Placenta 34, Supplement A, Trophoblast Research, Vol. 27 (2013) S73–S78

Contents lists available at SciVerse ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Review: Preeclampsia, acute atherosis of the spiral arteries and future cardiovascular disease: Two new hypotheses

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ARTICLE INFO

Article history:
Accepted 21 November 2012

Keywords:
Preeclampsia
Cardiovascular disease
Atherosclerosis
Atherosis
Hypertension
Pregnancy
Spiral artery

ABSTRACT

Preeclampsia is a serious complication of pregnancy, potentially lethal for women and offspring. Affected women have an augmented risk of later cardiovascular disease and premature death and may have risk factors in common with older persons developing cardiovascular disease. In some cases of preeclampsia, lipid-filled foam cells accumulate in the walls of the spiral arteries of the uteroplacental circulation (acute atherosis). These lesions resemble the early stages of atherosclerosis and are thought to regress after delivery. The mechanisms that contribute to acute atherosis are largely unknown, but are related to defective vascular remodeling of the spiral arteries in the first half of pregnancy. Spiral artery lipid deposition may also occur in normal pregnancies, which suggests that it may not be confined exclusively to maladapted spiral arteries or caused by hypertension. Our first hypothesis is that there are several pathways to the development of acute atherosis, which converge at the point of excessive decidual inflammation in the final common pathway. Our second hypothesis is that acute atherosis, evolving during the short time of pregnancy, identifies a subset of women at augmented risk for atherosclerosis and later chronic arterial disease better than the diagnosis of preeclampsia itself. If confirmed, this may enable better preventive management for the affected women.

1. Introduction: Two novel hypotheses for placental acute atherosis and cardiovascular disease

Our first hypothesis is that there are several pathways to the development of acute atherosis of uteroplacental spiral arteries, and we suggest that excessive decidual inflammation represents the final common pathway. This hypothesis may explain why acute atherosis is not restricted to preeclamptic pregnancies with dysfunctional remodeling of spiral arteries in the first half of pregnancy. Our second hypothesis is that acute atherosis, also in women without preeclampsia, identifies a subset of women that are more susceptible to atherosclerotic and cardiovascular disease (CVD) later in life.

2. Many roads to preeclampsia and possibly to acute atherosis

Preeclampsia is a common and potentially life-threatening pregnancy complication, defined by the American College of Obstetricians and Gynecologists by de novo hypertension (≥140/90 mmHg) and proteinuria (≥0.3 g per 24 h) after 20 weeks of gestation [1]. Its pathogenesis remains unclear. However, placental oxidative and endoplasmic reticulum stress, excess trophoblast-derived circulating factors (including antiangiogenic proteins, trophoblast-derived micro- and nanoparticles and other pro-inflammatory products), activating autoantibodies against the AT1-receptor, and genetic variance may all be important. It is proposed that, together, these factors stimulate maternal systemic inflammatory and endothelial dysfunction, which characterize the end-stage of the disorder [2].

The associated placenta pathology and its contribution to the syndrome varies and has led to the concept of “placental” and “maternal” components of the disorder. It is proposed that “placental preeclampsia” evolves in three stages [3]: poor remodeling of uteroplacental spiral arteries and poor placentation;

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0143-4004/$ – see front matter © 2012 Published by IFPA and Elsevier Ltd.
http://dx.doi.org/10.1016/j.placenta.2012.11.022

consequent dysfunctional perfusion, dysfunctional placenta function, placental and systemic oxidative stress; and later clinical features, which may include fetal growth restriction and early-onset disease. "Maternal preeclampsia" occurs where the mother has predisposing conditions of systemic inflammation, such as diabetes mellitus, chronic hypertension, obesity, or autoimmune disorders, which make her vessels react abnormally to the stress of even a normal pregnancy. She may therefore develop the clinical signs of preeclampsia despite normal placentation and uteroplacental arterial remodeling. Clinically, preeclampsia is not easily dichotomized into placental or maternal presentations, as many cases may be a mix of both, and maternal conditions may also affect placentation. Possible synergistic interactions between maternal and placental preeclampsia have been previously presented [4]. We have argued that even a normal placenta is an inflammatory burden to the mother, which increases with advancing gestation as the placenta grows. Hence, preeclampsia is not a different state from normal pregnancy, but one where placental-induced changes are exaggerated to the point of decompensation [5]. Just as there may be diverse roads to the clinical syndrome of preeclampsia, there may be several pathways to the development of acute atherosis. These may be associated with a specific susceptibility to atherosclerotic disease later in life.

3. Spiral artery remodeling and acute atherosis

Acute atherosis occurs only in the spiral arteries, which are the end arteries of the uteroplacental circulation [5]. About 30–60 such arteries supply maternal blood to the intervillous space of the placenta. Their remodeling from their non-pregnant state to the highly dilated thin-walled vessels of pregnancy is essential for a normal pregnancy. Endovascular and interstitial invasion by extravillous trophoblast (EVT) has been identified as an essential component of this process. There is complex interplay between EVT and decidual cells, including NK cells [6], macrophages and spiral artery smooth muscle and endothelial cells. We have previously reviewed the normal and abnormal remodeling of spiral arteries, the latter associated with the placental form of preeclampsia [2]. Inadequate maternal uterine spiral artery remodeling is thought to cause a dysfunctional uteroplacental circulation with irregular blood supply, placental oxidative and endoplasmatic reticulum stress, partly due to high flow velocity into the intervillous space, which could damage the villous surface architecture [7]. The retained smooth muscle cells in the non-remodeled spiral arteries increase the risk of spontaneous vasoconstriction and intermittent perfusion of the intervillous space, generating ischemia–reperfusion injury [7]. The ensuing oxidatively stressed placenta releases several placental factors into the maternal circulation [2] that cause maternal inflammatory and endothelial stress, thereby inducing the maternal clinical signs of preeclampsia with hypertension and proteinuria [3].

Defective artery remodeling has also been seen in other conditions than preeclampsia, such as fetal growth restriction (FGR), pregnancy induced hypertension (without proteinuria) and even rarely in normal pregnancy [2].

In contrast to the well described current understanding of the various stages of normal spiral artery remodeling processes [8], the time course and sequential development of acute atherosis is less understood. Also, we do not know whether the cellular processes that lead to lipid accumulation in the spiral artery wall may differentiate between different pregnancy groups. We argue that whatever the cause of lipid accumulation in the decidual spiral arteries, the consequence may be impaired uteroplacental circulation and placental dysfunction and oxidative stress.

4. Acute atherosis and its clinical consequences

Acute atherosis was first described by Hertig in 1945 [9], and is characterized by subendothelial lipid-filled foam cells (Fig. 1), fibrinoid necrosis and leukocyte infiltration [10]. It resembles early stages of atherosclerosis, so-called type I–II lesions, as defined by the American Heart Association [11], which affect coronary and other large arteries. The foam cells include CD68-positive macrophages. A key event early in atherosclerosis is that LDL (low density lipoprotein) delivers cholesterol to the activated macrophages, which scavenge lipids. In an inflammatory milieu, the cholesterol cannot be recycled back into the circulation to the liver, where normally it is excreted in bile. The lipids are, instead, trapped in the macrophages because reverse cholesterol transport [12] is impaired in acute and chronic inflammation.

Acute atherosis usually occurs at the tips of the spiral arteries, in the decidua, where the vessels are normally fully remodeled, even in preeclampsia. It is less prominent in the myometrial part of the spiral arteries [13,14]. The lesion does not necessarily affect all spiral arteries, or the whole artery circumference, or the whole length of the artery.

Acute atherosis also occurs in the decidua parietalis [15], therefore remodeling by trophoblast does not seem to be a prerequisite. Nor does it seem that dysfunctional spiral artery remodeling in the myometrial segment is necessary to develop downstream decidual acute atherosis, as it has been seen in conditions with presumed normal remodeling [16]. Acute atherosis is thought to regress after delivery, when the decidual portions are shed. Postpartum autopsies from women that died of eclampsia, without atherosis lesions, suggest rapid resolution after delivery [15].

Acute atherosis is not present in all preeclampsia pregnancies (20–40%) and is highly dependent on patient selection and tissue collection methods [15,16]. In addition, it is not unique to preeclampsia, as it occurs in intrauterine growth restriction without preeclampsia, diabetes mellitus, systemic lupus erythematosus and antiphospholipid syndrome [2]. Even in some healthy normotensive pregnancies, evidence of spiral arterial wall lipid accumulation, demonstrated by CD68-positive foam cells, has been demonstrated [2,16].

Acute atherosis is likely to impact on intervillous blood flow [7], as the lesions significantly reduce vessel caliber, and are associated with arterial thrombi and downstream placental infarcts [17]. The linking of acute atherosis to pregnancy phenotype has been inconclusive [2], probably owing to small and heterogeneous studies, although a recent study suggests that the acute atherosis is associated with more severe forms of preeclampsia [18].

5. Several pathways to acute atherosis

Animal studies have shown that endothelial shear stress due to caliber variations may promote lipid deposition in arterial walls [19,20], and we suggest that similar mechanisms may explain why acute atherosis develops in the decidual parts of spiral arteries downstream of non-remodeled myometrial segments, because the flow through these arterial segments is predicted to be abnormally fast and at higher pressures [7]. Other local decidual factors may augment the risk for lipid deposition in the spiral artery walls, such as immunological (inflammatory) factors. In pregnancy, fetal extravillous trophoblasts are a semi-allograft, bearing paternal (foreign) HLA-C, which is known to be detected by different receptors on decidual T and NK cells. Abnormal immune interaction in the decidua between maternal and fetal cells is thought to contribute to dysfunctional placentation in preeclampsia [21,22]. We revive the suggestion [23] that such immunological mismatch