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Actualities on prediction and prevention of preeclampsia - literature review

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Abstract

Preeclampsia is and remains an actual subject of obstetrics regarding the associated immediate high risk of morbidity and mortality for both mother and future risk for cardiovascular disease. Many different strategies to prevent preeclampsia have been studied, but none of the reported results presented a widely effectiveness, until now. Possibility of predicting preeclampsia would have a significant impact in decreasing the incidence of cases with tragic outcome related to this condition. For late-onset preeclampsia there is no prediction method at this time, in this context, the suitable approach is the diagnosis as early as possible in order of a better outcome. Low-dose aspirin (LDA) administrated in the first trimester to patients who are at increased risk for pre-eclampsia is the only drug that has proven benefits for reducing the frequency of this condition and associated adverse outcomes. In terms of prophylaxis with low molecular weight heparin in combination with LDA or as a single treatment, results are controversial, additional studies being required. We intend to summarize the latest proposals regarding the measures that can be taken to prevent maternal and fetal complications that may occur as a result of the development of preeclampsia, methods of early diagnosis and characteristics of atypical forms of preeclampsia.
Keywords: *preeclampsia, morbidity, treatment, aspirin, heparin*

Introduction

Preeclampsia continues to be an actual subject of obstetrics regarding the associated immediate high risk of morbidity and mortality for both mother and infant and future risk for cardiovascular disease. This condition is defined as a progressive multisystem pathology. The obligatory criterion is represented by hypertension occurred *de novo* in the second, third trimester or even in postpartum alongside symptoms characterizing various organs failure, such as proteinuria, liver failure or another organ dysfunction. Worldwide 10 to 15% of maternal death related to obstetric complications is associated with preeclampsia[(1)].

Hypertension overlaid to pregnancy includes the case as a high risk one and can reflect four contexts:

1. Preeclampsia defines hypertension occurred *de novo* and proteinuria or hypertension and an end organ damage with or without proteinuria after 20 weeks of gestation or postpartum to a woman with normal tension prior to pregnancy[(2)]. If for a long period of time, proteinuria was included as an obligatory criterion for the definition of preeclampsia, the American College of Obstetricians and Gynecologists in 2013[(2)] excluded this characteristic as an essential, implicitly they modified guidance specification for determining the severity of preeclampsia by excluding massive proteinuria (5g/24h), oliguria and fetal growth restriction. The course of preeclampsia can culminate with the development of grand mal seizures- eclampsia, in a neurological normal woman. Also, hemolysis, elevated liver enzymes, and low platelet P count syndrome is a severe form of preeclampsia characterized by hemolysis, elevated liver enzymes and low platelets, but actually its pathogenic link with preeclampsia or its development as an individual disorder is controversial.
2. Chronic/pre-existing hypertension. This condition is represented by the two forms of hypertension: primary and secondary hypertension, defined by a systolic value ≥140 mmHg and/or diastolic pressure ≥90 mmHg, pre-existent to pregnancy or present in early pregnancy, before 20 weeks of gestation or debuts in late postpartum period, 12 weeks after birth.
3. Preeclampsia in combination with chronic/pre-existing hypertension is a condition that reflects the existence of preeclampsia with and end organ damage or proteinuria developed after the completion of the 20 weeks of pregnancy superimposed to pre-existing arterial hypertension.
4. Gestational hypertension is defined as the occurrence of hypertension after 20 weeks of gestationin the absence of proteinuria which lasts until the twenty week postpartum. The signs and symptoms of preeclampsia have a potential to occurin context of gestational hypertension of 10 to 25%[(3)].

The prevalence of preeclampsia worldwide is estimated to be 4.6%, with significant variation depending

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on maternal age and parity[3]. Also, the prevalence is higher after the thirteen week of gestation, being 2.7%, and lower before the thirteen week of gestation, respectively 0.3%[4].

Prediction methods

Identifying as early as possible pregnancies that present a high risk for preeclampsia offer the possibility that using specific medication the complications related to this condition to be reduced.

A series of risk factors related to the potential preeclampsia development during pregnancy were described and evaluated in a series of systematic reviews of the literature[5,6].

Several risk factors of preeclampsia are described. Personal antecedents, respectively the development of preeclampsia in a prior pregnancy (RR 7.19, 95% CI 5.85-8.83) are especially correlated to severity of the symptoms. Primiparity (RR 2.91, 95% CI 1.28-6.61) increases the risk throughthe limited exposure to the paternal antigens with the lack of desensitization. Different comorbidities over existing pregnancy such as pregestational diabetes, high blood pressure ≥130/80 mmHg, antiphospholipid antibodies, body mass index (BMI) ≥26.1 and chronic kidney disease increase the risk of preeclampsia by different mechanisms (i.e. high plasma insulin levels or insulin resistance, abnormal lipid metabolism, autoimmune mechanism). Other risk factors are multiple pregnancy and advanced maternal age[7].

The listed above risk factors are divided into two categories. Thus, autoimmune disease, chronic kidney disease, history of hypertensive disease in previous pregnancy, diabetes mellitus and chronic hypertension are considered high risk factors;family history of preeclampsia, primiparity, advanced maternal age ≥40 years, interpregnancy interval >10 years, BMI ≥35 kg/m^2 are considered moderate-risk factors. In 2010, the National Institute for Health and Care Excellence (NICE)[7] implemented the guidelines for including a case in the high-risk group for developing preeclampsia. According to NICE for high risk the condition is the existence ofa high risk factor or two moderate-risk factors and in all high risk cases low-dose aspirin (LDA) should be recommended and administered[7]. Medical history is considered by the American College of Obstetricians and Gynecologists the only and the best method of screening for preeclampsia[2,8].

Regarding the screening and the prevention of preeclampsia, 11-13+6 weeks prenatal visit is crucial for identifying women with high risk for preeclampsia and initiate the treatment with LDA. Universal screening involves measurement of blood pressure on all visits throughout pregnancy[9] in order to establish the baseline blood pressure of the patient along to the evaluation in early pregnancy of the risk factors that includes the patient in the high risk class. It is estimated that medical history can predict about 30% of the cases that will develop preeclampsia during their pregnancy period[10]. In this context, a wide variety of laboratory and imaging tests have been proposed for an early detection of high risk cases for developing this condition. Besides the series of modified parameters resulted with the onset of preeclampsia, knowledge of baseline values (i.e. 24-hour urinary protein, platelet count, creatinine concentration and liver function tests) is mandatory[11].

The incidence of preeclampsia in general population is relatively low, thereby, the test that could predict the development of the disease should have high sensibility and specificity; systematic studies conducted by now concluded that a test of adequate sensibility and specificity does not exist[12]. Considering this fact, the American College of Obstetricians and Gynecologists recommendations include only the medical history, detailed without the use of laboratory and imaging screening tests[2]. However, using maternal characteristics, respectively medical and obstetrical history, mean arterial pressure, blood markers like placental growth factor (PLGF) and maternal serum pregnancy-associated plasma protein-A (PAPP-A) measured at 11-13 weeks of gestation and uterine artery pulsatility index the prediction proportion of pregnancy is significantly higher (75%)[13].

Modified parameters that according to data from both human and animal models precede the onset of clinical preeclampsia by several weeks or months are angiogenic modulators, namely soluble endoglin (sEng) truncated form of the full-length vascular endothelial growth factor (VEGF) receptor type-1 (Flt1), PLGF and VEGF. The alteration in absolute level of these angiogenic modulators have an important contribution in the pathogenesis of diffuse endothelial injury and increased capillary permeability[14,15,16]. Some authors concluded that the test performance of mentioned angiogenic factors is too poor to be recommended for screening use in early prediction of preeclampsia[17]. Instead, lower levels of PLGF were predictive of preeclampsia late in gestation[18]. Maternal blood markers alone (placental protein 13, beta human chorionic gonadotropin, PAPP-A and α-fetoprotein)[19] can predict with an insufficient strong association an adverse outcome of the pregnancy.

In 2008, in a systematic review of 74 studies which included almost 80.000 women was illustrated the use of uterine Doppler velocimetry[20]. There are two types of uterine artery waveform described that are predictive for the development of preeclampsia or other impaired placentation-related conditions: presence of diastolic notching and flow waveform ratios (i.e. high resistance or pulsatility index, and systolic/diastolic ratio).

However, uterine artery Doppler values are not recommended by some experts for use in the screening in early pregnancy due to the important false positive rate and implicitly excessive patient anxiety and health care costs[21].

Uterine artery Doppler ultrasonography, performed in the second or third trimesterhas a high predicti-

ve score. In the second trimester, a high pulsatility index has a specificity of 99% for the overall risk of preeclampsia and an elevated resistance index has a sensitivity of 80% and a specificity of 78 for the risk of severe preeclampsia when it is accompanied by uterine artery notching[21].

From the ineffective screening tests, we mention provocative biophysical tests. Namely roll-over test, angiotensin II challenge test and isometric exercise test. These tests appear to be unreliable expensive, and time-consuming.

Also, according to Cnossen and contributors[22] measurement of serum uric acid concentration before 25 weeks of gestation is not useful for predicting which women would develop preeclampsia. Data from prospective cohort studies, indicates that inherited thrombophilias (i.e. antithrombin deficiency, prothrombin gene mutation, factor V Leiden mutation and protein C or S deficiency) are not associated with preeclampsia, but the obtained results are controversial[21].

Antiphospholipid antibody syndrome is associated with the development of severe early preeclampsia, but screening for antiphospholipid antibodies in general population is not useful.

The Fetal Medicine Foundation (FMF) uses Bayes' theorem including a various combination of biophysical and biochemical measurements (mean arterial pressure, uterine artery pulsatility index, PAPP-A and PLGF, for estimating the risk of each case of developing preeclampsia during pregnancy[23] in the first trimester. N. O'Gorman et al.[24] examines in his study the performance of screening based on NICE and American College of Obstetricians and Gynecologists recommendations along to the method proposed by FMF. The main finding of this study was that the results obtained using the FMF algorithm was far superior to those obtained using the NICE and ACOG recommendations. FMF implemented a software, freely available with which the risk of preeclampsia can be easily assessed and an eventual delivery at a specific gestation can be established.

Prevention methods

Placental dysfunction is the key mechanism of preeclampsia. Decreased maternal blood supply due to altered vascular uterine remodeling result in placental hypoxia and oxidative stress and implicitly generalized dysfunction of the villous trophoblast. In the context of serum releasing of free radicals, oxidized lipids, cytokines and sFlt-1, generalized endothelial dysfunction is developed. The result of triggering these changes and biochemical reactions is the reversal of the platelet activator and vasoconstrictor and endothelial prostacyclin (i.e. platelet inhibitor and vasodilator) report[25].

To prevent the development of preeclampsia and implicitly its correlated complications, administration of LDA for high risk cases is suggested. Aspirin decrease apoptosis decreasing cell aggregation and fusion, lowers the production of specific cytokines improving defective trophoblast syncytialization with no effect on trophoblastic invasion[26,27]. LDA is safe in pregnancy, being the most adequate strategy in these cases. Next, we will address the main methods described for preventing and treating preeclampsia.

1. Rest. According to a Cochrane review[28] rest at home in addition to nutritional supplementation had a significant impact on the reduction of gestational hypertension and preeclampsia, but due to the small group of patients studied, these findingswere considered imprecise. In this context, advise to rest at home is not recommended as an intervention for primary prevention of preeclampsia, but different levels of rest should be recommended according to the situation.

2. Dietary salt restriction. A healthy diet should be promoted in general population including pregnant women. Considering the Cochrane systematic review[29] during pregnancy restriction in dietary salt intake does not prevent the development of preeclampsia and its complications.

3. Calcium supplementation. A large Cochrane systematic review[30] within which the effects of daily supplementation with 1 g of calcium were analyzed, concluded that calcium supplementation has reduced the risk for preeclampsia by more than half compared with placebo. A highest reduction of the risk was observed in the high-risk group, thereby, calcium supplementation (1.5-2 g/day) should be recommended for preeclampsia prevention especially in women with low dietary calcium intake and high risk. Still in the study phase is the impact of Vitamin D deficiency and respectively supplementation throughout pregnancy period in preventing preeclampsia. A known fact is however, that when vitamin D and calcium are combined, the risk of preterm birth is increases[31].

4. LDA therapy administered in early pregnancy is the key to a successful result in high-risk pregnancies. Regarding the fact that the pathophysiologic features of preeclampsia develop before the sixteenth week of pregnancy, the use of LDA after this gestational age of gestation does not prevent the development of this condition[32]. The recommendation on the initiation of the treatment and the adequate dose differ, but a well establish fact is that the discontinuation of aspirin is mandatory 5 to 10 days before expected delivery[33].

The American College of Chest Physicians guidelines for management of venous thromboembolism, thrombophilia, and pregnancy[34] recommended the administration of LDA in women with high risk of preeclampsia. The US Preventive Services Task Force recommendations includes administration of 81 mg/day LDA in women with high risk for preeclampsia (i.e. with at least 1 major risk factor present) initiated between the twelfth and the twenty-eighth week of pregnancy[35]. The American College of Obstetricians and Gynecologists recommendations correspond with those given by the US Preventive Services Task Force. The NICE guidelines include the use of 75 mg of aspirin for women with at least one major risk factor or at least

two moderate risk factors for preeclampsia present with a higher dose-modifying margin (75 to 162 mg/day) [7]. The Society of Obstetricians and Gynecologists of Canada recommends LDA for all the cases with high risk for preeclampsia[36].

Regarding the results obtained by the small and large trials, there is a discrepancy. According to the small study's conclusions, LDA had an efficient impact on the prevention of preeclampsia, leading to an absolute decrease in thromboxane production[37]. However, large trials conclusions showed an absence of the preventive effect of LDA in both high and moderate risk women for preeclampsia. The largest study, The Collaborative Low-dose Aspirin Study in Pregnancy[38] that include 9364 high risk for preeclampsia cases showed no benefit of administration of 60 mg aspirin at 12 to 32 weeks of gestation for preventing this condition.

Though modest, according to some results, LDA therapy for prevention of preeclampsia is sustained by meta-analyses due to the fact that a small decrease in the incidence of preeclampsia is always present under this treatment, even if this decrease is not always statistically significant[39]. A remark on the controversial results is the difference in the initiation time and administered dose in the presented studies.

A significant study, with the results recently published is Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial[40]. Authors examined the prophylactic effect of 150 mg aspirin administered from 11-14 to 36 weeks 'gestation in selected cases of high risk for preterm preeclampsia. This trial that included 26670 screened women and 1760 recruited to the randomized controlled trial, concluded that "Aspirin reduces with 82% the risk of early preeclampsia and with 62% the risk of preterm preeclampsia but not term preeclampsia, and only when it is initiated at ≤16 weeks of gestation and at a daily evening dose of ≥100 mg"[40].

5. Low molecular weight heparin (LMWH). There are limited data that support the use of LMWH as a prophylaxis method for women with previous preterm preeclampsia and poor fetal outcome. However, this anticoagulation therapy is relatively common offered. Most of recommendations have a case-by-case basis carefully considering the possible risks and benefits of the treatment. Another study published a meta-analysis on LMWH and recurrent placenta-mediated pregnancy complications[41]. The authors used data from eight randomized trials regarding the effects of LMWH use in women with antecedents of placenta-mediated complications. The results that was obtained included no significant decrease of the tardive severe or early preeclampsia, fetuses with intrauterine growth restriction, abruptio placentae and incidence of pregnancies loss aged over twenty weeks. It is worth mentioning the results obtained by Elmahashi et al.[42], namely, the superior effect of the use of LMWH in combination with LDA on miscarriages and on achieving higher rates of live births.

The mechanism by which low molecular heparin improves the pregnancy outcome consist in the binding to phospholipids and in this context, protecting the trophoblast phospholipids, encouraging a higher implantation success in early pregnancy. As mentioned, most available data does not support prophylactic anticoagulation to prevent preeclampsia, implicitly the association between thrombophilia and placental related conditions[43]. Two significant trials FRUIT[44,45] and TIPPS aimed to analyze the impact of LMWH plus aspirin or aspirin alone treatment in women with an inherited thrombophilia and medical history of uteroplacental insufficiency. Both trials concluded that LMWH does have no impact on the incidence of all recurrent hypertensive disorders specific for pregnancy irrespective of gestational age. Additional study on this matter are required due to the fact that there are many differences in LMWH protocol regarding the initiation of the therapy, the adequate dosage, the duration of treatment and also the randomization of the cases depending on the appropriate treatment[45].

Conclusions

By summarizing the latest data on prediction and prevention of preeclampsia we tried to highlight the need to continue the study of various preventive methods and the related complications. Our goal is to initiate in the near future a project for prevention of placenta-mediated condition in high risk patients for developing preeclampsia and to analyze comparatively the effect of LDA, LMWH and LDA plus LMWH in patients predisposed to develop this pathology. ■

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