How to identify pregnant women at risk of pre-eclampsia? — a review of the current literature

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ABSTRACT

Pre-eclampsia remains a major cause of poor perinatal outcome worldwide. As administering acetylsalicylic acid in a high risk population reduces the risk of PE, it is essential to identify women at risk of PE. Several algorithms for PE risk assessment have been developed. They include maternal factors combined with uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, placental growth factor, and serum soluble fms-like tyrosine kinase-1. Beside PE prophylaxis with acetylsalicylic acid, a proper management of women considered at a high risk of PE is essential. The sFlt-1:PlGF ratio between 20 and 34 + 6 weeks may be used to predict a short-term absence of PE or to predict the risk of PE diagnosis within 4 weeks and a significant shortening of the duration of pregnancy associated with it. The sFlt-1:PlGF ratio may be helpful in deciding about hospitalization or choosing the optimal time for corticosteroid administration in women at risk of PE. It may also help to reduce overall healthcare costs.

Key words: pre-eclampsia, prediction, PlGF, sFlt-1, risk factors

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INTRODUCTION

Hypertension affects about 6–8% of all pregnant women [1]. In Poland the estimated number of women suffering from hypertension during pregnancy is around 30,000 per year. Although pre-eclampsia (PE) affects 2–3 % of patients, it carries a great risk of maternal and perinatal mortality and morbidity [1–3]. According to the World Health Report of 2005, 12% of all maternal deaths were related to eclampsia worldwide [4]. In the USA the rate of any pre-eclampsia or mild pre-eclampsia was quite constant over the last three decades. On the other hand, over a two-fold increase in severe PE occurrence was observed during that period [5] which puts such women at the highest risk of poor perinatal outcome.

The results of the ASPRE Study were published in 2017. According to the study, administering acetylsalicylic acid (ASA) since the first trimester of pregnancy in a high-risk population reduced the occurrence of PE < 34 weeks by 80% and < 37 weeks by 63% [6]. A recently published meta-analysis by Roberge et al. included sixteen trials on ASA in PE prevention with 18,907 participants. The main finding was that ASA reduced the risk of preterm PE when it was initiated at ≤ 16 weeks of gestation at a daily dose of ≥ 100 mg [7]. Nowadays ASA is widely recommended in PE prevention [8, 9]. Therefore, it is essential do correctly identify women at risk of PE to manage them with proper care in order to minimize the risks.

MATERNAL RISK FACTORS OF PE

According to the Regulation of the Minister of Health as of the 9th of November 2015 maternal risk factors of PE are:
— a history of severe PE and/or intrauterine growth restriction,
— chronic hypertension,
— chronic renal diseases,
— pre-gravid diabetes mellitus,
— body mass index (BMI) > 30,
— autoimmune diseases (e.g. systemic lupus erythematosus),
— antiphospholipid syndrome or thrombophilia [8].

This list of risk factors is very similar to the one published by the American College of Obstetricians and Gynecologists (ACOG) in "Hypertension in Pregnancy" in 2013 [1]. ACOG

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recommends qualifying women at a high risk of PE according to the above mentioned risk factors and if they are over 40 years old, primiparous, in multiple pregnancy, after in-vitro fertilization procedure, or if their first-degree relative had a history of PE. The National Institute for Health and Care Excellence (NICE) published an overview on hypertension in pregnancy, which was last updated in 2017. According to this document two categories of risk factors of PE are distinguished. Women at a high risk of PE are those with hypertensive disease during the previous pregnancy, chronic kidney diseases, autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes or chronic hypertension. Primiparity, age > 40 years, pregnancy interval of > 10 years, pre-gravid BMI > 35, family history of PE and multiple pregnancy are considered to be moderate risk factors. The presence of two risk factors are considered equal to one high-risk factor [10].

Taking into account only the above mentioned maternal determinants results in the detection rate of PE of around 40%. Wright et al. developed a model for the prediction of PE on the basis of maternal characteristics and medical history. 120,492 women were screened for PE between 11 + 0 and 13 + 6 weeks of gestation. A total of 2,704 of them experienced PE in the further course of pregnancy (2.2%). The model including maternal characteristics and history predicted 40% of all PE cases, 48% of cases of PE requiring delivery < 37 weeks and 54% of cases of PE requiring delivery < 34 weeks of gestation [11]. This leads to a conclusion that about 50–60% of pregnant women with PE have no possibility to have the risk factors determined in the first trimester of pregnancy. Estimating the risk of PE only on the basis of maternal and family history causes an underestimation of the number of women at risk of PE during the current pregnancy.

ALGORITHMS OF PE PREDICTION

The utility of the predictive test depends on its sensitivity, specificity but also the overall prevalence of the disease. The best way to assess the utility of the test is to analyze its likelihood ratio. Positive likelihood ratio (LR) is the proportion of patients with a condition who have positive test results to those without the condition who have identical test results. As PE is a rare condition, the screening test should have a high positive LR for adequate prediction of the probability of PE with low negative LR to exclude the disorder with confidence. A useful prediction test of PE would require a positive LR > 10 for a positive test and a negative LR < 0.2 for a negative test [1].

A model of PE prediction based on maternal characteristics, biophysical and biochemical markers was published in 2016 by a group from King's College in London. Maternal factors were combined with uterine artery pulsatility index (UTPI), mean arterial pressure (MAP), serum pregnancy-associated plasma protein-A (PAPP-A), and placental growth factor (PlGF) expressed as multiples of the median values. The test was applied in almost 36,000 of pregnant women between 11 + 0 and 13 + 6 gestational weeks, 2.9% of whom subsequently developed PE. Combining all the above mentioned factors allowed to detect 82% of PE requiring delivery at < 32 weeks (95% coefficient interval (CI) 70–90), 59% of PE requiring delivery between 32 + 0 and 36+6 weeks (95% CI 52–65), 37% of PE requiring delivery between 37 + 0 and 39 + 6 weeks (95% CI 33–41) and 26% of PE requiring delivery beyond 40 weeks of gestation (95% CI 2132) at a 5% false positive rate. At false positive rate of 10% the detection rates are 89% (79–96), 71% (64–77), 54% (49–58) and 38% (32–44), respectively [12]. Different combinations of the above mentioned factors have lower detections rates. For example, taking into account maternal factors, MAP, UTPI and PAPP-A (without PlGF) allowed to detect 83% of all PE cases requiring delivery below 32 weeks of gestation (95% CI 72–91) with a 10% false positive rate [12].

Further algorithms of PE risk estimation during the second and third trimester of pregnancy have been developed. Gallo et al. presented a model of PE prediction between 19 and 24 gestational weeks. It included maternal factors, UTPI, MAP, PlGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1) [2]. sFlt-1, also known as soluble vascular endothelial growth factor (VEGF) receptor 1 binds both circulating VEGF and PlGF, thus decreasing their concentration in uteroplacental and maternal circulation [3]. In PE, circulating maternal serum levels of sFlt-1 are increased, and PlGF levels are decreased [13, 14]. sFlt-1 causes vasoconstriction and endothelial damage that may lead to PE [15]. Importantly, the increase in sFlt-1 and decrease in PlGF serum levels are ahead of the clinical symptoms of PE by 5 weeks [16]. The algorithm presented by Gallo et al. allowed to detect 52%, 47%, and 37% of PE at < 32, < 37, and ≥ 37 weeks of gestation, respectively, at a false-positive rate of 10% [2].

Similar algorithms have been developed for PE prediction at 30–34 weeks and 35–37 weeks of gestation. Predicting 98% (95% CI 88–100) of preterm-PE and 49% (95% CI 42–57) of term-PE at a false-positive rate of 5% [17] was possible with the implementation of the same factors as in the second trimester of pregnancy. The application of the algorithm to patients at 35–37 weeks of gestation predicted PE in 82% (95% CI 70–91) [18].

Basing on the above mentioned studies Fetal Medicine Foundation developed a calculator for PE risk estimations, which is available online (https://fetalmedicine.org/research/assess/preeclampsia). It allows to estimate the risk of PE using different algorithms in the first, second and third trimester of pregnancy. The questionnaire fields include all the risk factors used in the algorithm used for the specific

interval of pregnancy weeks. However, in case of the lack of any biomarkers, the calculator will use a different algorithm to calculate the risk of PE. The result is given with a comment qualifying it as low or high risk and with advice on further management.

A SHORT-TERM PREDICTION AND EXCLUSION OF PE

In 2016 the PROGNOSIS study on the predictive value of sFlt-1:PlGF ratio in women with suspected PE was published in the New England Journal of Medicine. A prospective multicenter observational research on 1,273 women between 24 and 36 + 6 weeks of gestation with suspected PE was performed. sFlt-1:PlGF ratio of 38 or lower was predictive of the absence of PE within one week (negative predictive value 99.3%, 95% CI 97.9–99.9), with 80% sensitivity (95% CI 51.9–95.7) and 78.3% specificity (95% CI 74.6–81.7). The positive predictive value of sFlt-1:PlGF ratio at or above 38 for a diagnosis of PE within 4 weeks was 36.7% (95% CI 28.4–45.7), with 66.2% sensitivity (95% CI 54.0–77.0) and 83.1% specificity (95% CI 79.4–86.3). In conclusion, the authors stated that sFlt-1:PlGF ratio of 38 or lower may be used to predict the short-term absence of PE in women in whom the syndrome is clinically suspected [19]. Moreover, sFlt-1:PlGF ratio above 38 was associated with a significantly shorter time to delivery regardless of PE status [20]. If the test was applied between 24 and 33 + 6 gestational weeks and the results were ≥ 38, the likelihood of imminent delivery was 2.9 fold greater than if the test result was < 38. In women with sFlt-1:PlGF ratio exceeding 38 the time to delivery was also 38% shorter than in women with the test ratio of 38 or below. In 250 women with sFlt-1:PlGF ratio above 38 the mean time from the test to delivery was 17 days (interquartile range 10–26 days) [20].

Recently, a meta-analysis and a systematic review of sFlt-1:PlGF ratio in the prediction of PE has been published in Hypertension by Agrawal et al. The meta-analysis consisted of 15 studies, 8 of which included pregnant women at a high risk of PE and 7 at a low risk of PE (534 cases of PE and 19,587 controls). The pooled sensitivity of sFlt-1:PlGF ratio in predicting PE was 0.80 (95% CI 0.68–0.88) and the pooled specificity was 0.92 (95% CI 0.87–0.96). The positive LR was 10.5 (6.2–18) and negative LR 0.22 (0.13–0.35), which are very similar to the expected performance of a useful prediction test for PE [3]. Therefore, if the test is positive, the probability of having PE increases to 78%, while if the test is negative, it decreases to 7%.

The presented performance of the test makes it useful in clinical practice. It allows a more accurate prediction of the onset of PE and better patient management. sFlt-1:PlGF ratio is helpful in deciding on follow-up and hospitalization of women at risk of PE and in deciding on the optimal time for corticosteroid administration in case of a high risk of preterm delivery [21]. The impact on budget by implying sFlt-1:PlGF ratio as a prediction test in women with suspected PE was analyzed in Italian population by Frusca et al. An economic model was developed to estimate the net financial impact on sFlt-1:PlGF ratio test in comparison with the current practice. A reduction in overall healthcare costs by 28% was observed. In particular, test implementation reduced 69.5% of unnecessary hospitalizations [22]. A similar cost-effectiveness study of PE testing in UK was published. The use of sFlt-1:PlGF ratio test translated into saving £344 per a pregnant woman [23]. NICE has been recommending using sFlt-1:PlGF ratio in the management of women with symptoms of PE since 2016 [24]. The test should be used to rule out PE in women with suspected PE between 20 and 34 + 6 weeks of gestation.

Nowadays further studies on biochemical markers of PE and their usefulness in algorithms of PE prediction are conducted. A new model of prediction of delivery with PE within one week in singleton pregnancies from 24 weeks to 36 + 6 weeks of gestation in patients with suspected PE has been recently developed. It included sFlt-1/PlGF ratio, NT-proBNP and the gestational week at the time of the measurement. The addition of NT-proBNP improved the short-term prediction of delivery due to PE compared to sFlt-1/PlGF ratio alone [25]. Further prospective studies on a large population are necessary to estimate which biomarkers of PE have the highest utility in PE prediction.

CONCLUSIONS

PE remains one of the most important causes of maternal and perinatal mortality and morbidity. It is well established that ASA administered at a dose of > 100 mg before 16 weeks of pregnancy reduces the risk of PE in a high risk population. Therefore, it is essential to identify women at risk of PE during the first trimester of pregnancy. Several algorithms for PE risk assessment have been developed and are available online. They include maternal factors combined with UTPI, MAP, PAPP-A, and PlGF expressed as multiples of the median values. Beside PE prophylaxis with ASA, a proper management of women considered to be at a high risk of PE is essential. sFlt-1:PlGF ratio between 20 and 34 + 6 weeks may be used to predict the short-term absence of PE in women in whom PE is clinically suspected or to predict the risk of PE diagnosis within 4 weeks and a significant shortening of duration of pregnancy associated with it. sFlt-1:PlGF ratio may be helpful in deciding about hospitalization or choosing the optimal time for corticosteroid administration in women at risk of PE. It may also help to reduce overall healthcare costs.

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Conflict of interest

Nothing to declare.

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