Journal of Reproductive Immunology 108 (2015) 26–32

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

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

Maternal–fetal interactions, predictive markers for preeclampsia, and programming

Berthold Huppertz*

Institute of Cell Biology, Histology and Embryology, Medical University of Graz, Austria

ARTICLE INFO

Article history:
Received 25 September 2014
Received in revised form 4 November 2014
Accepted 18 November 2014

Keywords:
Preeclampsia
Biomarker
Prediction
Pregnancy
Programming

ABSTRACT

During pregnancy close interactions between the maternal system and the fetal system via the placenta exist that result in a powerful crosstalk between both individuals. Looking for predictive biomarkers in maternal blood is extremely difficult because of this crosstalk as such markers may be derived from only maternal sources, only placental sources or both. In particular, the concentrations of markers derived from both sources may vary because of the huge variety of reasons and sources. During the last decade this has misled a number of scientists and clinicians who tried to decipher the sources of markers and the impact of the placenta and/or the maternal vascular system. A few examples for predictive biomarkers are presented, the placenta-specific marker placental protein 13 (PP13) and the angiogenic marker PlGF being released from both mother and placenta. Finally, a further reason why biomarkers may not be successful in predicting all cases of preeclampsia is that different causative routes lead to the development of preeclampsia. The differences in the development of preeclampsia not only explain why markers may or may not have a predictive value, but also why some mothers and/or children may display long-term effects later in life.

1. Introduction

During pregnancy in the human, fetal cells come into direct contact with maternal cells and tissues. This close contact brings together cells of two genetically different individuals. While this type of contact is typically associated with rejection processes, during normal pregnancy there is neither harm to the mother nor rejection of the baby.

Looking at the sites of contact, it becomes obvious that contact with the maternal cells is facilitated by fetal trophoblast, which is derived from the trophectoderm of the blastocyst. The trophoblast develops into two main subtypes, villous and extravillous trophoblast. The villous trophoblast develops into the epithelial cover of all placental villi with the syncytiotrophoblast as the outermost layer in direct contact with the maternal plasma in the first trimester of pregnancy and the maternal blood during the rest of gestation. The second layer, composed of villous cytotrophoblasts, does not come into direct contact with maternal tissues. If this happens accidentally, e.g., by local damage of the covering syncytiotrophoblast, then such cells are covered by fibrin-type fibrinoid and start to secrete their own matrix-type fibrinoid, similar to extravillous trophoblasts (Kaufmann et al., 1996). Extravillous trophoblasts invade into maternal uterine tissues, crossing the decidua and finally reaching the myometrium. On their way, extravillous trophoblasts

* Correspondence to: Institute of Cell Biology, Histology and Embryology, Medical University of Graz, Harrachgasse 21/7, 8010 Graz, Austria. Tel.: +43 316 380 7604.
E-mail address: bhuppertz@medunigraz.at

http://dx.doi.org/10.1016/j.jri.2014.11.003
0165-0378/

also migrate toward decidual arteries (spiral arteries) and toward uterine glands, opening both systems toward the intervillous space of the placenta (Burton et al., 2002; Moser et al., 2010, 2011). Opening of the uterine glands enables histiotrophic nutrition during the first trimester of pregnancy, when spiral arteries are still not opened toward the placenta or plugged by endovascular trophoblast. With the onset of maternal blood flow toward the placenta at the beginning of the second trimester, the opening of the spiral arteries ensures hemotrophic nutrition of the fetus until delivery (Burton et al., 2002; Moser et al., 2010).

2. Preeclampsia

Preeclampsia remains one of the major reasons for maternal, fetal, and neonatal mortality and morbidity. Worldwide, the rate of preeclampsia is about 2–8% of all pregnancies, the higher rates are mostly present in developing countries (ACOG, 2002; WHO, 2005). Here, preeclampsia accounts for 10–15% of maternal deaths, 12% of infants born small for gestational age (SGA), and up to 25% of stillbirths and neonatal mortality rates (Duley, 2009). Although preeclampsia is a pregnancy-specific syndrome, it has long-term consequences for those women who experience preeclampsia during pregnancy. Such women are at increased risk of a variety of diseases, including chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism, and even impaired memory (Williams, 2011).

There is a multitude of pregnancy-related pathological conditions that cause morbidities and mortality of mothers and children. One of the most common syndromes, preeclampsia, is still the syndrome of hypotheses as its etiology and progress are still unclear in a number of facets. At the same time, it is common knowledge today that the placenta is essential for the development of the clinical symptoms of preeclampsia, while a fetus is not necessarily needed. Hence, in preeclampsia the normal interplay between mother and placenta (and thus the fetus) is dysregulated, finally culminating in the maternal symptoms specific for preeclampsia. While the placenta is releasing factors even during normal pregnancy, it has been shown that in most cases of preeclampsia the release of trophoblastic factors from the placenta is altered because of a dysfunctioning syncytiotrophoblast. On the other hand, the response of the mother depends on her susceptibility to factors derived from the syncytiotrophoblast. The complex interplay between factors released from the placenta and the response of the maternal vascular system finally defines whether or not a pregnant woman develops preeclampsia. Specific features of the subtypes of preeclampsia, including severity, duration of progression, time of onset, and progress to eclampsia, can be explained by the fine tuning of the interactions between the maternal and the placental systems. This very much complicates the search for the etiology of preeclampsia and poses the need to broaden the view and include the interactions among fetus, placenta, and mother, even if the origin of preeclampsia can clearly be attributed to the placenta.

3. Predictive biomarkers for preeclampsia

The hype in identifying new biomarkers to predict preeclampsia is leaving us with not a single biomarker on the market that is of any predictive value. The last decade has seen a huge number of different biomarkers coming and going, leaving only a trace in the scientific literature. Generally, a marker should only be named predictive and is only valuable if the detectable changes of this biomarker occur prior to the onset of clinical symptoms of a disease or syndrome. It would be best to focus on only those markers that display significant differences as early as possible and as specifically as possible. In the case of preeclampsia a biomarker should show such alterations as early as the first trimester of pregnancy – or even prior to pregnancy. Early prediction of preeclampsia enables the planning of an appropriate management strategy and offers close surveillance of pregnant women at risk (Cetin et al., 2011).

Besides showing significant changes as early as possible, a predictive biomarker for preeclampsia should fulfill the following criteria (Cetin et al., 2011):

The marker should be specific for the syndrome and should not show a clear influence of other syndromes, such as IUGR or diabetes.
The marker should be obtained following a non- or minimally invasive procedure, such as blood, urine or saliva.
The marker should be stable in the sample or simple protocols should be available to maintain the marker's stability.
The marker should be unaffected by changes in other components in the sample such as hemoglobin, uric acid or lipids.
The test should be accurate and sensitive and recognize only the marker of interest.
The test should be able to predict preeclampsia before clinical symptoms are evident.
The test should be specifically for preeclampsia and not interfere with other pathological conditions such as IUGR or diabetes.

Since most of the biomarkers available today are based on proteins found in the blood/plasma/serum samples of pregnant women, kits have been developed to measure even very low concentrations (up to pg/ml) in such samples. However, what is still lacking for most if not all such biomarkers are the kinetics and knowledge of the composition of these biomarkers in maternal blood. The markers may only be of maternal or only of fetal (placental) origin, or they may be derived from both individuals.

If a marker is only derived from the placenta, a direct correlation with placental development and physiology may be possible. Such factors derived from the placenta may subsequently induce the release of maternal factors, leading to alterations in their blood levels as well. Such a maternal biomarker may be used as a biomarker, without anything being known about the signaling pathways leading to such alterations. The only marker known today to be of pure placental/fetal origin is placental protein 13 (PP13 or galectin 13), which is expressed in the placenta and released from the syncytiotrophoblast into maternal blood (Huppertz et al., 2008, 2013). Recently, it has been