**Aspirin is very effective;**   
**well… if taken, at appropriate dose, in a timely fashion: an editorial**

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Despite abundant evidence that Aspirin can be very effective in preventing pre-eclampsia, particularly preterm, severe pre-eclampsia variants such as HELLP, some clinicians still consider it only modestly effective.

A danger is that instead of focussing efforts on provision of Aspirin as recommended, maternity staff continue firefighting complications while academics divert research to more expensive drugs and diagnostics. The Cochrane review by Duley et al1 concludes that ‘low doses of aspirin slightly reduce the risk of pre‐eclampsia and its complications; the reassurance about the safety of aspirin may not apply to higher doses’. UK guidelines such as NICE2 and Saving Babies Lives3 (2023) recommend doses of 75-150mg, as opposed to 50-60mg used in older trials. Does over-interpretation of the Cochrane review incite low adherence to aspirin, with preventable harm to pregnant people and their babies globally?

**The right dose**

The Cochrane review1 examined dosages in a subgroup analysis. For women allocated aspirin < 75 mg, there was a possible slight (but uncertain) reduction in studies with individual patient data (11 trials, 22,618 women; RR 0.92, 95% CI 0.85 to 1.00). For studies with aggregate data, no difference was found between doses <75mg and 75mg or more, however they included trials with delayed initiation of aspirin, diluting the effect.

A systematic review by Roberge et al (2017)4 found that not only was there a dose-effect relationship between aspirin and prevention of pre-eclampsia, but the association was particularly strong (I2=100%) and significant for severe pre-eclampsia and fetal growth restriction. The dose-effect relationship was only apparent for studies with initiation of aspirin before 16 weeks. Not just the dose, but also the timing matters.

Roberge et al (2018)5 also looked at doses with regards to prevention of preterm versus term pre-eclampsia. They found that only dosages of >100mg were effective, and only for preterm pre-eclampsia. However, in this analysis Roberge et al lumped together all dosages under 100mg, diluting the effectiveness of 75-81mg with hundreds of participants who took only 50-60mg.

Two recent large trials provide robust evidence that both 81mg (ASPIRIN)6 (and its 75mg equivalent) and 150mg dosages (ASPRE)7 are more often effective than not (>50%). Interestingly, the effectiveness (including some women with suboptimal adherence) of aspirin in preventing preterm pre-eclampsia (ASPRE), or preterm delivery because of it, (ASPIRIN) was 62% in both trials; Odds Ratio 0.38 in both RCTs, and with similar 95% Confidence Intervals: 0.20-0.74 and 0.17-0.85 respectively.

**The right time**

Both in the UK and the US, NICE (2023)2 and ACOG (2021)8 endorse early commencement before 16 weeks to improve placentation and reduce the incidence and severity of Maternal Vascular Malperfusion.

Roberge et al4 showed that the effectiveness of Aspirin is compromised, unsurprisingly, if commenced after 16 weeks, as the critical stage of placentation is largely complete.

Meher et al9 (reproduced in the Duley et al systematic review1) investigated subgroups by gestational age at randomisation, but results were diluted by including low dosages (50-60mg). It is hardly surprising their findings were underpowered: ‘For women randomised at or after 20 weeks' gestation with IPD available, the results did not clearly indicate a risk reduction (13,173 women,26 trials; RR 0.93, 95% CI 0.84 to 1.04). However, the CIs overlap, so we are uncertain whether this is suggestive of real differences’.

If there was any residual doubt that timing matters, in both ASPRE6 and ASPIRIN7, where the effect size of Aspirin was undiluted and very high, the commencement of Aspirin was before 16 weeks for all participants.

Additional evidence on the importance of early commencement comes from the study by Mendoza et al.10 Their non-inferiority trial showed that aspirin can even be discontinued at 24-28 weeks with no reduction in its effectiveness, such is the importance of its action on early placentation. Whereas Mendoza et al restricted the discontinuation of aspirin to women with normal (sFlt-1:PlGF), of 1984 women only 7 (<1%) had high ratio at 24-28 weeks, and overall 1604 women were able to take part after losses and exclusions.

The EAGeR trial11 went even beyond the NICE and ACOG recommendations to commence aspirin at the beginning of the second trimester, and randomised women attempting conception after pregnancy loss to either 81mg aspirin or placebo, continued throughout pregnancy. Those taking aspirin had higher conception rates (RR 1.10, 95% CI 1.01-1.19) and possibly higher livebirth rates (RR 1.10, 95% CI 0.98-1.22, 5.1% absolute difference). Despite a higher risk of vaginal bleeding, this was not associated with pregnancy loss. Although this trial only included women who had experienced pregnancy loss, this raises the question – should we be commencing aspirin even earlier in pregnancy, or even pre-conception?

**Adherence matters**

Well, aspirin does not work if not taken at all and works only ‘slightly’ if not taken regularly. Bombarded with conflicting messages as to whether Aspirin is effective in the first place, or safe in pregnancy, it is to be expected that many women may be prescribed Aspirin but not take it. In the ASPRE trial, adherence mattered, a lot. Effectiveness of aspirin was 76% for adherence more than 90%, but only 41% if it dropped below 90%. Factors such as young age, smoking, race, and history of pre-eclampsia all influenced adherence. Women may receive conflicting messages from general practitioners or pharmacists as to the safety of aspirin.

The authors have experience of two individuals who never commenced aspirin, despite previous pre-eclampsia, because they were breastfeeding. The British National Formulary states: ‘Avoid’ in breastfeeding.12 Conversely, LactMed affirms the compatibility of low-dose aspirin and breastfeeding, stating for doses of 75-325mg “no aspirin is excreted into breastmilk and salicylate levels are low”.13

Whatever the reasons for it, suboptimal adherence does explain the massive dilution of the effect of aspirin in the Cochrane review. Table 1 illustrates that in the large trials dominating the Cochrane review, only 1:4 participants took 75mg or more daily aspirin, and of those only 1:10 with good adherence. Only 3:5 participants started aspirin before 16 weeks.

The Cochrane review may have reported on thousands of participants, but if only about 1:10 took appropriate dose with good adherence, the apparent ‘slight’ effectiveness is unsurprising.

**Conditions with special considerations**

***Preterm pre-eclampsia and preterm birth***

Aspirin is particularly good at preventing preterm pre-eclampsia. The ASPRE trial,7 using 150mg of aspirin, showed that the incidence of delivery with pre-term pre-eclampsia was reduced by much more than 50% (OR 0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004); women with aspirin delivered later than women on placebo.

The ASPIRIN trial6 also demonstrated decreased preterm delivery among women taking 81mg aspirin (RR 0·89, 95% CI 0·81 to 0·98, p=0·01), and similarly to ASPRE found more than 50% efficacy for the prevention of early preterm delivery with hypertensive disorders (OR 0·38 [0·17–0·85).

***HELLP and abruption***

Severe preeclampsia and HELLP have similar placental histopathologic findings; both are associated with higher rates of placental maternal vascular malperfusion and SGA. HELLP is essentially a severe manifestation of the same underlying pathophysiology, likely preventable by the same mechanisms.14

While some studies have suggested an increased risk of placental abruption with aspirin,15 subgroup analyses4 show that early (by 16 weeks) commencement may prevent pre-eclampsia related abruption by improving placentation, whereas late start may be detrimental.

This is critical for clinical practice and counselling. Women with catastrophic complications such as HELLP may hesitate ever getting pregnant again, driven by a misconceived futility, when it is likely that Aspirin will help them, if not to avoid pre-eclampsia, at the very least to avoid its most severe forms and delay its onset.

**Complications of pre-eclampsia are largely preventable**

If complications are the result of pre-eclampsia, then aspirin is likely to prevent them.

Whereas there should remain little doubt that preterm birth caused by pre-eclampsia can be prevented with aspirin,6,7 for other, rarer, complications it appears easy to forget that the absence of evidence is not evidence of absence. Misinterpretation of the limitations of systematic reviews may be responsible.

***Chronic Hypertension***

A meta-analysis has shown that in women with chronic hypertension before pregnancy, aspirin does not change the odds of pre-eclampsia.16 However, aspirin did reduce significantly the risk of pre-term delivery. It is possible aspirin improves blood flow within the placenta, but not blood flow before and to the uterus where there may be pre-existing vessel damage. A partial effectiveness would result in a later, milder onset of pre-eclampsia, possibly explaining the reduction in preterm birth. It is therefore still advisable to give aspirin to women with chronic hypertension, but lifestyle modifications before and between pregnancies, as well as other measures to prevent atherosclerosis, may be more important.

***Diabetes***

Recent studies have shown that forms of placental dysfunction, such as delayed villous maturation, or fetal vascular malperfusion, may be prevalent in diabetes in pregnancy,17 particularly if under-diagnosed and under-treated.18 A recent study19 identified that pregnancies with normal PAPP-A and abnormal uterine artery Dopplers uncommonly develop pre-eclampsia, but there is a high incidence of neonatal hypoglycaemia similarly to poorly controlled diabetes. For pregnancies at risk of glucose dysmetabolism, for example with history of PCOS, aspirin may be useful in preventing MVM but may not be enough.

***Renal Disease***

Chronic kidney disease (CKD) is both a strong indication for aspirin, and also a caution in case of side-effects. Some authors have excluded only women with renal failure, others all women with CKD regardless of function. This has limited the available evidence to guide their management, the same way pregnant women have historically been systemically excluded from clinical trials without reason. Women with CKD should not suffer from misplaced fatalism. Neither ASPRE nor ASPIRIN excluded women with CKD. In the UK, the Saving Babies Lives initiative3 recommends 150mg for most women, but 75mg for women with renal disease.

**Conclusion**

Whereas the Cochrane review on Aspirin is admirable for its consideration to trials with individual patient versus aggregate data, the review is guilty of ‘aggregation’ when it comes to examining key issues critical to clinical practice. The true efficacy of aspirin is obscured as pregnant persons who took aspirin at a very low dose (50-60mg), only late in the third trimester for ‘treatment’ of pre-eclampsia or took it with poor adherence or not at all, are all lumped together to conclude that Aspirin is only ‘slightly’ effective. A presumption of ‘slight’ effectiveness might then be used as an excuse to neglect the focus required on early, consistent use in women at risk.

The emerging evidence is that Aspirin is a highly effective strategy to prevent pre-eclampsia. Even in the minority where it does not fully prevent pre-eclampsia, despite being taken at the right time and right dose, at the very least it likely delays its onset until after 34-37 weeks and reduces its severity.

What maternity care needs is not despondence. We need universal, early implementation of aspirin for at-risk individuals, within a framework of other risk-reducing strategies.

**Conflict of interest**

Neither author has a conflict of interest to declare

**Contribution to Authorship**

DS wrote an initial draft of this editorial, with additional sections and revisions by BA. The final version of the editorial was reviewed and agreed by both authors.

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**References**

1. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev [Internet]. 2019 Oct 30 [cited 2024 Oct 14];2019(10). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004659.pub3/full>

2. Hypertension in pregnancy: diagnosis and management: NICE Guidance NG133 [Internet]. NICE; 2019 Jun [cited 2023 May 17]. Available from: <https://www.nice.org.uk/guidance/ng133/chapter/recommendations>

3. NHS England. Saving babies’ lives: version 3: A care bundle for reducing perinatal mortality [Internet]. 2023 Jul [cited 2024 Oct 14]. Available from: <https://www.england.nhs.uk/long-read/saving-babies-lives-version-3/>

4. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The Role of Aspirin Dose on the Prevention of Preeclampsia and Fetal Growth Restriction: Systematic Review and Meta-Analysis. Obstet Anesth Dig. 2017 Mar;37(1):9–9.

5. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol [Internet]. 2018 Mar 1 [cited 2024 Oct 14];218(3):287-293.e1. Available from: <http://www.ajog.org/article/S0002937817323268/fulltext>

6. Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, 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. Lancet [Internet]. 2020 Jan 25 [cited 2024 Oct 14];395(10220):285–93. Available from: <http://www.thelancet.com/article/S0140673619329733/fulltext>

7. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O’Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol [Internet]. 2017 Oct 1 [cited 2024 Oct 14];50(4):492–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/28741785/>

8. Low-Dose Aspirin Use During Pregnancy: ACOG [Internet]. 2018 Jul [cited 2023 May 17]. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/07/low-dose-aspirin-use-during-pregnancy>

9. Meher S, Duley L, Hunter K, Askie L. OC08.06: Antiplatelet therapy before or after 16 weeks’ gestation for preventing pre-eclampsia: an individual participant data meta-analysis. Ultrasound Obstet Gynecol [Internet]. 2016 Sep [cited 2024 Oct 14];48(S1):15–15. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/uog.16066>

10. Mendoza M, Bonacina E, Garcia-Manau P, López M, Caamiña S, Vives À, et al. Aspirin Discontinuation at 24 to 28 Weeks’ Gestation in Pregnancies at High Risk of Preterm Preeclampsia: A Randomized Clinical Trial. JAMA [Internet]. 2023 Feb 21 [cited 2024 Oct 14];329(7):542–50. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2801678>

11. Schisterman EF, Silver RM, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, et al. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. Lancet (London, England) [Internet]. 2014 [cited 2024 Oct 14];384(9937):29–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/24702835/>

12. Aspirin | Drugs | BNF | NICE [Internet]. [cited 2024 Oct 14]. Available from: <https://bnf.nice.org.uk/drugs/aspirin/#breast-feeding>

13. Aspirin. Drugs Lact Database [Internet]. 2024 Sep 15 [cited 2024 Oct 14]; Available from: <https://www.ncbi.nlm.nih.gov/books/NBK501196/>

14. Weiner E, Schreiber L, Grinstein E, Feldstein O, Rymer-Haskel N, Bar J, et al. The placental component and obstetric outcome in severe preeclampsia with and without HELLP syndrome. Placenta [Internet]. 2016 Nov 1 [cited 2024 Oct 14];47:99–104. Available from: <https://pubmed.ncbi.nlm.nih.gov/27780546/>

15. Souter V, Painter I, Sitcov K, Khalil A. Propensity score analysis of low-dose aspirin and bleeding complications in pregnancy. Ultrasound Obstet Gynecol [Internet]. 2024 Jan 1 [cited 2024 Oct 14];63(1):81–7. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/uog.27472>

16. Richards EMF, Giorgione V, Stevens O, Thilaganathan B. Low-dose aspirin for the prevention of superimposed preeclampsia in women with chronic hypertension: a systematic review and meta-analysis. Am J Obstet Gynecol. 2023 Apr;228(4):395-408. doi: 10.1016/j.ajog.2022.09.046. Epub 2022 Oct 7. PMID: 36209937.

17. Scifres CM, Parks WT, Feghali M, Caritis SN, Catov JM. Placental maternal vascular malperfusion and adverse pregnancy outcomes in gestational diabetes mellitus. Placenta [Internet]. 2017 Jan 1 [cited 2024 Oct 14];49:10–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/28012449/>

18. Siassakos D, Bourne I, Sebire N, Kindinger L, Whitten SM, Battaglino C. Abnormal placental villous maturity and dysregulated glucose metabolism: implications for stillbirth prevention. J Perinat Med [Internet]. 2022 Jul 1 [cited 2024 Oct 14];50(6):763–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/35357795/>

19. Jie M, Jaufuraully S, Lambert J, Napolitano R, Siassakos D. Second trimester abnormal uterine artery Dopplers and adverse obstetric and neonatal outcomes when PAPP-a is normal. J Matern Fetal Neonatal Med [Internet]. 2023 [cited 2024 Oct 14];36(2). Available from: <https://pubmed.ncbi.nlm.nih.gov/37401032/>