigens and fibrin degradation products (D-dimers). We found that the values of tPA (Fig. 3A) and PAI-1 were significantly higher in PE, without changes in D-dimers (Catarino et al., 2008b). The high levels of tPA and PAI-1 suggest endothelial dysfunction in this syndrome, as both substances are produced by the endothelial cell and exert antagonic roles in the fibrinolytic process. In addition, both PAI-1 and tPA present positive correlations with proteinuria, suggesting that the severity of PE is associated with increased activation/endothelial dysfunction (Catarino et al., 2008b). Furthermore, the maternal endothelial (dys)function, appears to be related to placental (dys)function, considering the positive correlation that we observed between tPA and sVEGFR-1 values in normal and PEc pregnancy (Catarino et al., 2009a).

As already mentioned, different hemostatic modifications are recognized in normal and in PEc pregnancy; however, the exact pattern of these changes in the fetus is still poorly understood. Some authors have reported a decrease in fibrinogen levels, but there were no differences in tPA, PAI-1 and D-dimer (Zanardo et al., 2005), while others reported an increase in PAI-1, however with no differences in tPA values (Roes et al., 2002). Higgins et al. (2000) suggest that infants are somehow protected, at hemostatic system level, since no differences in D-dimers were observed in newborns whose mothers developed PE (Higgins et al., 2000). In a study performed by our group (Catarino et al., 2008b), we also observed similar values of D-dimers. However, and similarly to what we observed in PEc mothers, significantly increased tPA values were found in the newborns of these women (Fig. 3B). Our results suggest that these changes do not arise in response to activation of coagulation, but as a result of endothelial cell dysfunction. Furthermore, we observed a relationship between placental dysfunction and endothelial dysfunction in fetal circulation in PE, suggested by the positive significant correlation that we identified between the levels of tPA and sVEGFR-1 in umbilical cord blood (Catarino et al., 2009a).

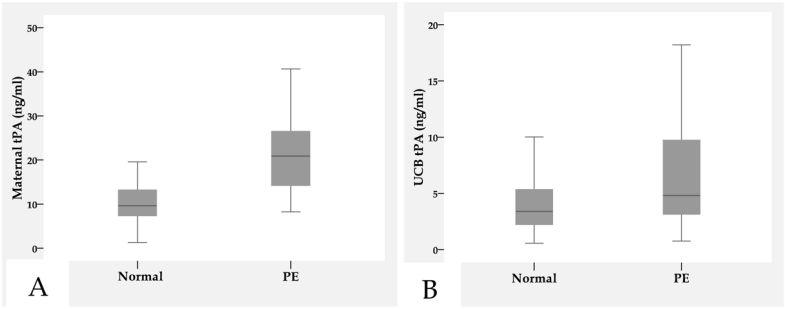

Fig. 3. Maternal (A) and fetal (B) tPA levels in PE and normal pregnancy. (Adapted from Catarino et al., 2008b)

3.4 Oxidative stress

In PE there is evidence of oxidative stress that results from an increased production of oxidizing agents that is not counteracted by antioxidant activity. In fact, an increase in reactive oxygen species, namely in superoxide anion, and a decrease in superoxide dismutase (SOD) activity is observed in trophoblast cells from PEc women (Wang & Walsh, 2001). Different studies demonstrate the development of oxidative stress in PE (Raijmakers et al., 2004; Roberts & Gammil, 2005); either by decreased concentrations of antioxidants, or indirectly by increased lipid peroxidation in maternal circulation, that results from the action of oxygen metabolites, provided by leukocyte activation and/or increased cellular metabolism. The oxidative stress can also take place at the placenta, as a result of the hypoxia/reoxygenation mechanism (intermittent placental perfusion) observed in placentas of pregnant women with PE (Hung & Burton, 2006).

The preterm infants have a lower antioxidant capacity and are therefore more susceptible to oxidative stress triggered at birth, which appears to be associated with complications, including retinopathy and bronchopulmonary dysplasia (Saugstad, 2003). However, there are conflicting results considering oxidative stress in newborns. Some studies describe an

increase of lipid peroxidation (MDA), followed by decreased total antioxidant capacity and ascorbic acid levels in newborns whose mothers developed PE (Mehendale et al., 2008; Howlader et al., 2009), while other studies report no difference in lipid peroxidation (Tastekin et al., 2005; Braekke et al., 2006).

Experimental studies (Poston et al., 2006; Rahimi et al., 2009; Xu et al., 2010), performed in pregnant women at risk, showed no beneficial effect on the antioxidant consumption such as vitamins E and C, in preventing the development of PE, despite the evidence for the involvement of a state of oxidative stress in PE. In fact, according to these trials, antioxidant therapy does not appear to be sufficient to prevent the development of the PE, further increasing the risk of neonatal complications, including increased rate of newborns with low birth weight (Poston et al., 2006; Rahimi et al., 2009).

3.5 Inflammation

There are various mechanisms by which oxidative stress is linked to the inflammatory process. During the inflammatory response production and release of reactive oxygen metabolites occurs leading to oxidative stress. On the other hand, products of oxidative stress, such as those resulting from lipid peroxidation, are considered pro-inflammatory.

PE may be considered as an exacerbated inflammatory condition compared with physiological pregnancy, which appears to contribute to endothelial dysfunction. Initially, there is a localized inflammatory response within the placenta, while in a second phase predominates a systemic inflammatory response. Numerous studies have reported an increase of pro-inflammatory cytokines such as IL-6 and TNF-α (Bernardi et al., 2008b; Guven et al., 2009; Ouyang et al., 2009) in pregnant women with PE, when compared with normotensive pregnant women.

Concerning acute phase proteins, C-reactive protein (CRP) is probably the most studied one, mainly due to its sensibility in detecting inflammation, with a significant increase being observed in PEc pregnancy (Belo et al., 2003; Tjoa et al., 2003; Guven et al., 2009). Tjoa et al. reported an increase in plasma concentration of CRP between 10 and 14 weeks of gestation in pregnant women who subsequently developed PE and gave birth to newborns with growth restriction (Tjoa et al., 2003).

Cell adhesion molecules (CAM), necessary for the adhesion of leukocytes to vascular endothelium, are also altered in PE. Despite some contradictory results, plasma levels of (sICAM)-1, soluble vascular cell adhesion molecule (sVCAM)-1, soluble platelet endothelial cell adhesion molecule (sPECAM)-1 and soluble E-selectin are raised in PEc pregnant women (Kim et al., 2004; Chavarrva et al., 2008).

The neutrophil activation also seems to be associated with PE, as some studies mentioned an increase in circulating levels of myeloperoxidase (Mellembakken et al., 2001; Gandley et al., 2008) and elastase (Belo et al., 2003; Gupta et al., 2006), both released during the degranulation of neutrophils in the inflammatory process.

The increase in inflammatory markers in the maternal circulation could result from the release of substances from the placenta (local inflammation), then triggering a systemically inflammatory response. Some authors have suggested that tissue hypoxia resulting from

reduced placental perfusion, determines an unregulated production of different cytokines, including TNF-α, which is reflected in an increase in the maternal circulation (Rusterholz et al., 2007; Redman & Sargent, 2009).

There is little information for the assessment of inflammatory markers in newborns. Braekke et al. (2005) found no evidence of inflammation in cord blood of newborns from pregnant women with PE, because no differences in CRP or in calprotectin where detected. For studies addressing CAM, the existing information is somewhat contradictory, as is the case for oxidative stress. Some authors have reported an increased expression of L-selectin and integrins on the surface of neutrophils (Mellembakken et al., 2001; Saini et al., 2004) in the fetal circulation in PEc pregnancy, demonstrating an activation of neutrophils. It was also described a decrease in sL-selectin and sE-selectin in the fetal circulation of PEc pregnancy. However, other researchers found no differences between the fetal circulation to a normal pregnancy and PE on levels of sICAM, sVCAM and sE-selectin (Kraus et al., 1998).

The marked inflammatory response in maternal circulation, in the case of PE, seems to be also accompanied by increased inflammatory markers at umbilical cord blood level. Both CRP and α1-antitrypsin are elevated in cord blood, suggesting the presence of an inflammatory response, although less intense than in the maternal circulation (unpublished data).

3.6 Lipid profile

The physiological hyperlipidemia observed in healthy pregnant women is further exacerbated in PE. PE is characterized by intense changes of lipid profile (Ray et al., 2006) similar to what happens in atherosclerosis. Several studies indicate a significant increase in serum triglycerides (TG) in PEc pregnancy, compared with normal pregnancy (Belo et al., 2002b; Baksu et al., 2005b; Bayhan et al., 2005). This is probably the most consistent finding in lipid profile. In a study performed by our group the most pronounced lipid modification that we found was for TG levels (Fig. 4A), which doubled its value in PE in relation to normal pregnancy (Catarino et al., 2008a). Furthermore, TG levels correlated positively and significantly with proteinuria, a known marker of PE severity (Catarino et al., 2008a). In agreement with this, free fatty acids also appear to be higher in PE (Villa et al., 2009).

It is also referred an increase in LDLc (Bayhan et al., 2005) and total cholesterol (Bayhan et al., 2005) and a decrease in hight HDLc (Belo et al., 2002b; Baksu et al., 2005b; Bayhan et al., 2005) in PE compared with normal pregnancy. However, these parameters are not always altered in PE (Baksu et al., 2005b; Manten et al., 2005) and, when they do, the extent of modification is not so pronounced as with TG.

Another biochemical parameter also subject to some controversy is the lipoprotein (a) [Lp(a)]; some studies reported no significant differences in Lp(a) levels in PEc pregnancy (Belo et al., 2002c; Baksu et al., 2005b), while others described an elevation of Lp(a) in PE (Bar et al., 2002; Bayhan et al., 2005). Moreover, Mori et al. described a positive correlation between maternal Lp(a) levels and the severity of PE (Mori et al., 2003).

In PE there is a change in the lipoprotein subclasses profile, particularly a predominance of small and dense LDL (Sattar et al., 1997). The increase of small, dense LDL fraction is especially important, since this is considered the most atherogenic and also more susceptible to oxidation (Wakatsuki et al., 2000), resulting in the formation of oxidized LDL. The oxidized LDL appears to play a crucial role in endothelial (dys)function observed in PE and some authors report that PE is associated with an increase in oxidized LDL levels (Uzun et al., 2005; Kim et al., 2007). However, other articles referred that there are no significant differences in relation to normal pregnancy (Belo et al., 2005; Qiu et al., 2006). Since oxidized LDL is immunogenic, the formation of autoantibodies to oxidized LDL occurs in circulation; some authors also confirm the increase of autoantibodies to oxidized LDL in the circulation of PEc pregnant women (Uotila et al., 1998). In contrast, other study report no changes (Jain et al., 2004). Additionally, it was proposed that pregnant women who present an increase in oxidized LDL plasma levels are associated with increased risk of developing PE (Qiu et al., 2006). Most changes found in lipid profile, including increased plasma TG and VLDL (TG-rich), decreased HDLc and an increase in small, dense LDL subfraction represent a risk profile similar to that predisposing to atherosclerosis and cardiovascular disease (Crowther, 2005). Some authors also propose that changes in lipid metabolism may contribute to the endothelial dysfunction, a key step in the atherosclerotic process (Bayhan et al., 2005; Ray et al., 2006).

Hypertriglyceridemia may contribute to endothelial dysfunction, but may also reflect placental dysfunction, since, unlike free fatty acids and cholesterol, TG does not cross the placenta and have no receptors in the placenta (unlike what happens with lipoproteins). For this, it is necessary that the lipoprotein lipase, which is abundant in the placenta, ensures the TG hydrolysis to be transferred in the form of free fatty acids to the fetus. It is possible that this hydrolysis is impaired in PE, causing a TG accumulation in maternal blood and a reduction in the nutrients uptake by the fetus. On the other hand, the significant increase of TG in maternal blood can be regarded as a physiological mechanism to increase the nutrients supply to the fetus, take into consideration the greater difficulty of nutrients transfer through the placenta.

Considering that in PE also occurs a change in placental perfusion, fetal lipid profile may also be affected due to disturbances in placental transfer of lipids. Rodie et al. (2004) reported an increase in TG levels, total cholesterol and total cholesterol/HDLc ratio in newborns of pregnant women who developed PE, although no correlation between the lipid and lipoprotein levels between mothers and newborns was observed. In turn, Ophir et al. (2006) found no differences in TG or total cholesterol, only observed an increase of LDLc in umbilical cord blood from PEc pregnancy. In our previous study, newborns of mothers with PE showed decreased levels of lipids and lipoproteins (exception for HDLc), but a significant increase in TG (Fig. 4B) (Catarino et al., 2008a).

As already noted, the increase of TG in maternal blood can result from a physiological mechanism of compensation. The high levels of TG in newborns of mothers with PE may, therefore, be a reflection of increased values in the maternal circulation.

Some authors argue that to compensate the difficulty of transferring these nutrients will notice an increased expression of a particular type of receptor, for example to LDL. Other authors propose that there is an increased blood flow to overcome the difficulty in transferring nutrients and/or gas and that this adaptation is that justifies the increase in maternal blood pressure characteristic of PE.

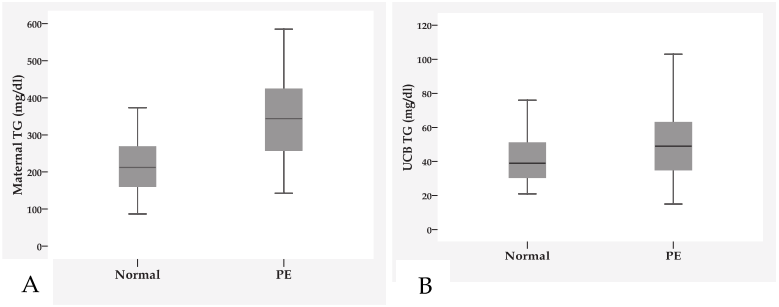

Fig. 4. Maternal (A) and UCB (B) TG levels in PE and normal pregnancy (N). (Adapted from Catarino et al., 2008a)

The impact of the changes in lipid profile in the future of newborns from PEc mothers is uncertain. However, the increase in TG, the ratio LDLc/HDLc and Apo B/Apo AI, suggest that these infants present an increment in their cardiovascular risk.

3.7 Hematologic system

When compared with normal pregnancy PE presents an exacerbation of inflammatory and oxidative stress markers. The release of mediators resulting from inflammatory cell activation can trigger changes in surrounding cells. These cell activation products may contribute to erythrocyte damage, accelerating their aging process and its premature removal. This hypothesis can be tested by evaluating markers of erythrocyte production, damage/aging and removal.

3.7.1 Plasma volume/erythrocyte number

Throughout pregnancy, plasma volume increases gradually, reaching its maximum at about 30 weeks of gestation. This increase would correspond to about 50% of the average plasma volume in non-pregnant woman (Gordon, 2002) and is essential to face the decrease in vascular resistance within the feto-placental unit, protecting the mother and the fetus from hypotension. It is also important in case of bleeding during the delivery (Gordon, 2002). The erythrocyte number increases progressively until the end of pregnancy. This increase may reach 18% in pregnant women without iron supplementation or 30% when diet is accompanied by iron supplements (Gordon, 2002).

Since plasma volume increases at an earlier stage of pregnancy and more rapidly than the increase in the erythrocyte number, the hematocrit decreases until the end of the second trimester. This hemodilution leads to anemia, commonly known as "physiologic anaemia of pregnancy". Therefore, only when pregnant women present a hematocrit below 0.33 l/l and hemoglobin below 11g/dL, there is a true anemia. From the third trimester, when the increase in plasma volume is accompanied by an equivalent increase in erythrocyte number, the hematocrit stabilizes or increases slightly until the end of pregnancy. During pregnancy, in response to the increased "turnover" of hemoglobin, due to the increased demand of oxygen consumption, there is an increased synthesis of erythropoietin (Gordon, 2002) - a specific erythropoiesis growth factor. Erythropoietin acts at bone marrow, stimulating the

erythrocyte differentiation, proliferation and the early release of reticulocytes in peripheral blood. The decreased affinity for oxygen of maternal hemoglobin, caused by increased 2,3-diphosphoglycerate within erythrocytes, represents a compensation mechanism for the increased oxygen consumption needed for oxygen transfer to fetus. This transfer is also favoured by the higher oxygen affinity of fetal hemoglobin, which is the predominant form of fetal hemoglobin.

To respond to the erythropoietic stimulation, there is a mobilization of maternal iron stores and an increase in intestinal iron absorption (Gordon, 2002). To overcome this increase in iron demands during pregnancy, iron supplements are usually given to maintain maternal iron stores, usually after 20 weeks of gestation (Cunningham et al., 2005). During normal pregnancy there is an increase of younger erythrocytes, as shown by an increased number of circulating reticulocytes and, consequently, an increase in "red cell distribution width" (RDW) (Shebat et al., 1998). Tissue hypoxia that occurs physiologically during pregnancy appears to stimulate erythropoietin production, resulting in reticulocyte release from bone marrow into the bloodstream (Lurie & Mamet, 2000).

3.7.2 Erythrocyte membrane protein band 3

The human erythrocyte has a lifespan of about 120 days, being removed from the circulation, mainly, by the spleen. Mature erythrocyte has no nuclei and organelles, and presents a very limited biosynthetic capacity, accumulating physical and/or chemical changes throughout its life span. Several modifications occur with cell aging, namely, reduction in cell volume, enzyme activity, antioxidant capacity and deformability.

The erythrocyte membrane protein band 3 is a transmembrane protein, also known as an anion channel, as it mediates the exchange of HCO^{-}_{3} and Cl^{-} ions, which is important for the transport of CO_2 from the tissues to the lungs. Band 3 links the cytoskeleton to the membrane lipid bilayer, participating in the maintenance of cell morphology. Band 3 is also involved in the removal of senescent/damaged erythrocytes (Wang, 1994).

The development of oxidative stress may occur when exogenous oxygen metabolites diffuse through the membrane or when oxygen metabolites result from autoxidation of hemoglobin, and the red blood cell (RBC) is unable to detoxify the cell, due to depletion in antioxidant defenses. Accumulation of oxygen metabolites can cause hemoglobin oxidation that has a high affinity for the cytoplasmic domain of band 3 (Fig. 5) (Low et al., 1985). This linkage causes band 3 oligomerization and/or aggregation (Waugh et al., 1987), which is recognized by natural autoantibodies anti-band 3 IgG (Fig. 5). The autoantibodies anti-band 3 have a higher affinity for Band 3 oligomers than for band 3 monomers (Lutz, 1992). The band 3 aggregates will act as a neoantigen on the erythrocyte membrane surface, marking the aged or injured erythrocyte for removal by macrophages of the reticulo-endothlial system. Thus, an increase in membrane-bound hemoglobin (MBH) (Santos-Silva et al., 1998) and in band 3 aggregation are good markers of erythrocyte senescence and/or damage.

Changes in band 3 profile (% of band 3 monomers, aggregates and proteolytic fragments), besides that associated to erythrocyte aging, were also reports in different inflammatory models, namely, in myocardial infarction (Santos-Silva et al., 1995), ischemic stroke (Santos-Silva et al., 2002) and in high competition physical exercise (Santos-Silva et al., 2001). In

vitro studies showed that neutrophil activation and elastase, a leukocyte activation product, trigger changes in band 3 profile that are similar to those found in inflammatory conditions and senescent erythrocyte (Santos-Silva et al., 1998). Senescent and/or damaged erythrocyte show an increase in band 3 aggregates and a decrease in band 3 monomers and fragments.

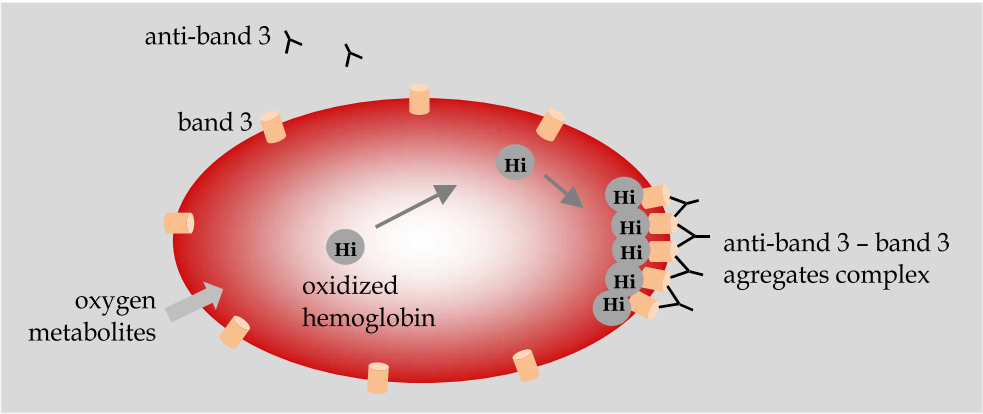

Fig. 5. Illustration of erythrocyte removal mechanism, mediated by band 3 aggregation.

Belo et al. (2002d) reported changes in band 3 profile, in pregnancy and in puerperium. In the first trimester, pregnant women, when compared with non-pregnant women, showed decreased aggregates of band 3 and increased total fragments. During pregnancy, an increase of total fragments was also observed, suggesting a rise in younger erythrocytes (Belo et al., 2002d).

The exacerbated inflammatory process of pregnancy (which can limit the absorption and mobilization of iron for erythropoiesis), the development of oxidative stress (triggering cumulative oxidative damages in erythrocytes) and the changes in placental perfusion (reduction of feto-maternal oxygen transfer and placental hypoxia), all observed in PE, seems to cause oxidative modifications in erythrocytes and disturbances in the erythropoietic process. In a study by our group, PEc mothers showed an increase in erythrocyte number, reticulocyte number and reticulocyte production index (RPI), reflecting an erythropoietic stimulus, which may be triggered by an accelerated removal of aged/damaged erythrocytes (Catarino et al., 2009b). In fact, in PEc women, an increase in MBH and changes in band 3 profile (with an increase in band 3 aggregates) were observed (Fig. 6) (Catarino et al., 2009b). The increase in bilirubin levels, suggests that these lesions led to the early removal of damaged erythrocytes. In fact, high MBH levels are consistent with increased oxidative stress and inflammation associated with PE. The band 3 profile, observed in PE, seems to reflect the existence of a heterogeneous erythrocyte population, ie, a senescent erythrocyte subpopulation (more band 3 aggregates) and a younger erythrocyte subpopulation (reticulocyte, less band 3 aggregates). This reflects a stimulation of the erythropoietic response that seems to mask the erythrocyte injury.

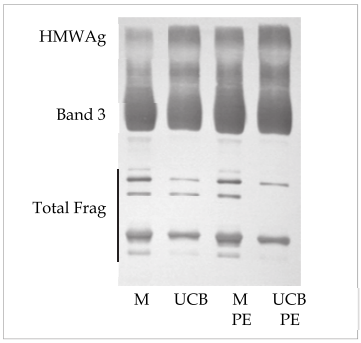

Fig. 6. Erythrocyte band 3 profile in maternal (M) blood and umbilical cord blood (UCB), in normal pregnancy and preeclampsia (PE) (Adapted from Catarino et al., 2009b)

As was observed in PEc mothers, their newborns had significantly higher MBH and evidences of an erythropoietic stimulation, with an increase in erythrocytes, in nucleated red blood cell (NRBC), reticulocyte count and RPI (Catarino et al., 2009b). This erythropoietic stimulation can occur in response to tissue hypoxia, due to the reduced placental perfusion, with lower oxygen transfer to fetal erythrocytes. Erythropoietic stimulation may also be triggered by tissue hypoxia resulting from increased erythrocyte removal, due to increased RBC injury and/or aging. There were no significant differences in the band 3 profile (Fig. 6) (Catarino et al., 2009b). As already mentioned, the increase of NRBC and reticulocytes, a younger erythroid population, prominent in the fetal circulation, may mask the injury observed in the mature erythrocyte population. The increase in MBH in PEc cases, shows an increase of oxidative stress in erythrocytes, as a result in raised hemoglobin oxidation with subsequent membrane binding.

4. Concluding remarks

PE is a hypertensive disorder of pregnancy that affects several organs and systems. Although important quantitative information exists regarding maternal blood modifications in PE, few studies have addressed the influence of this syndrome in newborns from PEc mothers. Moreover, many of the results available in the literature are controversial. The main changes that our group observed in biochemical and hematological umbilical cord blood of newborns from PEc pregnancy when compared with the newborn from normal pregnancy are described in table 3.

The placental dysfunction associated with hypoxia/reoxygenation of the placenta in PE, in the maternal circulation appears to trigger endothelial dysfunction (Fig. 7). To this dysfunction may contribute the hypertriglyceridemia, oxidative stress and the exacerbation of the inflammatory condition. Placental dysfunction, associated with the changes observed in maternal blood, seem to limit the transfer of oxygen and nutrients and, eventually, an abnormal release of products synthesized by the placenta to the fetal circulation; these changes seem to trigger a fetal response in order to adapt to this condition, with the development of endothelial dysfunction, dyslipidemia, and inflammatory response, similar to what occurs in the mother, although less intense. The reduction of oxygen transfer to the fetus associated with oxidative stress, determines oxidative damage in erythrocytes and an erythropoietic stimulation (Fig. 7).

Placental dysfunction	↓↓↓PlGF ↑↑sVEGFR-1 ↓VEGF
Endothelial dysfunction	↑tPA ↓↓PAI-1/tPA
Lipid profile	↑TG ↓↓↓HDLc ↓↓Apo A-I ↑↑↑LDLc/HDLc
Inflammation	↑α1- antitrypsin ↑CRP
Leukocyte activation	↑sVCAM ↓↓sL-Selectin
Oxidative stress	↑↑↑Uric acid
Erythrocyte (damage/remove/production)	↑↑↑MCV ↑↑↑MCH ↑NRBC ↑Reticulocytes ↑RPI ↑↑↑MBH

PlGF, placental growth factor; sVEGFR-1, soluble vascular endothelial growth factor receptor type 1; VEGF, vascular endothelial growth factor; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor; TG, triglycerides; HDLc, HDL cholesterol; LDLc, LDL cholesterol; Apo, apolipoprotein; CRP, c-reactive protein; sVCAM, soluble vascular cell adhesion molecule; MCV, mean cell volume; MCH, mean cell hemoglobin; NRBC, nucleated red blood cell; RPI, reticulocyte production index; MBH, membrane-bound hemoglobin ↑↑↑ - P<0.001; ↑↑ - P<0.01; ↑ - P<0.05

Table 3. Main changes observed in biochemical and hematological umbilical cord blood of newborns from PEc pregnancy when compared with the newborn in normal pregnancy.

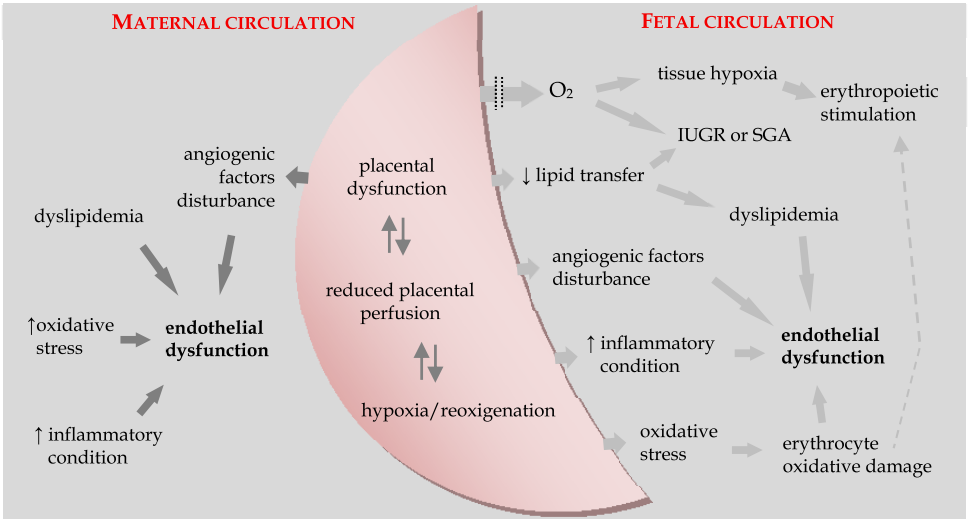

Fig. 7. Schematic of some modifications observed in maternal and cord blood. IUGR, intrauterine growth restriction; SGA, small for gestational age.

In summary, most of the changes observed in the maternal circulation in PE women are also present in the cord blood of their newborns, although these changes are less pronounced.

PE shares several similarities with atherosclerosis, such as modifications in the lipid profile, amplification of the inflammatory process and increased oxidative stress. These changes may contribute to disturbe cell activation with subsequent endothelial dysfunction. Some studies have suggested that pregnant women who developed PE have a predisposition to

develop, at long term, cardiovascular diseases. Changes in the inflammatory response and endothelial dysfunction observed in umbilical cord blood of newborns from mothers with PE, may also have an increased risk to develop cardiovascular diseases in the future.

It would be especially interesting to study these and other parameters associated with cardiovascular risk in children born from mothers who developed PE during pregnancy at different stages of its growth and also to study in women with a history of PE.

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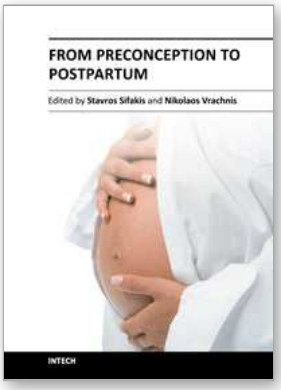

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