REVIEW PAPER / OBSTETRICS

Prediction of preeclampsia developing at term

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ABSTRACT

Preterm preeclampsia (PE), occurring at < 37 weeks' gestation, can be predicted from as early as 11-13 weeks and prevented with the use of aspirin. In contrast, term PE, which is more common than preterm-PE and it can be associated with important maternal morbidity and mortality, cannot be effectively predicted at 11-13 weeks and cannot be prevented by the prophylactic use of aspirin. This paper briefly reviews the pathogenesis of term PE and discusses strategies available for its prediction.

Key words: preeclampsia, aspirin, pravastatin, SFLT-1, PLGF

Ginekologia Polska 2018; 89, 4: 206–209

INTRODUCTION

Preeclampsia (PE) is one of the leading causes of maternal and fetal morbidity and mortality worldwide [1] and complicates about 3% of all pregnancies [2]. The pathogenesis of PE is not yet completely understood with some considering it a single disorder with a wide range of clinical manifestations [2–4] while others, as two distinct conditions [5].

Recent evidence suggests that preterm-PE, occurring at < 37 weeks' gestation, is to a great extent predictable and preventable. Effective screening for preterm-PE can be provided by a combination of maternal factors, mean arterial pressure (MAP), Doppler assessment of the uterine artery pulsatility index (UTPI) and placental growth factor (PLGF) at 11–13 weeks' gestation with detection rate (DR) of 75% at false positive rate (FPR) of 10% [2–4]. Prophylactic use of aspirin (aspirin 150 mg/day from 11–14 weeks' gestation to 36 weeks) on the high-risk group by first-trimester combined screening reduces the risk of preterm-PE by > 60% [6, 7]. In contrast, the performance of first-trimester combined screening for term-PE is poor, with DR of 45% at FPR of 10% [2] and prophylactic use of aspirin is not beneficial [6, 7].

In this article we discuss available models of prediction for term PE.

IMPORTANCE OF TERM PREECLAMPSIA

One-third of all the cases of PE occur preterm and are associated with high levels of neonatal morbidity and mortality and severe maternal complications. Two-thirds of cases are term-PE (Fig. 1) [2].

Although term PE is traditionally considered less dangerous, mainly because delivery is safe at this stage for the fetus, it is not deprived of maternal complications and, because term PE is much more common than preterm PE, most of the maternal complications that will be diagnosed in association with PE will be actually confined to this group. In the Confidential Enquiry into Maternal Deaths form the United Kingdom, 50% of all cases of maternal deaths attributable to PE were due to term PE [8]. The same point is made by a study from the United States where the authors reported 985 cases of severe maternal morbidity in association with PE developing after 34 weeks and only 289 with
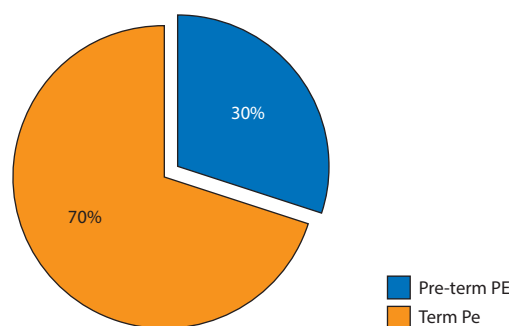
Figure 1. Incidence of preterm and term preeclampsia

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early-onset PE in a studied population of 670,120 singleton pregnancies [9]. Therefore, term-PE is not an innocuous condition; it should not be overlooked and prediction models and prevention strategies should be put forward.

PATHOGENESIS OF TERM PREECLAMPSIA

The development of PE requires both placental and maternal contributions (Fig. 2).

Preterm-PE in likely to reflect impaired placentation with failure of physiological transformation of the spiral arteries between 8 and 18 weeks of pregnancy. It is associated with fetal growth restriction, prominent placental pathology and abnormal Doppler velocimetry in the uterine arteries. By contrast, in term-PE the placental contribution seems less important, UTPI is often normal and there is usually normal fetal growth [10–13]. Rather, it seems that for term-PE, a maternal threshold for "tolerance" to the burden of pregnancy is achieved and that maternal characteristics such as being obese, having metabolic syndrome, comorbid conditions or insulin resistance are more likely to play a role [14–17].

Preterm- and term-PE, also appear to develop from different hemodynamic states. Term-PE appears to be more frequent in patients with high body mass index, increased cardiac output and relatively unchanged total vascular resistance; whereas patients with preterm-PE have lower BMI and relatively increased vascular resistance [18].

The angiogenic marker profile also seems to be different in preterm- and term-PE. Both are associated with altered serum levels of the anti-angiogenic marker soluble fms-like tyrosine kinase-1 (SFLT-1) and the pro-angiogenic PLGF, however the alterations are more pronounced in preterm- than term-PE [19]. Interestingly, for suspected PE before 35 weeks, a decrease in the maternal serum levels of PLGF has been shown to rule in women requiring delivery within 14 days. However, this test's performance falls off in women presenting after 35 weeks [20, 21].

PREDICTION OF PREECLAMPSIA DEVELOPING AT TERM

The traditional approach to screening for PE is to use a risk-scoring system based on maternal demographic characteristics and medical history (maternal factors) [22]. However, the performance of such approach, which essentially treats each risk factor as a separate screening test with additive detection rate and screen positive rate, is poor [23].

Another approach in screening for PE has been proposed by the Fetal Medicine Foundation (FMF) [2, 3] This approach, which is based on a survival time model, assumes that if the pregnancy was to continue indefinitely, all women would develop PE and whether they do so or not before a specified gestational age depends on a competition between delivery before or after development of PE. The effect of variables from maternal characteristics and history (maternal factors) and biomarkers is to modify the mean of the distribution of gestational age at delivery with PE, so that in pregnancies at low risk for PE the gestational age distribution is shifted to the right with the implication that in most pregnancies delivery will occur before the development of PE. In high-risk pregnancies the distribution is shifted to the left. An algorithm combining maternal risk factors such as age, weight, racial origin, obstetric history, family history of PE, method of conception, comorbidities as chronic hypertension, diabetes mellitus, systemic lupus erythematosus, antiphospholipid syndrome and MAP, UTPI, serum PLGF and SFLT-1 is used at different stages in pregnancy to detect those at high risk for PE and offer various interventions.

The performance of screening for term-PE by a combination of maternal factors with biomarkers (MAP, UTPI, PLGF and SFLT) at 12, 22 or 32 weeks' gestation is relatively poor with respective DR of about 45%, 45% and 65%, at FPR of 10% [2, 24, 25]. The best performance of screening for term-PE is achieved when screening is performed at 35–37 weeks, with DR of about 85% at FPR of 10% (Fig. 3) [26]. The values of MAP, UTPI and SFLT-1 are increased and serum PLGF is decreased compared to unaffected pregnancies. For all biomarkers the deviation from normal is inversely related to the gestational age at which delivery becomes necessary for maternal or fetal indications. We have therefore proposed that all women, irrespective of whether they had prior screening or not, should have assessment of risk at 35–37 weeks [27].

On the basis of the results from screening at 35–37 weeks the pregnancies can be stratified into three different management pathways (Fig. 4) [27].
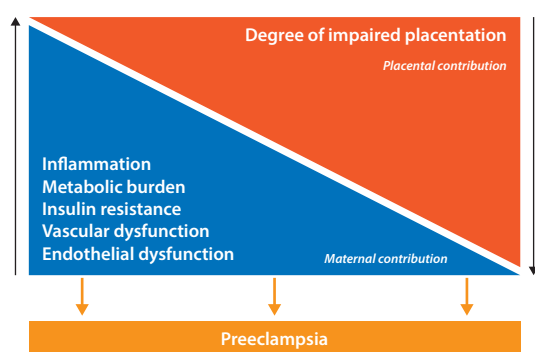
Figure 2. Preeclampsia requires both placental and maternal contributions for its development. An important degree of placental impairment would lead to manifestations of PE even in the absence of significant maternal contribution, while, in a mother with severe metabolic and vascular derangements, as with chronic hypertension, PE could develop with minimal placental contribution
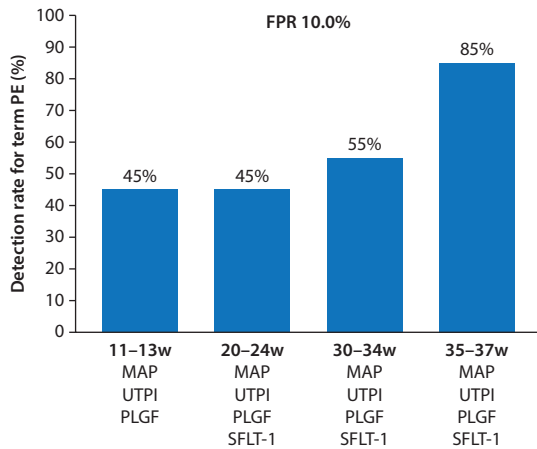
Figure 3. Detection rates in screening for term PE at 11–13, 20–24, 30––34 and 35–37 weeks using the FMF algorithm that combines maternal factors and characteristics with mean arterial pressure (MAP), doppler assessment of the uterine artery pulsatility index (UTPI), placental growth factor (PLGF) and soluble Fms-like tyrosine kinese-1 (SFLT-1)

FPR — false positive rate
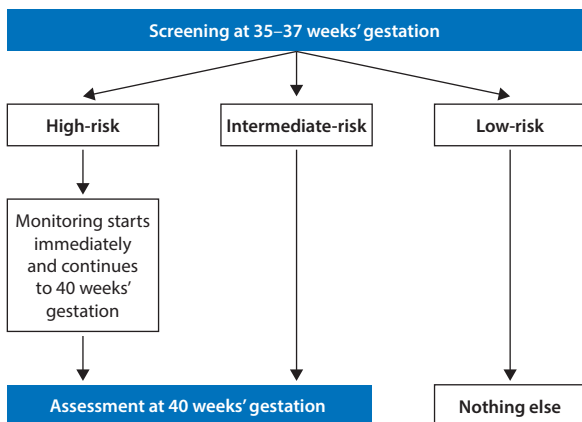
Figure 4. Stratification of pregnancies into high-, intermediate- and low-risk management groups based on the estimated risk for preeclampsia at 35–37 weeks' gestation. The high-risk group would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, the intermediate-risk group would require reassessment at 40 weeks' gestation and the low-risk group would be managed expectantly

First, a low-risk group (risk for PE of < 1 in 200) constitutes about 40% of the total and has a > 99.9% chance of not developing PE; this group can be reassured that development of PE is very unlikely and in the absence of any abnormal ultrasound findings or other obstetric indications the pregnancies can be managed expectantly awaiting for spontaneous onset of labor.

Second, a high-risk group (risk for PE at < 40 weeks of ≥ 1 in 100) constitutes about 20% of the total and contains > 90% of those that develop PE at < 40 weeks. This group can be monitored by measurement of blood pressure and urinalysis at least on a weekly basis and the women can be advised to report any of the symptoms associated with severe PE, such as visual disturbance and epigastric pain. An alternative strategy that is currently being investigated by a major multicenter randomized study is to treat these pregnancies by pravastatin with the aim of reducing the risk of developing PE.

Third, an intermediate-risk group (risk between the high- and low-risk groups above). This group, together with the high-risk group that remains undelivered by 40 weeks' gestation, constitutes about 60% of the total and contains almost all cases of PE at > 40 weeks. These pregnancies require reassessment at 40 weeks to decide the best time for delivery.

The cut-offs in risks to define the proportion of the population stratified into each of the three management groups and the protocols for such management will inevitably vary according to local preferences and health economic considerations. Future studies will examine whether the implementation of such protocols could improve perinatal outcome.

CONCLUSIONS

Term-PE is the most common form of PE and it can be associated with important maternal morbidity and mortality. The best performance of screening for term-PE is achieved by a combination of maternal factors, MAP, UTPI, PLGF and SFLT at 35–37 weeks' gestation. Using this approach, a DR of 85% can be achieved for FPR of 10%. On the basis of the results from screening the pregnancies can be stratified into three different management pathways.

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