REVIEW ARTICLE

Prediction of Preeclampsia

Mayumi Tokunaka[1], Minako Goto[2], Hiroko Takita[3], Mizue Saito[4], Shoko Hamada[5], Ryu Matsuoka[6], Akihiko Sekizawa[7]

Abstract

Preeclampsia (PE) remains one of the leading causes of perinatal morbidity and mortality. Several guidelines recommend assessing the risk of PE based on maternal risk factors. A combination of maternal risk factors such as maternal demographic characteristics, medical history, and biomarkers such as maternal arterial blood pressure, uterine artery Doppler pulsatility index, and maternal serum biochemical markers (placental growth factor and pregnancy-associated plasma protein-A) is considered the best predictor for preterm PE, but not for term PE. The combined screening was superior to screening for maternal risk factors only in terms of predictive ability for preterm PE. According to the ASpirin for evidence-based PREeclampsia prevention (ASPRE) trial, when low-dose (150 mg/day) aspirin was administered to high-risk women from 11 to 14 weeks to 36 weeks of gestation, preterm PE reduced by 62%. Low-dose aspirin started before 16 weeks of gestation (>100 mg/day) reduced the risk of preterm PE. To prevent PE occurrence, it is crucial to assess the risk of PE in early pregnancy.

Keywords: Aspirin, Combined risk assessment, Literature review, Placental growth factor, Preeclampsia, Pregnancy-associated plasma protein-A, Uterine artery pulsatility index.

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Introduction

Preeclampsia (PE) presents in 2–8% of pregnant women and remains one of the leading causes of perinatal morbidity and mortality.[1–3] Over 500,000 PE-related fetal and neonatal deaths and >70,000 PE-related maternal deaths are reported each year.[4] Early-onset PE (with delivery before 34 weeks of gestation), in particular, is related to an increased risk of maternal and perinatal complications. In cases of early-onset PE and preterm PE (with delivery before 37 weeks of gestation), the pros and cons of continuing pregnancy to avoid preterm birth must be assessed.[5]

Current guidelines recommend prescriptions of low-dose aspirin for high-risk pregnant women to prevent PE. Early implementation of the steps necessary to decrease the prevalence of PE requires effective prediction in early pregnancy to identify women with a high risk of developing PE. Preeclampsia screening with biomarkers has been reported recently for this purpose; multi-marker PE screening in the first trimester is recommended by the International Federation of Gynecology and Obstetrics (FIGO).[5] In this follow-up review, we summarize the literature on PE prediction in the first trimester by using maternal risk factors such as maternal demographic characteristics with a medical history and a multi-marker screening with maternal risk factors and biomarkers including maternal blood pressure, uterine artery Doppler pulsatility index (PI), and placental growth factor (PlGF).

Definitions of PE

Preeclampsia is defined as a disorder characterized by hypertension and proteinuria that develops during pregnancy.[6] The definition assigned by the International Society for the Study of Hypertension in Pregnancy (ISSHP) is currently used internationally. According to the ISSHP, gestational hypertension is defined as systolic blood pressure (sBP) of ≥140 mm Hg and/or diastolic blood pressure (dBP) of ≥90 mm Hg.[4] Moreover, PE is defined as gestational hypertension after 20 weeks of gestation with one or more newly developed conditions such as proteinuria, other maternal organ dysfunctions, or placental insufficiency (Table 1).[4] Proteinuria is not mandatory to diagnose PE.

Preeclampsia is subclassified into early-onset, late-onset, preterm, and term PE. Early-onset PE is PE occurring before 34 weeks of gestation, whereas late-onset PE is PE occurring from 34 weeks of gestation onward. Preterm PE is PE occurring before 37 weeks of gestation, whereas term PE is PE occurring from 37 weeks of gestation.

Maternal Factors: Maternal Characteristics and Medical History

Maternal risk factors, including several demographic characteristics and previous medical history, are associated with PE development. Screening for PE onset by maternal risk factors is recommended by several institutes: the ISSHP,[4] American College of Obstetricians and Gynecologists (ACOG),[7] National Institute for Health and Care Excellence (NICE),[8] and World Health Organization[9] (Table 2). In 2019, the FIGO recommended recording the following maternal factors: maternal age, weight, height, ethnicity, obstetric history (nulliparous, parous with prior PE, gestational age of previous pregnancy, and birth weight of previous pregnancy),

[1–7]Department of Obstetrics and Gynecology, Showa University School of Medicine, Hatanodai, Shinagawa-ku, Tokyo, Japan

Corresponding Author: Mayumi Tokunaka, Department of Obstetrics and Gynecology, Showa University School of Medicine, Hatanodai, Shinagawa-ku, Tokyo, Japan, Phone: +81-(0)3-3784-8551, e-mail: mtokunaka@med.showa-u.ac.jp

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Table 1: Definition of hypertensive disorders provided by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[4]

Gestational hypertension
• Systolic blood pressure (sBP) ≥140 mm Hg and/or diastolic blood pressure (dBP) at ≥90 mm Hg
PE
• Gestational hypertension with one or more of the following new-onset conditions at or after 20 weeks of gestation
• Proteinuria (urinary protein ≥300 mg/day, protein/creatinine ratio 0.3 mg/dL)
• Other maternal organ dysfunction
• Acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL)
• Liver involvement (elevated transaminases, e.g., ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
• Neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
• Hematological complications (thrombocytopenia—platelet count <150,000/µL, DIC, hemolysis)
• Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)
PE superimposed on chronic hypertension
• Chronic essential hypertension developed any of the above maternal organ dysfunctions consistent with PE
• New-onset proteinuria in the setting of a rise in blood pressure in the absence of preexisting proteinuria

interpregnancy interval, method of conception, smoking habit, family history of PE, history of chronic hypertension, type 1 or type 2 diabetes mellitus, and autoimmune disease.[5]

In 2013 in the USA, the ACOG recommended prescribing low-dose aspirin daily from the late first trimester for pregnant women who had previous early-onset PE and preterm delivery before 34 weeks of gestation or for pregnant women who had more than one previous PE experience.[10] In 2018, the ACOG updated the target recommendation: low-dose aspirin should be prescribed for women who have one or more high-risk factors (a history of PE, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, and/or autoimmune disease) or more than one moderate-risk factors [primiparous, body mass index (BMI) >30 kg/m^2, family history of PE, age ≥35 years, certain sociodemographic characteristics, and various personal history factors].[7] In the UK, the NICE promoted the prescription of low-dose aspirin to pregnant women with any high-risk factors (parous with hypertensive disease, chronic hypertension, chronic renal disease, autoimmune disease, and type 1 or type 2 diabetes) or any two moderate-risk factors (nulliparity, age ≥40 years, interpregnancy interval >10 years, BMI ≥35 kg/m^2, family history of PE, and multifetal pregnancy).[8]

Thus, several guidelines internationally recommend prescribing low-dose aspirin to women who meet the criteria of the presence of certain risk factors. Identifying women whose risks for PE are high based on maternal risk factors may be useful; however, these factors do not predict PE with sufficient accuracy. In a screening conducted according to the NICE guidelines, the detection rate for preterm PE was 39%, and that for term PE was 34%, with a 10.3% false-positive rate.[11] In contrast, while screening according to the ACOG recommendations of 2013 for prescribing aspirin, the detection rate for preterm PE was 5% and that for term PE was 2%, with a 0.2% false-positive rate.[11]

Biomarkers of Prediction for PE

An alternative risk assessment for PE involves combining maternal risk factors and biomarkers: maternal blood pressure, uterine artery Doppler PI, and serum biochemical markers. Each biomarker is described below.

Mean Arterial Pressure

Mean arterial pressure should be taken to assess PE risk. To measure blood pressure (BP) accurately, validated automated devices (http://www.dableducational.org/sphygmomanometers/devices_1_clinical.html#ClinTable) should be used. The three most commonly used protocols for measuring BP are the British Hypertension Society Protocol, Association for the Advancement of Medical Instrumentation Standard, and International Protocol of the European Society of Hypertension.[12–17]

When BP is measured, pregnant women must be in a sitting position with their arms at heart level. Depending on the circumference of the mid-arm, an adult cuff of an appropriate size (small <22 cm, normal 22–32 cm, or large 33–42 cm) should be selected. After 5 minutes of rest, the first set of BP is measured on both arms at the same time, and following a 1-minute interval, the second set of BP is measured again on both arms. Thus, a total of four sets of sBP and dBP values are obtained.[5,18] Mean arterial pressure is used for prediction because it has been reported to be a better predictor of PE than sBP and dBP.[19] Mean arterial pressure is defined as (dBP + 1/3 × [sBP–dBP]).[19] When all sBP and dBP values have been entered into the risk calculator, an average of the four sets of measurements is calculated automatically as the final MAP measurement.[5]

In a prospective cohort study of 4,749 women, MAP in the first trimester was found to predict 34% of term PE cases, 48% of preterm PE cases, and 60% of early-onset PE cases, with a 10% false-positive rate.[20]

Uterine Artery Pulsatility Index (UTPI)

Uterine artery resistance of the spiral arteries decreases significantly as pregnancy progresses.[5] Impaired placentation with abnormal resistance in placental vessels is associated with PE.[21] In preterm PE cases, increased uterine artery resistance is apparent from early pregnancy, which may be attributed to impaired trophoblastic infiltration into the maternal spiral arteries.[22] Incomplete deformation of the spiral artery can be quantified by measuring the resistance or impedance of the uterine artery with Doppler assessment.[23] The systolic/diastolic ratio, resistance index, and PI are three famous indicators that can describe the waveform of arterial flow-velocity. Pulsatility index is used most frequently because the calculation of PI includes the mean of all maximum velocities throughout the cardiac cycle. Additionally, PI is more stable than other indices and does not reach infinity even with absent or reversed diastolic values.[24]

Either transabdominal or transvaginal ultrasound examination can be chosen depending on local preferences and resources to perform Doppler assessment of the uterine arteries during the first trimester.[23] To assess the uterine arteries transabdominally,

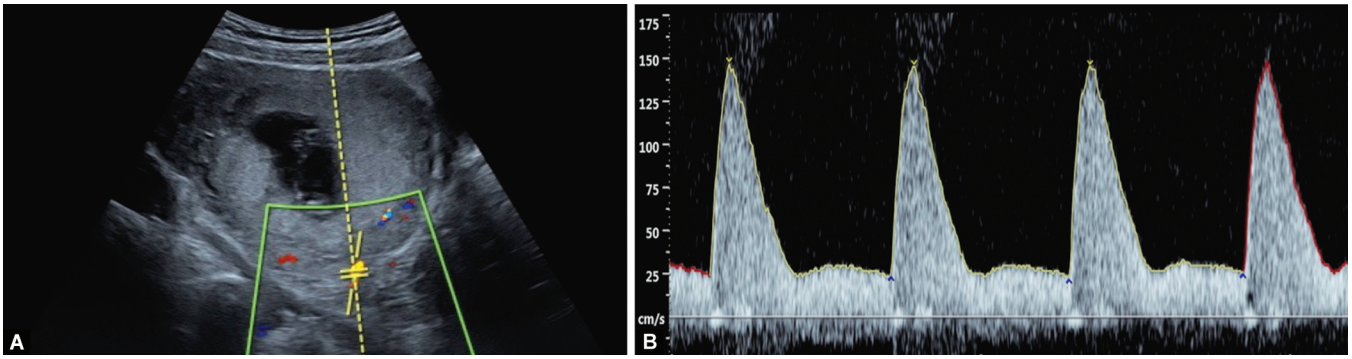
Table 2: Maternal factors for preeclampsia (PE) and indications for aspirin in guidelines

	ISSHP 2018[4]	*ACOG 2018*[7] *(USA)*	*NICE 2019*[8] *(UK)*	*WHO 2011*[9]
High-risk maternal factors	• Prior PE • Chronic hypertension • Multiple gestation • Pregestational diabetes • BMI >30 kg/m^2 • APS/SLE • ART	• History of PE • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • APS/SLE	• Previous hypertensive disease • Chronic kidney disease • APS/SLE • Type 1 or 2 diabetes • Chronic hypertension	• Previous PE • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy
Moderate risk maternal factors	• Advanced maternal age • Family history of PE • Short duration of sexual relationship (<6 months) before pregnancy • Primiparity • Chronic kidney disease • Connective tissue disease	• Nulliparity • BMI ≥30 kg/m^2 • Family history of PE • Age ≥35 years old • African American race • Low socioeconomic status • >10 years pregnancy interval • Previous adverse pregnancy outcome • Low birthweight or small for gestational age	• First pregnancy • Age ≥40 years • Pregnancy internal of ≥10 years • BMI ≥35 kg/m^2 • Family history of PE • Multifetal pregnancy	
Indications for aspirin	• Prior PE • Chronic hypertension • Chronic renal disease • Pregestational diabetes • BMI >30 kg/m^2 • APS • ART • Multiple pregnancy	• One or more high-risk factors • Two or more moderate risk factors	• One or more high-risk factors • Two or more moderate risk factors	• Previous PE • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy
Dose and timing of aspirin	• 100–150 mg/day (75–162 mg/day) • Start before 16 weeks (at least before 20 weeks)	• 81 mg/day • Start before 16 weeks (between 12 and 28 weeks) • Continue until delivery	• 75–150 mg/day • Start from 12 weeks • Continue until delivery	• 75 mg/day • Start before 20 weeks (as early as 12 weeks if possible)

BMI, body mass index; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; ART, assisted reproduction therapies

a midsagittal plane of the uterus, cervix, and cervical canal is identified.[23] When the probe is gently tilted to the side using color Doppler, the uterine arteries are recognized based on the high-velocity blood flow lateral to the cervix.[23] The sampling gate of the pulsed-wave Doppler should be narrow (about 2 mm) and should be placed on the ascending branch of the uterine artery as close to the internal cervical os as possible, and the insonation angle should be <30°.[23,25] To confirm that the artery is the uterine artery, the peak systolic velocity should exceed 60 cm/second.[23] The UTPI can be measured when three or more identical waveforms are obtained (Fig. 1).[23]

With the transvaginal approach, the patient should be in the lithotomy position after urinary bladder emptying.[23] To assess the uterine artery, after a sagittal plane of the cervix is confirmed, the transvaginal probe is tilted laterally until obtaining the paracervical vascular plexus.[23] The uterine artery can be identified at the level of the internal cervical os.[23] Measurements are taken with an insonation angle <30°.[23]



Figs 1A and B: (A) Ascending branch of the uterine artery was identified transabdominally with color Doppler; (B) Waveforms from the uterine artery are obtained in the first trimester. When PI is measured, at least three identical waveforms are recorded

According to a previous meta-analysis of 38,611 women, abnormal UTPI in the first trimester was detected in 47.8% of women who developed early PE.[21] Additionally, based on a meta-analysis of 37,971 women, uterine artery Doppler screening in the first trimester detected 26.4% of women who developed PE at any gestational age.[21]

Placental Growth Factor

Placental growth factor (PlGF) is a vascular endothelial growth factor (VEGF) expressed in the placenta.[26] Placental growth factor is involved in promoting the improvement and maturation of the placental vascular system.[26] Placental growth factor binds to VEGF receptor-1 or fms-related tyrosine kinase-1 and its soluble variant, soluble fms-like tyrosine kinase-1 (sFLT-1), which increases during pregnancy.[5,26] In the early stages of pregnancy, PlGF levels are lower in pregnant women who will develop PE than in those who will not; however, sFLT-1 levels were not different between these groups, signifying that PlGF expression in the placenta is reduced in women with a risk of PE.[26] Placental growth factor expression is hypothesized to be suppressed by persistent placental hypoxia arising from underdeveloped uteroplacental circulation.[26]

Low PlGF concentrations in early pregnancy are associated with an increased risk of developing PE, especially early-onset PE.[27] A systematic review and meta-analysis demonstrated that maternal PlGF concentrations alone could detect 40% of PE cases with a 10% false-positive rate, and they could detect 56% of early-onset PE cases with a 9% false-positive rate.[28] Placental growth factor is more predictive of PE than other biomarkers.[28]

Pregnancy-associated Plasma Protein-A

Pregnancy-associated plasma protein-A (PAPP-A) is an insulin-like growth factor-binding protein-4 protease.[29] Pregnancy-associated plasma protein-A is already an established biomarker for the screening purposes of trisomies 21, 18, and 13 in the first trimester. Pregnancy-associated plasma protein-A is thought to fulfill a significant role in the trophoblastic invasion of the decidua.[30] Low PAPP-A levels are related to insufficient trophoblastic invasion during the first trimester, which is involved in the development of PE.[30]

Low PAPP-A levels, i.e., less than the 5th percentile, have been reported to be associated with PE; however, the sensitivity was 7.9% with a false-positive rate of 5.2% (positive-predictive value, 3.5%; negative-predictive value, 97.8%).[30] A systematic review and meta-analysis has shown that maternal PAPP-A <0.4 multiples of the median (MoM) can detect PE with 16% sensitivity and 93% specificity.[28] The predictive value for early PE (sensitivity, 39%; specificity, 87%) was generally better than that for late PE (sensitivity, 29%; specificity, 82%).[28] Although low PAPP-A levels are associated with PE, PAPP-A alone is not sufficient to predict PE.

Combined Risk Assessment for PE

Combined risk assessment for PE involves assessing individual risks by using both maternal risk factors (medical history and characteristics) and biomarkers (MAP, UTPI, and PlGF, with or without PAPP-A). This was shown to be a useful approach for reducing preterm PE with low-dose aspirin. Using an individual biomarker modified to MoM, a patient's individual risk for preterm PE can be assessed with the Bayes-based method. On the website https://fetalmedicine.org/research/assess/preeclampsia/first-trimester, the risk calculator for PE is accessible free of charge. Additionally, the calculator can be used in medical software. When a woman's calculated risk is ≥1 in 100, she is categorized as high risk for PE.

A previous study sought to develop an algorithm model for predicting PE at 11–13 weeks of gestation. The study screened 58,884 singleton pregnancies, including 1,426 PE cases.[31] Screening based on the maternal characteristics, MAP, UTPI, PlGF, and PAPP-A detected 96% of early-onset PE cases, 77% of preterm PE cases, and 54% of all PE cases at a fixed false-positive rate of 10%.[31] Moreover, screening based on the maternal characteristics, MAP, UTPI, and PlGF without PAPP-A detected 96% of early-onset PE cases, 77% of preterm PE cases, and 53% of all PE cases at a fixed false-positive rate of 10%.[31]

In a prospective multicenter study, 35,948 singleton pregnancies, including 1,058 PE pregnancies, were screened.[32] Combined screening with maternal characteristics, MAP, UTPI, PlGF, and PAPP-A detected 75% of preterm PE cases and 48% of term PE cases at a false-positive rate of 10%, and combined screening with maternal characteristics, MAP, UTPI, and PlGF without PAPP-A detected 75% of preterm PE cases and 47% of term PE cases at a false-positive rate of 10%.[32]

A previous study analyzed data from three prospective non-intervention screening studies in 61,174 singleton pregnancies, including 1,770 PE cases, at 11–13 weeks of gestation.[33] While screening used a 1 in 100 risk cutoff based on maternal characteristics, MAP, UTPI, and PlGF, the screen-positive rate was about 15% and the detection rates for PE at <32 weeks, preterm PE, and term PE were 94, 80, and 51%, respectively.[33] When PAPP-A was added as a predictor, the screen-positive rate was about 15%, and the detection rates for PE at <32 weeks, preterm PE, and term PE were

94, 81, and 51%, respectively.[33] The detection rate of these three studies was compared with those detected by screening using the NICE and ACOG guidelines. The NICE guideline considered high-risk women as those with any high-risk factors (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, or autoimmune disease) or any two moderate-risk factors (nulliparity, age ≥40 years, BMI ≥35 kg/m^2, family history of PE, or interpregnancy interval >10 years).[8] The 2013 ACOG guideline considered high-risk women as those who had any of the following risk factors: PE in a previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age >40 years, BMI ≥30 kg/m^2, family history of PE, or conception with *in vitro* fertilization.[10] In their 61,174 investigated pregnancies, the screen-positive rate according to the NICE guideline was 11.5%, and the NICE screen-positive group detected 42% of preterm PE cases and 32% of term PE cases.[33] The screen-positive rate using the ACOG guidelines was 66.1%, and the ACOG screen-positive group detected 89% of preterm PE cases and 90% of term PE cases.[33]

In another prospective multicenter study with 8,775 singleton pregnancies, of which 239 cases developed PE, the combined algorithm for predicting PE was compared with screening using the NICE and ACOG guidelines.[11] In screening based on maternal factors, MAP, UTPI, and PlGF, the detection rates for preterm PE and term PE were 75 and 43%, respectively, with a false-positive rate of 10%.[11] In screening using the NICE guidelines, the detection rates for preterm PE and term PE were 39 and 34%, respectively, with a 10.3% false-positive rate.[11] Screening using the 2013 ACOG recommendations indicated detection rates for preterm PE and term PE of 90 and 89%, respectively, with a 64.2% false-positive rate.[11] Screening using the 2013 ACOG recommendations for prescribing aspirin, which considered women with previous early-onset PE and preterm delivery before 34 weeks or with more than one previous PE pregnancy as high risk, the detection rates for preterm PE and term PE were 5 and 2%, respectively, with a 0.2% false-positive rate.[11]

The combined screening algorithm using the maternal factors, MAP, UTPI, and PlGF was the best predictor of preterm PE, however, not of term PE.[5] Combined screening was a more preferable predicting method than the methods using maternal factors recommended by the NICE and ACOG.[5,11,33] Pregnancy-associated plasma protein-A is a useful biomarker when PlGF or UTPI measurements are not attainable; however, PAPP-A cannot provide significant improvement in the prediction if PlGF is already included.[5,33] If it is difficult to measure the biochemical markers or UTPI, combined risk assessment using maternal factors and MAP might be better than using maternal factors only.[5]

Prevention of PE: Low-dose Aspirin

In 1979, Crandon and Isherwood reported that patients who took aspirin for any reason were less likely to develop PE than patients who did not take aspirin.[34] In the same year, Masotti et al. demonstrated that low-dose aspirin inhibited platelet cyclo-oxygenase and that 3.5 mg/kg of aspirin produced consistent inhibition of platelet aggregation and prostacyclin production.[35] In 1985, antiplatelet therapy with 150 mg/day of aspirin from 12 to 14 weeks of gestation in high-risk patients reduced the risk of developing PE and fetal growth restriction.[36] Since then, studies have been conducted on PE prevention using aspirin administration with various doses, timings, and subjects.

In 2017, the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial screened 26,941 singleton pregnancies in the first trimester with a combined algorithm using maternal factors, MAP, UTPI, PlGF, and PAPP-A.[37] A total of 1,776 high-risk women were randomized into taking either 150 mg/day of aspirin or a placebo from 11 to 14 weeks of gestation to 36 weeks of gestation.[37] Of these high-risk patients, 798 were assigned to the aspirin group and 822 to the placebo group.[37] In the aspirin group, 13 women (1.6%) developed preterm PE, while 35 women (4.3%) from the placebo group developed preterm PE.[37] This implies that the preterm PE rate was reduced by 62% when high-risk women took low-dose aspirin from 11 to 14 weeks to 36 weeks of gestation.[37]

According to a systematic review of 16 trials including 18,907 patients, if aspirin was started before 16 weeks of gestation and the dose was ≥100 mg/day, low-dose aspirin administration was associated with a reduced risk of preterm PE.[38] In contrast, if the start time of aspirin administration was later than 16 weeks of gestation and the aspirin dose was <100 mg/day, there was no reduction in the risk of preterm PE.[38] In addition, low-dose aspirin did not reduce the risk of term PE.[38]

Prescribing low-dose aspirin for high-risk patients to prevent PE is recommended by several organizations (Table 2). The FIGO recommends that women with an increased risk of preterm PE should be prescribed aspirin, starting at 11–14 weeks of gestation, with a dose of 100–162 mg/day.[5]

Prevention of PE: Other Recommendations

In low dietary calcium intake areas, calcium supplementation during pregnancy is recommended to prevent PE.[4,9] High-dose calcium (≥1 g/day) may reduce the risk of PE in individuals with low-calcium diets; however, the evidence for this is limited.[39]

Conclusion

Pregnant women at high risk of developing PE are recommended to take low-dose aspirin at a dose of 100 mg/day or more starting in the early stages of pregnancy to reduce the risk of preterm PE. To assess risk, a combination of maternal factors and biomarkers (MAP, UTPI, PlGF, and PAPP-A) should be considered for first-trimester PE screening. Risk assessment of PE in early pregnancy may lead to prevention of PE, and it should be prioritized.

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