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FIGO COMMITTEE REPORT

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# Good clinical practice advice: First trimester screening and prevention of pre-eclampsia in singleton pregnancy☆

FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine*,[a]

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## PREMISE

Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality. Globally, this condition is associated with 80 000 maternal and more than 500 000 infant deaths annually.[1] Evidence suggests that pre-eclampsia can be further subdivided into preterm pre-eclampsia, with delivery before 37 weeks' gestation, and term pre-eclampsia, with delivery at 37 weeks or later.[2] Preterm pre-eclampsia is associated with a higher incidence of fetal growth restriction and both short-term and long-term maternal and perinatal mortality and morbidity.[3,4] Obstetricians managing cases of preterm pre-eclampsia are faced with the challenge of balancing the need for achievement of fetal maturation with the risks to mother and fetus from continuing pregnancy. For the mother, short-term risks include progression to placental abruption, HELLP syndrome (a group of signs in pregnant women including hemolysis, elevated liver enzymes, and low platelet count), eclampsia, cerebrovascular accident, and death.[3] Additionally, the condition is associated with an increased risk of death from future cardiovascular disease, hypertension, stroke, and diabetes, and the life expectancy of women affected by preterm pre-eclampsia is reduced on average by 10 years.[5] For the fetus, preterm delivery is, in itself, associated with higher mortality rates and increased morbidity resulting from thrombocytopenia, bronchopulmonary dysplasia, cerebral palsy, and an increased risk of various chronic diseases in adulthood.[6] There are major cost implications for management of women with pre-eclampsia and their babies, especially when the condition is severe and associated with fetal growth restriction.[7,8]

## SCREENING

Professional bodies currently recommend the prophylactic use of low-dose aspirin (60–80 mg/d) in women considered to be at high-risk of pre-eclampsia (Box 1). In the UK, the National Institute for Health and Care Excellence (NICE) recommends selection of the high-risk group on the basis of ten factors from maternal characteristics, medical history, and obstetric history.[9] However, the performance of such screening is poor, with detection of about 40% of preterm pre-eclampsia cases and 33% of term pre-eclampsia cases at a screen-positive rate of 11%.[10] In the USA, the American College of Obstetricians and Gynaecologists (ACOG) recommends use of aspirin for women with a history of pre-eclampsia in more than one pregnancy or history of pre-eclampsia requiring delivery before 34 weeks of gestation[11]; however, this subgroup constitutes about 0.3% of all pregnancies and

**Box 1 Risk factors for pre-eclampsia.**

**High (one risk factor or more)**

- History of pre-eclampsia
- Chronic hypertension
- Type 1 or 2 diabetes
- Renal disease
- Autoimmune disease
- Multifetal gestation

**Moderate (two or more risk factors)**

- Nulliparity
- Obesity (body mass index >30 kg/m$^2$)
- Family history of pre-eclampsia
- Age >35 years
- Personal history (low birth weight >10-year pregnancy interval, previous adverse outcome)
- In-vitro fertilization

contains only 5% of those that would develop preterm pre-eclampsia and 2% of term pre-eclampsia.[12]

Extensive research over the last decade has identified a series of biomarkers of impaired placentation. With use of Bayes' theorem to combine the a priori risk from maternal factors with uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), and serum placental growth factor (PlGF) at 11–13 weeks' gestation, a study involving about 60 000 singleton pregnancies reported that such screening detected 76% and 40% of pregnancies at high-risk of preterm and term pre-eclampsia, respectively, at a false-positive rate of 10%.[13] A prospective external validation study of 8775 singleton pregnancies, including 239 (2.7%) cases that developed pre-eclampsia, has further confirmed that the first trimester combined test achieves detection rates of 75% and 43%, respectively, for preterm and term pre-eclampsia, at a 10% false-positive rate.[14]

## PREVENTION

In 1979, a study reported that women who had taken aspirin regularly during pregnancy were less likely to develop pre-eclampsia than women who did not.[15] In subsequent decades, more than 30 trials investigated the value of low-dose aspirin (50–150 mg/d) for prevention of pre-eclampsia, and a meta-analysis of these studies reported that such therapy was associated with a 10% decrease in the incidence of pre-eclampsia.[16] Individual participant data meta-analysis of the trials reported that the effect of aspirin was not affected by the gestational age at onset of therapy.[17] By contrast, other meta-analyses found that aspirin started at or before 16 weeks halved the rates of pre-eclampsia, fetal growth restriction, and perinatal death, whereas aspirin started after 16 weeks had no significant benefit.[18,19] Additionally, the beneficial effect of aspirin started at or before 16 weeks was dose dependent, being higher if the dose of aspirin was 100 mg or more.[20]

There is now substantial evidence from the ASPRE trial (www.aspre.eu)[21] that the rate of preterm pre-eclampsia can be reduced by more than 60% with aspirin started at 11–14 weeks' gestation in high-risk women.[21] In this multicenter, double-blind, placebo-controlled trial, 1776 women with singleton pregnancies at high-risk of preterm pre-eclampsia were randomly assigned to receive aspirin at a dose of 150 mg/d, or placebo from 11 to 14 weeks' gestation until 36 weeks. A total of 798 pregnant women completed the study in the aspirin group and 822 in the placebo group. Preterm pre-eclampsia was significantly reduced in participants in the aspirin group versus those in the placebo group (13 [1.6%] vs 35 [4.3%] participants; adjusted odds ratio in the aspirin group 0.38, 95% confidence interval [CI] 0.20–0.74; $P$=0.004).[21]

The latest systematic review and meta-analysis, which included 16 randomized controlled trials with a total of 18 907 participants, demonstrated that administration of aspirin was associated with a reduction in the risk of preterm pre-eclampsia (relative risk [RR] 0.62, 95% CI 0.45–0.87).[22] This reduction was even greater in the subgroup in which aspirin was started at 16 weeks' gestation or earlier at a dose of 100 mg/d or more (RR 0.33, 95% CI 0.19–0.57; $P$=0.0001). Initiation of aspirin at 16 weeks or more, or a daily dose of less than 100 mg, was not associated with a reduction in preterm or term pre-eclampsia.[23]

## WHEN ASPIRIN ADMINISTRATION SHOULD BE RECOMMENDED

Prophylactic aspirin should be given to women identified by screening as being at high risk of developing pre-eclampsia, rather than to the whole population.[23] The traditional approach has been to define the high-risk group based on factors in maternal characteristics and medical history.[9,24] However, evidence suggests that the most effective way of identifying the high-risk group is through a combination of maternal factors with biophysical and biochemical markers[10,12] as described in the ASPRE trial.[21] Large screening studies have shown that use of the approaches advocated by NICE[9] and ACOG[24] would only identify about 40% of cases at a 10% false-positive rate and 5% at a 0.2% false-positive rate, respectively.

## WHAT IS THE OPTIMAL DOSAGE RECOMMENDED FOR ASPIRIN PROPHYLAXIS?

Professional bodies recommend the use of aspirin at a dose of 75–80 mg/d for the prevention of pre-eclampsia.[9,24] However, results of the latest meta-analysis suggest that this recommendation should be updated to emphasize that the onset of treatment should be before 16 weeks' gestation, the dose of aspirin should be at least 100 mg/d, and the outcome measure should be preterm pre-eclampsia.[22] Pregnant women will be asked to stop taking tablets at 36 weeks' gestation or, in the event of early delivery, at the onset of labor (maximum duration of 25 weeks).

## POTENTIAL HARM OF ASPIRIN INTAKE

The relative safety of first-trimester use of low-dose aspirin has been demonstrated in large cohort and case-control studies, which reported that the drug is not associated with an increased risk of congenital heart defects or other structural or developmental anomalies.[25–27] Randomized studies reported that 10% of women receiving low-dose aspirin presented with gastrointestinal symptoms; however, there was no evidence of an increase in any type of maternal bleeding.[28–30] No additional adverse effects related to epidural anesthesia have been reported in women taking low-dose aspirin compared with those taking placebo.[31] Prospective and case-control studies did not find an association between daily consumption of 60–150 mg of aspirin during the third trimester and antenatal closure of the ductus arteriosus.[32–34] A meta-analysis including more than 26 000 women randomly assigned to low-dose (80–150 mg) aspirin or placebo/no treatment during pregnancy demonstrated that aspirin use was not associated with an increase in intraventricular hemorrhage or other neonatal bleeding.[35] On the basis of currently available evidence, it would be reasonable to continue with low-dose aspirin well into the third trimester of pregnancy.

Considering that aspirin reduces the risk of preterm pre-eclampsia with no potential harm, and only when it is initiated before 16 weeks of gestation and at a daily dose of 100 mg or more, FIGO recommends the following (Box 2):

1. All pregnant women should undergo screening for preterm pre-eclampsia by the combination of maternal factors with mean arterial pressure, measurement of uterine artery pulsatility index, and serum placental growth factor (combined test) at 11–13 weeks.
2. Uterine artery Doppler studies alone have a low predictive value for development of early onset pre-eclampsia and no randomized clinical trials have shown improved maternal or fetal outcomes in women who had undergone early Doppler screening. This is an area for further research.
3. Low-dose aspirin has been found to reduce the risk of early pre-eclampsia, intrauterine growth restriction, and preterm birth by improving disordered placentation.
4. Prophylactic aspirin should be administered to women who are considered at high risk for development of preterm pre-eclampsia identified by the first-trimester combined test.
5. These women should be offered low-dose aspirin (75–150 mg) daily from as early as possible (at least 12 weeks and before 16 weeks), to achieve its intended protection. Administration should be continued until 37 weeks of gestation or stopped 2 weeks before a planned early delivery (maximum duration of 25 weeks).
6. Women should be advised to take aspirin in the evening as evidence supports better efficacy at this time.
7. Monitoring of platelet levels or bleeding time on aspirin therapy is not necessary unless the patient develops unexplained bruising or bleeding that may require investigation. Aspirin should be stopped in these circumstances.
8. Mode of delivery, timing of delivery, and analgesic requirements should not be influenced by administration of aspirin but by clinical indications.
9. Low-dose aspirin is not associated with an increased adverse outcome or bleeding tendencies in the mother or the neonate.

**Box 2 Advice on prevention of preeclampsia in singleton pregnancy.**

**Population**

- Women with singleton pregnancy at gestational age $11–13^{+6}$ weeks' gestation

**Recommendation**

- Daily administration of aspirin starting at ≤16 weeks and at a dose of ≥100 mg/d at night

**Scientific evidence**

- Grade A

**Time using aspirin**

- Administration should begin at ≤16 weeks' gestation and should continue until 36 weeks' gestation or presence of labor signs

**Risk assessment for pre-eclampsia**

- Combination of maternal factors with uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor at 11–13 weeks' gestation

**Recommendation from other associations**

- International Society for the Study of Hypertension in Pregnancy

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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