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REVIEW ARTICLE

Suitable application of selected biochemical and biophysical markers during the first trimester screening

Przemysław Kosiński, Dorota A. Bomba-Opoń, Robert Brawura Biskupski Samaha, Mirosław Wielgoś

1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

Correspondence to: Przemysław Kosiński
1st Department of Obstetrics and Gynecology, Medical University of Warsaw
Starynkiewicza 1/3, 02-015 Warsaw, Poland.
TEL: +22 502 14 60; FAX: +22 502 21 57; E-MAIL: pkosinski@wum.edu.pl

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Abstract

Normal trophoblast growth is one of the more important stages of early pregnancy that has a deciding factor on its later development and normal outcome. Identifying pregnant women who have a high risk of complications connected to hypertension during pregnancy is currently one of the most important tasks of perinatal medicine. Abnormal placentation is related not only to the appearance of preeclampsia, but also to many other complications, such as premature placental abruption, intrauterine fetal demise, and intrauterine growth restriction. Preeclampsia and eclampsia are one of the major causes of maternal morbidity and mortality and appear in about 5% of all pregnancies.

Clinical symptoms are a far-removed consequence of abnormal placentation. When they become visible, it is definitely too late for preventive action, and there is essentially no effective treatment. New research data suggests that a chance of prophylactic intervention might exist as early as in the first trimester of the pregnancy. One of the clinically documented possibilities is to apply low doses of acetylsalicylic acid before the 16th week of gestation. Despite the great importance of the placenta in the physiology of pregnancy, not much attention has been paid to the way it functions. This paper reviews selected biochemical and biophysical markers which are, or could be, used in clinical practice in the future.

INTRODUCTION

In this era of exceptional medical and scientific achievements, it is hard to imagine modern obstetrics without early detection of pregnancy complications resulting from abnormal placentation, identification of fetal birth defects or estimation of the risk of genetic abnormalities in the fetus. It is considered that normal trophoblast growth is one of the more important developmental stages in the early stage of the pregnancy, which determines its later course and normal outcome. The normal process of placentation mediates the remodelling of the spiral arteries. Trophoblast penetrates the decidua, causing the spiral arteries to increase in diameter and block their sensitivity to vasopressin-like substances, which consequently leads to an increased blood flow through the uterus. The diameter of spiral arteries is 4–6 times larger in comparison to their pre- pregnancy state. Formation of uteroplacental vessels ensures normal perfusion of the intervillous space. In the initial

stage of preeclampsia, the invasion of spiral arteries is limited to their interdecidual areas, excluding the part inside the uterine muscle. Also, in the case of patients who eventually develop preeclampsia, the number of spiral arteries is lower, and their diameter is reduced by half in comparison to normal pregnancies. One of the results of this is reduced uteroplacental flow (Roberts 2000). A number of data series suggest that obtaining the right previous medical history from the patient during the first visit allows the identification of those groups of patients whose risk of complications related to abnormal placentation is higher than the rest of the population. The most important risk factors in preeclampsia are considered to be: being of Afro-American race, pharmacologically treated chronic hypertension, preeclampsia in an earlier pregnancy, and pharmacologically induced ovulation. Other risk factors that lead to hypertension during pregnancy, including subsequent preeclampsia, include increased BMI, nulliparity, advanced age of the pregnant woman, or a mother or sister with eclampsia. Normal blood flow from the mother to the fetus is essential for exchanging gases, delivering nutrients and eliminating metabolic waste. That is why abnormal placentation is related not only to preeclampsia, but also to many other complications, such as premature placental abruption, intrauterine fetal demise and intrauterine growth restriction (Arroyo & Winn 2008; Salafia *et al.* 2006). Many proteins and cytokines present in the maternal blood serum have been described as being useful in anticipating preeclampsia. Many of them are direct placental products and other biochemical substances connected to its functioning, such as: pregnancy-associated plasma protein A (PAPP-A), placental protein 13 (PP13), metalloproteinases, a disintegrin and metalloprotease 12 (ADAM12), inhibin A, elements of the complement system, and soluble compounds modulating the placental angiogenesis (Masuyama *et al.* 2007; Cohen *et al.* 2012).

Identifying pregnant women with a high risk of complications related to hypertension is one of the most important tasks of perinatal medicine. Several studies suggest that there might be a chance of therapeutic intervention as early as in the first trimester. One of the clinically documented possibilities consists of the application of low doses of acetylsalicylic acid before the 16th week of gestation. A meta-analysis of 34 clinical studies (Bujold *et al.* 2010) showed that prophylactic implementation of acetylsalicylic acid led to a lower number of cases of preeclampsia (0.7% in the treated group vs. 15% in the control group) and a lower number of cases of hypertension during pregnancy (16.7% in the treated group vs. 29.7% in the control group). Therefore, it seems that implementing low doses of acetylsalicylic acid could significantly reduce the frequency of preeclampsia and hypertension in pregnant women, and would also lower maternal and neonatal mortality (Bujold & Pasquier 2011; Bujold 2011; Bujold *et al.* 2011).

Despite the importance of the placenta in the physiology of pregnancy, its structure and functioning have hitherto not received much attention. Only the introduction of new biophysical and biochemical markers that assess the functioning of the placenta in a direct or indirect way have allowed the creation of screening models for numerous complications. This paper reviews selected biophysical and biochemical markers that are, or could be, implemented in clinical practice in the future.

UTERINE ARTERIES BLOOD FLOW

One of the causes of preeclampsia is thought to be due to abnormal placental perfusion, which is demonstrated by an elevated average uterine artery pulsatility index. In order to measure the pulsatility index (PI), it is necessary to determine the maximum systolic velocity (S), the maximum diastolic velocity (D), and the average blood flow velocity (V). PI is measured according to the formula: PI=(S–D)/V. The higher the vascular resistance, the lower the maximum diastolic velocity, leading to an elevated PI. Abnormal implantation leads to abnormal transformation of the spiral arteries into the uteroplacental blood vessels and causes higher resistance in uterine arteries. Therefore, the blood flow in uterine arteries can be a useful marker in anticipating complications during pregnancy. The blood flow in uterine arteries was first described as a method for assessing the placental flow in 1983. Numerous papers confirmed clinical application of uterine arteries blood flow in the first trimester screening for preeclampsia. (Kosinski *et al.* 2014; Staboulidou *et al.* 2009; Yu *et al.* 2005) Poon *et al.* also confirmed in their work that using patient history, uterine artery pulsatility index, mean arterial pressure (MAP), and PAPP-A concentration allows for the detection of 93% of early onset preeclampsia, 36% of late onset preeclampsia, and 18% of hypertension cases in pregnancy (Poon *et al.* 2009a). In another paper from 2008 by Plasencia *et al.* which evaluated over 3,000 patients, the detection rate (DR) of early and late onset preeclampsia was 90% and 30%, respectively (Plasencia *et al.* 2008).

PAPP-A

Currently used in routine risk assessment of chromosomal abnormalities (standard evaluation of potential genetic defects), the concentration of pregnancy associated plasma protein A (PAPP-A) is also a very useful marker for screening preeclampsia. PAPP-A is a placental product, and its activity and concentration increase from week 6 of gestation until delivery. Fetuses with trisomy 21 have lower PAPP-A concentration; its average is 0.5 MoM (multiple of median). In fetuses with a normal karyotype, a lower PAPP-A concentration is related to a higher risk of preeclampsia in the second half of pregnancy (Ong *et al.* 2000). It is estimated that

in 8–23% of patients with preeclampsia in the first trimester of pregnancy, their PAPP-A concentration is below 5 percentiles, which is 0.4 MoM. It has also been found that lower PAPP-A concentration is related to an earlier onset of preeclampsia (Spencer *et al.* 2005). Poon *et al.* had similar observations and showed that PAPP-A concentration at 11^{+0} to 13^{+6} weeks of pregnancy in women with preeclampsia was significantly lower than in the control group. It was also lower in the case of early onset preeclampsia as opposed to late onset preeclampsia and pregnancy-induced hypertension. The average PAPP-A concentration in the group with early onset preeclampsia was 0.53 MoM, and 0.93 MoM for the late onset preeclampsia group. 22% of patients with early preeclampsia and 6.5% with late onset preeclampsia had PAPP-A concentration levels below 5 percentiles (Poon *et al.* 2009b). Subsequent research confirmed that the earlier the preeclampsia was diagnosed and the more severe course it had, the lower the PAPP-A concentration in the maternal blood serum between 11^{+0} to 13^{+6} weeks of gestation (Staboulidou *et al.* 2009; Odibo *et al.* 2011).

PLACENTAL GROWTH FACTOR (PLGF)

Many studies have confirmed that the placental growth factor (PlGF) is useful in screening not only genetic defects, but also preeclampsia. The placental growth factor is a vascular growth factor. Its function is related to processes connected to the normal trophoblast implantation. Many authors have confirmed that the concentration of PlGF between 11^{+0} to 13^{+6} weeks of pregnancy in the blood serum of women who developed preeclampsia was lower than in the control group, and was also lower in women with early onset preeclampsia, as opposed to late onset preeclampsia ($p<0.01$) (Akolekar *et al.* 2011; Savvidou *et al.* 2008). Introducing additional variables, such as significant obstetrical history, mean arterial pressure or uterine artery pulsatility index have significantly improved the predictive value of screening tests for preeclampsia.

SOLUBLE FMS-LIKE TYROSINE KINASE (SFLT-1)

In recent years, there have also been an increasing number of reports about using anti-angiogenic factors in screening for preeclampsia. The maternal blood serum contains a soluble fms-like tyrosine kinase, which is an antagonist of PlGF. Its role is to block the effect of placental growth factor on the target cells. It is thought that both the angiogenic and anti-angiogenic factors significantly influence the vascular resistance in maternal circulation. Existing literature confirms that sFlt-1 concentration is not only higher in patients with preeclampsia, but also that the increase in concentration of sFlt-1 is already detectable a few weeks before preeclampsia occurs. It is often increasingly claimed that the sFLT1/PlGF concentration ratio has the highest predictive importance. This ratio was indeed statistically higher in pregnancies complicated by preeclampsia, but also in the case of pregnancies with intrauterine growth restriction (IUGR). The earlier preeclampsia and/or IUGR had occurred, the higher the value of SFLT1/PlGF. It has also been noted that the median concentration of sFLT1 is almost 5 times higher in patients with preeclampsia than among patients with normal blood pressure (Maynard *et al.* 2003; Crispi *et al.* 2008).

ACTIVIN A AND INHIBIN A

These are proteins present in the blood serum of pregnant women. They control the process of blood vessel formation. The concentration of these substances was increased at 11^{+0} to 13^{+6} weeks in patients who developed preeclampsia. Some publications suggest that the predictive value of these proteins is low if they are used as individual markers. Other authors have confirmed that the difference between the concentration of inhibin A and activin A is statistically significant in patients with preeclampsia compared to the control group: inhibin A (average ± SD, respectively: 1.57 ± 0.34 MoM vs. 1.08 ± 0.43 MoM, $P < 0.001$) and the concentration of activin A (average ± SD, respectively: 1.68 ± 0.38 MoM vs. 1.06 ± 0.42 MoM, $P < 0.001$). The same authors concluded that when combined with other markers (such as PI in uterine arteries, MAP, and medical history data), the concentration of inhibin A and activin A may have a predictive value in clinical practice (Akolekar *et al.* 2011; Yu *et al.* 2011). Also, the concentration of inhibin A is significantly higher in other complications of pregnancy, such as chromosomal anomalies or threatened miscarriage.

A DISINTEGRIN AND METALLOPROTEASE-12 (ADAM12 PROTEIN)

ADAM12 is a glycoprotein of the metalloprotease domain produced by the placenta. It is implicated in the processes of cell growth and differentiation. Some papers suggest that reduced concentration of ADAM12 can be statistically significant enough to use it in predicting preeclampsia (Laigaard *et al.* 2005). However, existing data is not unambiguous, and the use of this protein in clinical practice is currently limited. The application of ADAM12 in screening for aneuploidy in the first trimester of pregnancy has also been established.

PLACENTAL PROTEIN 13 (PP-13)

PP-13 is a protein dimer synthesized by the placenta (syncytiotrophoblast) and is involved in the remodelling of the spiral arteries in the early stages of preg-

nancy. Evidence suggests that reduced concentration of PP-13 in the first trimester of pregnancy can increase the risk of preeclampsia (average 1.0 MoM in the control group vs. 0.59 MoM in the group with preeclampsia). The same researchers have also confirmed that in pregnant women with subsequent hypertension in the second half of their pregnancy, concentrations of PP-13 are significantly reduced compared to the control group (Romero *et al.* 2008). Research conducted by Nicolaides *et al.* showed that combining the concentration of PP-13 with PI in uterine arteries in the first trimester of pregnancy allows for an improvement in the detection rate of preeclampsia (Nicolaides *et al.* 2006). Combining these two markers allows for the identification of 90% of pregnant women with a high risk of preeclampsia with 6% false-positive results.

CONCLUSION

Preeclampsia is still one of the most serious causes of maternal mortality and morbidity. It is increasingly postulated that patients who develop signs of preeclampsia in early stages of pregnancy have significantly higher risks of multi-organ complications compared to patients who develop preeclampsia after 34 weeks of gestation. There are therefore two separate diseases – early onset preeclampsia and late onset preeclampsia, with different consequences and different prognoses. Early onset preeclampsia is related to abnormal maternal-placental perfusion and abnormal structure of trophoblastic villi. Patients with early onset preeclampsia have a higher risk of abnormal blood flow in uterine arteries umbilical artery and other pregnancy complications, such as HELLP syndrome (*hemolysis, elevated liver enzymes, and low platelet count*), or premature placental abruption. Increasingly often, another case is put forward, suggesting different pathomechanisms of preeclampsia – a disease that can have a placental or maternal origin. It is thought that the placental form develops earlier in pregnancy and is related to intrauterine growth restriction. In the maternal form of preeclampsia, the symptoms of preeclampsia become detectable later in pregnancy and fetal growth restriction is much less common (Zhang *et al.* 2006). Identifying patients with a high risk of developing hypertensive disorders in early pregnancy before the clinical symptoms become visible is one of the biggest challenges in modern obstetrics. Finding sensitive markers for preeclampsia will allow early treatment and for the reduction in a number of serious complications. Further research concerning more sensitive biophysical and biochemical methods is likely, which will allow assessment of the risk of developing preeclampsia. Reports of new markers increasingly appear in existing literature. Expectations are focused mainly on assessing the fetal DNA and RNA (whose concentration increases in the blood serum of pregnant women with preeclampsia) as well as on substances controlling the processes of forming blood vessels, and on agents whose production is stimulated by tissue hypoxia. One of the examples is erythropoietin (EPO), a peptide hormone produced in the kidneys and the liver. In pregnancy, erythropoietin is also produced by the placenta. Metaloproteins, vascular cell adhesion protein 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), platelet endothelial cell adhesion molecule (PECAM-1), as well as the vascular endothelial growth factor (VEGF) are examples of biochemical markers whose clinical application has been already studied. Their

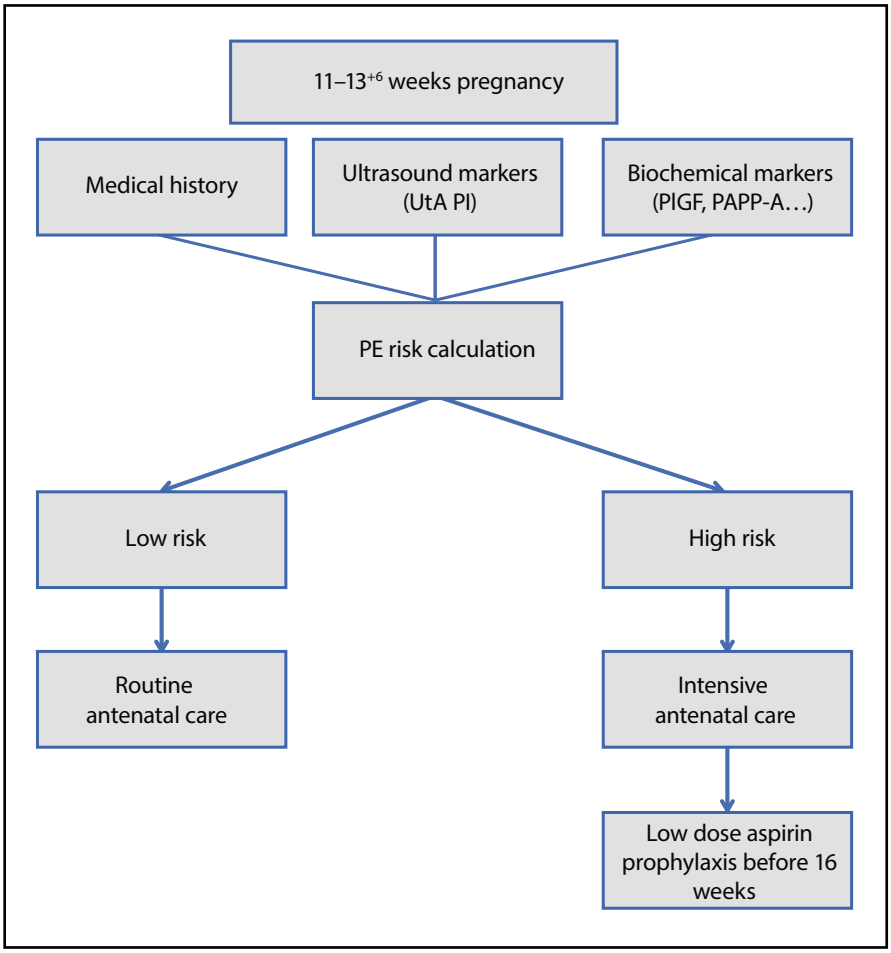

Fig. 1. First-trimester prediction of preeclampsia algorithm.

concentration in the maternal bloodstream prior to preeclampsia was increased or reduced, however, due to their low predictive value, approval of use has not been permitted into standard clinical practice. New biophysical and biochemical markers may improve detection of high risk patients, which may lead to the reduction of maternal morbidity and mortality. The best time to screen women for chromosomal disorders and pre-eclampsia is the first trimester of pregnancy (Figure 1). The practical application of the inverted pyramid of antenatal care, an idea proposed by Nicolaides, may determine valuable information on the future of the fetus and the pregnant mother during just one visit at the early stages of pregnancy (Nicolaides 2011).

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