



# Aspirin summaries: Aspirin to prevent complications in pregnancy

# Aspirin to prevent complications in pregnancy

Pre-eclampsia is a complication of pregnancy that features both high blood pressure and protein in the urine. This is usually mild but, in some cases, (0.5%) it can develop into a life-threatening condition (eclampsia) for both the baby and the mother<sup>1</sup>. It affects around 8% of pregnancies globally and is an important cause of maternal and neonatal ill health and death<sup>2</sup>. Symptoms of pre-eclampsia include; headache, visual changes e.g. blurred or flashing vision, severe pain below the ribs, vomiting and a sudden onset swelling of the hands, face or feet<sup>2</sup>.

Aspirin is currently the only drug with evidence for use in pre-eclampsia prevention and is recommended by professional groups<sup>3</sup>. International guidelines from the International Federation of Gynecology and Obstetrics<sup>4</sup> recommend that women identified as high risk of pre-eclampsia during first trimester screening should be given aspirin prophylaxis (150mg at night from 11-14 weeks gestation until delivery or the diagnosis of pre-eclampsia). They do not advocate a policy of low-dose aspirin for all pregnant women<sup>4</sup>. A recent Cochrane review concluded that low-dose aspirin does slightly reduce the risk of pre-eclampsia and its complications but that further research is required to identify those most likely to benefit<sup>5</sup>.

The U.S. Preventative services Task Force (USPSTF) recommends (Grade B) low-dose aspirin (81 mg

per day) after 12 weeks gestation as a preventative medication in women at high risk of pre-eclampsia<sup>6</sup>.

NICE<sup>2</sup> recommends that women who are at high risk of pre-eclampsia take 75-150mg of aspirin daily from 12 weeks until the birth of the baby. They define women at high risk as those with; hypertension during a previous pregnancy, chronic kidney disease, an autoimmune disease (e.g. systemic lupus erythematosus or antiphospholipid syndrome), diabetes (type 1 or 2) and/or chronic hypertension. In addition, they advise women with more than one moderate risk factor for pre-eclampsia to take low-dose aspirin from 12 weeks until birth. Moderate risk factors for pre-eclampsia are; first pregnancy, age 40 or above, a pregnancy interval of more than 10 years, obesity, family history of pre-eclampsia and a multiple foetus pregnancy.

Aspirin is used off-label for the prevention of pre-eclampsia.

The following aspirin summary reviews some recent publications looking at aspirin's role in preventing pregnancy complications.

The ongoing clinical trial work will help to define the best dose and strategy for aspirin in the prevention of pre-eclampsia.

## References

1. Royal College of Obstetricians and Gynaecologists Pre-eclampsia 08082012 accessed 22/05/2020 @ <https://www.rcog.org.uk/en/patients/patient-leaflets-pre-eclampsia/>.
2. NICE NG133 Hypertension in pregnancy: diagnosis and management. 2019 @ <https://www.nice.org.uk/guidance/ng133/chapter/Recommendations>
3. Maayeh M, Rood KM, Kniss D et al. Novel Interventions for the prevention of pre-eclampsia. *Current Hypertension Reports*. 2020; 22, 17.
4. Poon LC, Shennan A, Hyett JA et al The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynecol Obstet*. 2019; 145 (Suppl.1) 1-33. @ <https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.12802>
5. Duley L, Meher S and Hunter KE et al. Antiplatelet agents for preventing pre-eclampsia and its complications *Cochrane Database of Systematic Reviews* Oct 2019 <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004659.pub3/full>
6. USPSTF Low-dose aspirin use for the prevention of morbidity and mortality from pre-eclampsia: preventative medication. 2014 (currently being updated) available @ <https://www.uspreventiveservicestaskforce.org/uspstf/recommendations/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-pre-eclampsia-preventative-medication>

# Low-dose aspirin results in a lower incidence of pre-eclampsia in high risk pregnancies (The ASPRE trial).

This was a pivotal study in helping to demonstrate aspirin's role in the prevention of pre-eclampsia. It was a double-blind, placebo-controlled multicentre trial in which 1776 pregnant women, at high risk of pre-eclampsia before term with their singleton pregnancies, were randomised to receive either 150mg aspirin daily or placebo from 11-14 weeks until 36 weeks gestation. Adherence was found to be good with nearly 80% of the participants taking over 85% of their allocated tablets.

After 152 women withdrew from the study and 4 were lost to follow up there were 798 participants in the aspirin arm of the study and 822 in the placebo group. The primary outcome measure of preterm pre-eclampsia was significantly lower in the treatment arm of the study; in the aspirin group 13 women [1.6%] [P=0.004] experienced preterm pre-eclampsia compared with 35 [4.3%] of those taking the placebo.

No significant difference was found in the incidence of other pregnancy complications or adverse foetal or neonatal outcomes between the two groups, but it is important to note the study was not adequately powered to detect these secondary outcomes.

The authors conclude:

*“This randomized trial showed that among women with singleton pregnancies who were identified by means of first-trimester screening as being at high risk for preterm pre-eclampsia, the administration of aspirin at a dose of 150 mg per day from 11 to 14 weeks of gestation until 36 weeks of gestation resulted in a significantly lower incidence of preterm pre-eclampsia than with placebo.”*

## For further information please see:

Rolnik DL, Wright D, Poon LC et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Pre-eclampsia. N Engl J Med. 2017, Jun, 28; 377:613-622. DOI:10.1056/NEJMoal1704559.



# Low-dose aspirin helps reduce the incidence of preterm delivery and reduces perinatal mortality in low- and middle-income countries.

Preterm birth, a common cause of infant mortality, is particularly challenging in low- and middle-income countries (LMIC). Babies that are delivered preterm have also been found to experience less favourable health and socioeconomic outcomes than those born at term. This study built on previous evidence from meta-analyses of low-dose aspirin, initiated prior to 16 weeks, to help prevent pre-eclampsia and preterm birth. It is the first large trial of low-dose aspirin, started early in pregnancy, with reducing preterm birth as the primary outcome measure. Following screening 11976 women from India, Democratic Republic of the Congo, Guatemala, Kenya, Pakistan and Zambia were randomised to receive low-dose aspirin (81 mg daily) or placebo between 6 and 13 weeks of pregnancy in a double-masked protocol.

The results confirmed a benefit in taking low-dose aspirin to reduce the risk of preterm birth. Those taking low-dose aspirin from early in their pregnancy were found to be 11% less likely to deliver their baby before 37 weeks gestation. The study also found that the risk of early preterm delivery, before 34 weeks gestation was reduced by 25% and that perinatal mortality was reduced by 14% in those taking low-dose aspirin.

In their discussion the authors note that previous studies have suggested that doses of aspirin greater

than 100 mg daily may further reduce the incidence of pre-eclampsia and that the optimal dose of aspirin for this indication remains unclear.

Low-dose aspirin was found to be a safe intervention for nulliparous women in these 6 LMIC with no increase in adverse events for mothers or their babies in the low-dose aspirin group when compared with the placebo group. In addition, aspirin's low cost makes it a readily accessible intervention for use globally.

## The authors state:

*“this trial showed that the administration of aspirin at a daily dose of 81 mg, initiated between 6 weeks 0 days of gestation and 13 weeks 6 days of gestation up to 37 weeks, reduced the incidence of preterm births in populations of nulliparous women with singleton pregnancies from LMICs.”*

## For further information please see:

Hoffman MK, Goudar SS, Kodkany BS et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *The Lancet* .2020, Jan, 25; 395; 10220 :285-293. [https://doi.org/10.1016/S0140-6736\(19\)32973-3](https://doi.org/10.1016/S0140-6736(19)32973-3)

# Twin pregnancies and the role of low-dose aspirin to prevent adverse outcomes

This preliminary, two centre, observational cohort study in China assessed 932 women with twin pregnancies to see if aspirin at a dose of 100 mg taken daily from 12-16 weeks to 35 weeks gestation had a beneficial effect on pregnancy outcomes. The main outcome measure was to compare the incidence of preeclampsia in the 277 women at the First Affiliated Hospital of Chongqing Medical University who were treated with aspirin with the 655 attending the Chongqing Health Centre for Women and Children who were not taking aspirin.

The researchers found that low-dose aspirin use significantly reduced the risk of pre-eclampsia (OR:0.48, 95% CI: 0.24-0.95, p=0.048 and preterm birth before 34 weeks (OR:0.50, 95% CI: 0.29-0.86, p=0.013). The risk of postpartum haemorrhage was not found to be increased by aspirin.

The authors conclude;

*“treatment with low-dose aspirin in women pregnant with twins could offer some protection against adverse pregnancy outcomes in the absence of any significantly increased risk of postpartum haemorrhage.”*

## For further information please see:

Ye Y, Wen L, Liu X et al. Low-dose aspirin for primary prevention of adverse pregnancy outcomes in twin pregnancies: An observational cohort study based on propensity score matching. *Authorea*. 2020, Oct,15; <https://doi.org/10.22541/au160278522.21360749/v1>



# Women in Dutch study were not well informed of the benefits of aspirin use in reducing the risk of hypertensive disorders of pregnancy

This quantitative survey was set up in collaboration with the Dutch HELLP foundation (a patient group for women who have experienced hypertensive disorders of pregnancy HDP) in order to understand knowledge levels, among women in the group, with a prior history of HDP, about the benefits of aspirin for reducing pregnancy complications caused by high blood pressure.

Interestingly, only around half of the 189 women interviewed (51.9%) were aware that aspirin could reduce the risks from HDP. The researchers argue that the implementation of aspirin use to reduce pregnancy risks lags behind the research evidence. The women preferred to be informed both verbally and in writing so that the information about aspirin is not forgotten.

Ideally, they wanted to be informed by their gynaecologist but also wanted other clinicians involved in their care to be aware of and discuss aspirin's beneficial effects with them.

## The authors state:

*“We want to emphasize the importance of aspirin use in the prevention of HDP in joint guidelines with midwives and general practitioners.”*

## For further information please see:

Bij de Weg JM, Abheiden CNH, de Boer MA et al. Patients' perspective on aspirin during pregnancy: a survey. Hypertension in Pregnancy. 2020, Jun;20; DOI: 10.1080/10641955.2020.1777299

# Adherence to aspirin therapy for the prevention of pre-eclampsia in high risk pregnant women.

Women with high-risk pregnancies that fail to adhere well to their prophylactic aspirin have a higher incidence of pre-eclampsia, preterm birth and intrauterine growth restriction. Finding ways to help women adhere well to aspirin therapy is therefore important.

This survey carried out in South Western Sydney, Australia collected quantitative (n=122) and qualitative face to face data (n=6). The researchers identified the following reasons for non-adherence amongst their women with high-risk pregnancies:

- Pill burden (women reported an average of 3.5 medicines to take during pregnancy)
- Non-intention omission
- Communication with healthcare professional
- Relationship with healthcare professional

Good adherence (missing none or only one dose) was reported by 53% of the women in the survey. They used mobile phone reminders, a pill box or good medication routine in order to achieve this.

Around half the women in the study discussed aspirin use with more than one health care professional e.g. obstetrician, GP, midwife and a positive consistent message from all these clinicians was found to result in good adherence.

## For further information please see:

Shanmugalingam R, Mengesha Z and Notaras S et al. Factors that influence adherence to aspirin therapy in the prevention of preeclampsia amongst high-risk pregnant women: A mixed method analysis. PLoS ONE 2020, Feb, 27; 15(2): e0229622. <https://doi.org/10.1371/journal.pone.0229622>



# Low-dose aspirin use in pregnant women at increased risk of pre-eclampsia

In this Dutch study a pre-eclampsia risk assessment tool was used to identify and then counsel women on the benefits of low-dose aspirin for those with high risk pregnancies.

In total 865 women between 2017 and 2018 were recruited from multiple centres and the rate of and determining factors for low-dose aspirin use were assessed. These results were compared with a similar cohort of pregnant women in the Netherlands where no risk-based counselling was undertaken.

The risk-based counselling resulted in higher aspirin use. Daily low-dose aspirin use was positively linked to both predicted risk and the women's concern about pre-eclampsia. Non or incomplete use of aspirin was linked to a lack of awareness of the benefits of low-dose aspirin, concerns about adverse effects and doubts about the benefit.

This study found that among women with an increased risk of pre-eclampsia 29.4% used low-dose aspirin in the risk-based counselling setting compared with only 1.5% of the women with a high risk of pre-eclampsia in the Netherlands care-as-usual setting.

The authors conclude:

*“Implementation of risk-based care improved LDA [low-dose aspirin] usage by pregnant women with an increased PE [preeclampsia] risk, especially among high-risk women. Nevertheless, general usage rates were relatively low.”*

## For further information please see:

van Monfort P, Scheepers HC, van Dooren IMA et al. Low-dose-aspirin usage among women with increased preeclampsia risk: a prospective cohort study. *Acta Obstetrica et Gynecologica Scandinavica* 2020, Jan, 18; 99; 7  
<https://doi.org/10.1111/aogs.13808>

# Comment on aspirin as a simple and safe strategy for preventing preterm birth globally.

Commenting on Hoffman et al 2020 article in the Lancet, Professor Julie Quinlivan from the Institute for Health Research, University of Notre Dame, Australia, explains how a public health approach maybe a better solution to preventing preterm birth globally rather than expensive interventions. She explains how the new study by Hoffman and colleagues adds to the body of evidence supporting aspirin use for the prevention of preterm birth. Quinlivan recommends that a randomised trial is also carried out in high-resource settings to compare the use of aspirin with current selective screening and that an observational post-implementation trial is used to monitor subsequent trends in preterm birth in resource-limited settings.

Overall, Quinlivan advocates minimum standards of evidence-based care to be implemented across all settings. These include:

- Smoking cessation early in pregnancy
- Dietary advice and supplements

She concludes:

*“before resources are diverted to expensive interventions, governments need to ensure they have the basic rights when it comes to maternal care and preterm birth risk reduction.”*

## For further information please see:

Quinlivan JA. Simple and safe: preventing preterm birth with aspirin. The Lancet. 2020, Jan, 25; 395: 250-252.



# Low-dose aspirin for the prevention of pre-eclampsia

In an editorial to the Drug and Therapeutics Bulletin, Joanna Girling, Consultant in Obstetrics and Gynaecology, in London, calls for a national patient group direction (PGD) to allow all community pharmacists to supply low-dose aspirin to pregnant women who have been advised by their midwives to take it due their risk of pre-eclampsia. She believes this will increase the uptake of this medicine which is recommended in national guidelines, is low-cost and has the potential to save lives.

Girling explores the issues for women deemed to be at risk of pre-eclampsia in obtain low-dose aspirin and the reasons why the uptake is only around 50% in eligible pregnant women. Firstly, despite being able to recommend it most maternity units do not have a policy or PGD to allow midwives to supply low-dose aspirin. Instead midwives usually need to advise women to see their GP and ask them to prescribe it.

Community pharmacists cannot legally sell aspirin for pre-eclampsia because it does not have a UK marketing license for this indication. In addition, some women may have safety concerns but signposting them to <https://medicinesinpregnancy.org/Medicine--pregnancy/Aspirin/> can offer reassuring advice.

## Joanna Girling states:

*“There is well-established high-quality evidence that low-dose aspirin is effective in reducing pre-eclampsia (as well as reducing the risk of preterm birth, fetal growth restrictions and still birth) in women at risk of this condition and that it is safe for mother and baby.”*

## For further information please see;

Girling J. Low-dose aspirin for prevention of pre-eclampsia: when over the counter just isn't. Drug and Therapeutics Bulletin April 2020 @ <https://dtb.bmj.com/content/early/2020/04/23/dtb.2020.000003>

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