Journal of Clinical and Experimental Pathology

Benagiano, et al., J Clin Exp Pathol 2022, 12:2

Short Communication Open Access

Placental Vascular Bed Pathology: An Emerging Cause of Future Cardiovascular Events

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Received: 07-Feb-2022, Manuscript No. JCEP-22-53648; **Editor assigned:** 09-Feb-2022, PreQC No. JCEP-22-53648(PQ); **Reviewed:** 21-Feb-2021, QC No. JCEP-22-53648; **Revised:** 24-Feb-2021, Manuscript No. JCEP-22-53648(R); **Published:** 03-Mar-2021, DOI: 10.4172/2161-0681.1000405.

Citation: Benagiano M, Mancuso S, Benagiano G (2022) Placental Vascular Bed Pathology: An Emerging Cause of Future Cardiovascular Events. J Clin Exp Pathol 12: 405.

Abstract

Evidence is accumulating that hypertensive disorders of pregnancy and, specifically, preeclampsia produce long-term effects on the pregnant woman, as well as lasting consequences for the fetus.

At the root of these consequences is the phenomenon coined defective deep placentation, characterized by profound placental vascular lesions. These in turn induce long-term adverse consequences for the pregnant woman's entire arterial system. Vascular pathology in pregnancy and cardiovascular diseases may share a common etiology and may have common risk factors.

Placental growth restriction and function can also cause a decreased blood supply to the fetus, with long-lasting effects as part of the theory of a fetal origin of a number of adult diseases.

Keywords: Placental vascular bed pathology; Preeclampsia; Pregnancy hypertensive disease; Cardiovascular risk

Introduction

We have recently detailed the indirect long-term consequences of perturbing the unique hemodynamic phenomenon occurring in the pregnant uterus, consisting in a major reshaping of its spiral arteries, necessary to accommodate a massive increase in the blood supply to the uterus during pregnancy [1].

Structural changes take place in the terminal portion of spiral arteries, characterized by an invasion followed by substitution with trophoblast of the arterial intima [2]. This occurs thanks to the interaction between uterine natural killer cell receptors and the Major Histocompatibility Complex (MHC) class I molecules on trophoblast cells. Killer-like immunoglobulin receptors, that can bind to paternal HLA-C allotypes which are the only polymorphic MHC class I molecules present on the extravillous trophoblast cells, seem to be responsible of the balanced transformation of spiral arteries [3].

As recently summarized, severe Hypertensive Disease of Pregnancy (HDP) and Preeclampsia (PE) are associated with a phenomenon coined defective deep placentation where a defective or absent transformation of the myometrial segment of the uteroplacental arteries occurs [4]. Failure of the physiological transformation of spiral arteries is considered today the anatomical basis for the reduced placental perfusion that characterizes all Great Obstetrical Syndromes (GOS).

A great number of common pathogenetic factors, such as high blood pressure, inflammation, atherosis/atherosclerosis, proangiogenic/antiangiogenic factors imbalance, metabolic syndrome, oxidative stress, genetic factors and epigenetic modifications, provide striking evidence of a link between Placental Vascular Pathology (PVP) and Cardiovascular Diseases (CVDs).

In turn, the profound placental vascular lesions characteristic of GOS can induce long-term adverse consequences for the pregnant woman's entire arterial system. In addition, impaired placental function can also cause a decreased blood supply to the fetus, with long-lasting effects.

Long-Term Consequences of HDP for the Pregnant Woman

A large number of investigations have today documented the existence of an association between HDP and risk of CVDs later in life.

Thus, compared with subjects who had normal pregnancies, women with a history of HDP have an increased CVDs risk.

As stated, vascular pathology developing during pregnancy may share a common etiology and has common pathogenetic risk factors with CVDs, unmasked by the "stress" of pregnancy. A strong link between PE and CVDs has been pointed out, so that "for high-risk women, PE may be considered a first cardiovascular event that requires secondary prevention and an appropriate follow-up" [5].

Furthermore, endothelial dysfunction, generated by pregnancy-induced hypertension that persists after delivery, is an important cause

of additional risk for future adverse cardiovascular event. Indeed, the possibility that endothelial lesions may be produced as a sequela of HDP and PE should not be minimized or, even worse, ignored.

Long-Term Consequences of HDP for the Offspring

Today, a new model, based on the importance of the intrauterine environment in fetal life, provides accumulating evidence of the fetal origin of chronic adults disease.

The theory of a fetal origin developed by Barker in 1990 [6], postulates that adverse living conditions during pre-natal life and childhood increase the risk of ischemic heart disease in adulthood.

Today it seems proven that intrauterine malnutrition represents a significant risk factor for the development of chronic hypertension, diabetes, stroke and death from coronary artery disease in adults [7].

Clearly, besides conditions in utero, a number of additional variants can influence the development of hypertension, coronary and myocardial disease in later life; these include genetic predisposition, epigenetic modifications, the extent of endothelial dysfunction, and the lifestyle of the affected individual.

Possible mechanisms for these effects are chronic inflammation, permanent changes in lipid metabolism and coagulation cascade.

In our study we tried to accurately describe the pathogenesis of HDP in general and, more specifically of PE, focusing on histologically-confirmed lesions that develop in the spiral arteries of affected women. We tried to highlight how these lesions will then also affect the cardiovascular system of the subjects, over time causing serious and even fatal complications.

We showed evidence that the poorly developed placenta with its major consequence of fetal hypoxia and restricted development, may cause, as a compensatory mechanism a kind of centralization of fetal blood supply. In turn mechanisms aimed at preserving blood supply to the brain and heart at the detriment of other organs, lead to a restriction of intrauterine growth and a possible permanent damage to the nephrons, hepatocytes and Langerhans Islets.

Menopausal and postmenopausal women are particularly vulnerable to CVDs and in particular myocardial infarction, that after menopause occurs with the same prevalence as in men, because they lack the protective effect of estrogen and relaxin. Indeed, the presence of HDP and PE in the clinical history of these women represents an aggravating anamnestic element that seems to have been too often neglected both by cardiologists and gynecologists who should pursue the goal of prescribing a correct and personalized hormone replacement therapy.

Conclusion

In conclusion, there is a need to define the trajectory, not only of women with a history of PVP and HDP, but also of their offspring.

In this respect, the placenta is the only organ with a transient life of less than 9 months, characterized by rapid growth and rapid structural and functional changes, thus providing a unique model. Future research should therefore be oriented towards a better understanding of this one and only phenomenon.

More importantly, although developing within the mother, it is genetically identical to the fetus, thus representing a potential source of new fundamental information regarding the link to future CVDs risk.

In spite of the numerous markers utilized for an early identification of CVDs and to determine their severity, none of them have so far been applied for prognostic purposes to identify the presence of lesions following PVP and to monitor the extent of the risk and of its progression over the years.

Therefore, prospective longitudinal studies aimed at identifying such markers are urgently needed especially for adolescents and elderly primigravidae who experienced HDP and PE, and wish to utilize combi--ned contraceptives, but also for the consistent and continuously growing population of menopausal women.

Although biochemical molecules and biophysical markers of PE abound, information on markers for a comparative evaluation in the various groups is still lacking. The identification of well-established biomarkers will represent the best approach to the development of effective screening, risk stratification, and preventive measures.

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