Dr Elisa Llurba

Aspirin Tributes

Elisa Llurba is a maternal and foetal medicine specialist at University hospital Sant Pau, Barcelona, with an interest in preeclampsia, intrauterine growth restriction and foetal loss. After a PhD exploring oxidative stress as a mechanism behind endothelial damage in preeclampsia, Elisa became interested in prediction and using aspirin as a preventive strategy to manage development of preeclampsia.

Elisa has undertaken studies exploring use of biomarkers to identify women at risk of developing preeclampsia and a meta-analysis showing the combination of aspirin with low molecular weight heparin is more effective than aspirin alone for preventing preeclampsia in high-risk women.

She is now involved in a range of studies exploring aspirin, including giving it to women undergoing Invitro Fertilization (IVF) prior to implantation and to women who suffered preeclampsia to see if it benefits their long-term cardiovascular (CV) health.

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Celebrating the 125th anniversary of the synthesis of acetylsalicylic acid

What is preeclampsia?

Preeclampsia, affecting 2 to 8% of all pregnancies, represents one of the world's leading causes of maternal and perinatal morbidity and mortality.[1] Statistics from the World Health Organization (WHO) for 2014 showed that globally preeclampsia was associated with 76 000 maternal and 500 000 infant deaths.[2]

Preeclampsia is a multisystem disorder of pregnancy, usually defined as hypertension and proteinuria diagnosed after 20 weeks of gestation, occurring in women whose blood pressure was previously in the normal range. We still don't really understand why preeclampsia occurs. Current theories include pathogenesis being due to release of anti-angiogenic factors into the maternal circulation, causing systemic inflammation and oxidative stress. This in turn affects the endothelium throughout the mother's body, ultimately resulting in preeclampsia. We now know that the problem starts early in pregnancy when there is an impairment in remodelling of the spiral arteries in the uterus and placental dysfunction. Overall, these changes, lead to higher resistance to placental blood flow, and ultimately reduced blood flow to the foetus.

For mothers complications include seizures (eclampsia), cerebral ischemia, kidney and/or liver failure, pulmonary oedema, and low levels of platelets leading to disseminated intravascular coagulation. For babies, the disorder can lead to intrauterine growth restriction, hypoxia, and being born early with all the complications that prematurity entails. Additionally, we're now becoming aware how preeclampsia can increase the risk of both mother and baby developing cardiovascular disease (CVD) in later life.[3]

Preeclampsia can have devastating consequences. Overnight pregnant women go from a 'happy place' anticipating the birth of their baby to being in ICU fearing for the life of their unborn child. The best scenario is that they have a preterm baby, the worst is that they lose the pregnancy or even die themselves. After such harrowing experiences, many women are often too traumatised to consider subsequent pregnancies.

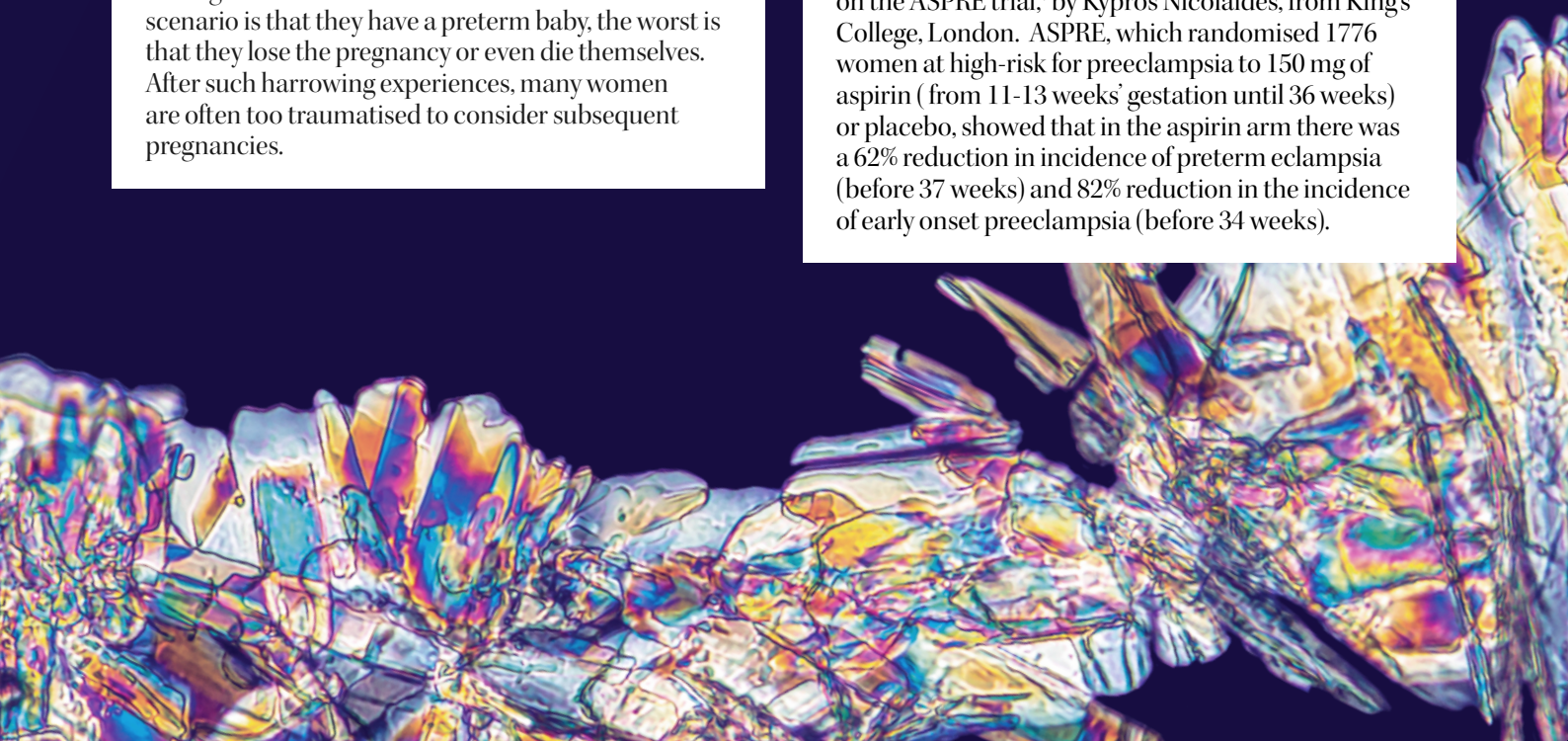
How has management of preeclampsia evolved?

The only cure for preeclampsia is for women to give birth as soon as possible because once the placenta is removed symptoms clear. However, a recent advance has been our ability in the first trimester to predict which women are likely to develop preeclampsia later in their pregnancy. Algorithms have been developed using combinations of maternal characteristics, biophysical markers (mean arterial blood pressure and mean uterine artery pulsatility index) and biochemical markers which can identify 80%–90% of pregnant women who would go on to develop preeclampsia without treatment.[4,5]

The PROGNOSIS study,[6] which I was involved with, established that the ratio of soluble fms-like tyrosine kinase 1 to placental growth factor levels was an effective biomarker for predicting preeclampsia. Using ratios above 38 as our cut-off, we were able to demonstrate a positive predictive value for preeclampsia development within four weeks of 36.7% and more importantly, the negative predictive value was 98% at week one and 95% at week four. The result is that we're now able to distinguish with a high sensitivity and specificity which women need to be admitted to hospital (or have close follow-up) to avoid maternal and foetal complications from those who can be reassured about the condition and sent home.

What role can aspirin play in preeclampsia?

For women found to be at high-risk of developing preeclampsia we now give 150 mg aspirin daily from 12 weeks to 36 weeks gestation. This practice is based on the ASPRE trial,[7] by Kypros Nicolaides, from King's College, London. ASPRE, which randomised 1776 women at high-risk for preeclampsia to 150 mg of aspirin (from 11-13 weeks' gestation until 36 weeks) or placebo, showed that in the aspirin arm there was a 62% reduction in incidence of preterm eclampsia (before 37 weeks) and 82% reduction in the incidence of early onset preeclampsia (before 34 weeks).



Who is your aspirin hero?

Emmanuel Bujold, from Université Laval, Quebec, Canada, is my hero because he created order from the chaos of the early preeclampsia and aspirin studies. Without Emmanuel's visionary work it's doubtful that anyone would still be using aspirin to prevent preeclampsia.

In 1979 an observational study had first shown that women who took aspirin regularly during pregnancy were less likely to develop preeclampsia than women who did not.[8] In the subsequent decades, studies investigated low dose aspirin (50 to 150 mg per day) for preventing preeclampsia. However, the difficulty here was lack of unity between the studies – they used different criteria for diagnosing preeclampsia, involved heterogenous groups of patients with hypertension as well as preeclampsia, and made no distinction between women starting treatment before and after 16 weeks gestation. The result was that in a meta-analysis there was only found to be a marginal benefit (10% reduction),[9] leading to the dismissal of aspirin as being of limited use in preeclampsia.

Emmanuel sorted out the confusion by undertaking a meta-analysis only including studies involving low dose aspirin started before 16 weeks.[10] He also considered patients in separate groups according to whether they had severe or mild preeclampsia. It's telling that out of 352 studies reviewed for the meta-analysis, only four (involving 392 women) met his strict criteria.

Results showed when compared with controls, aspirin started at <16 weeks was associated with a significant reduction in severe (relative risk: 0.22, 95% CI: 0.08 to 0.57) but not mild (relative risk: 0.81, 95% CI: 0.33 to 1.96) preeclampsia. From this, Emmanuel concluded that severe and mild preeclampsia have different pathophysiologies and that only severe preeclampsia is susceptible to the benefits of aspirin.

Everything changed with the publication of this paper. It really opened our eyes to the possibility of using aspirin in preeclampsia, and led my other hero, Kypros Nicolaides, to undertake the definitive ASPRE study[7] (see earlier) demonstrating that preeclampsia can be avoided by taking aspirin. Above anyone, Kypros can be credited with establishing our modern approach to treating preeclampsia with aspirin.

Why are you such a big aspirin fan?

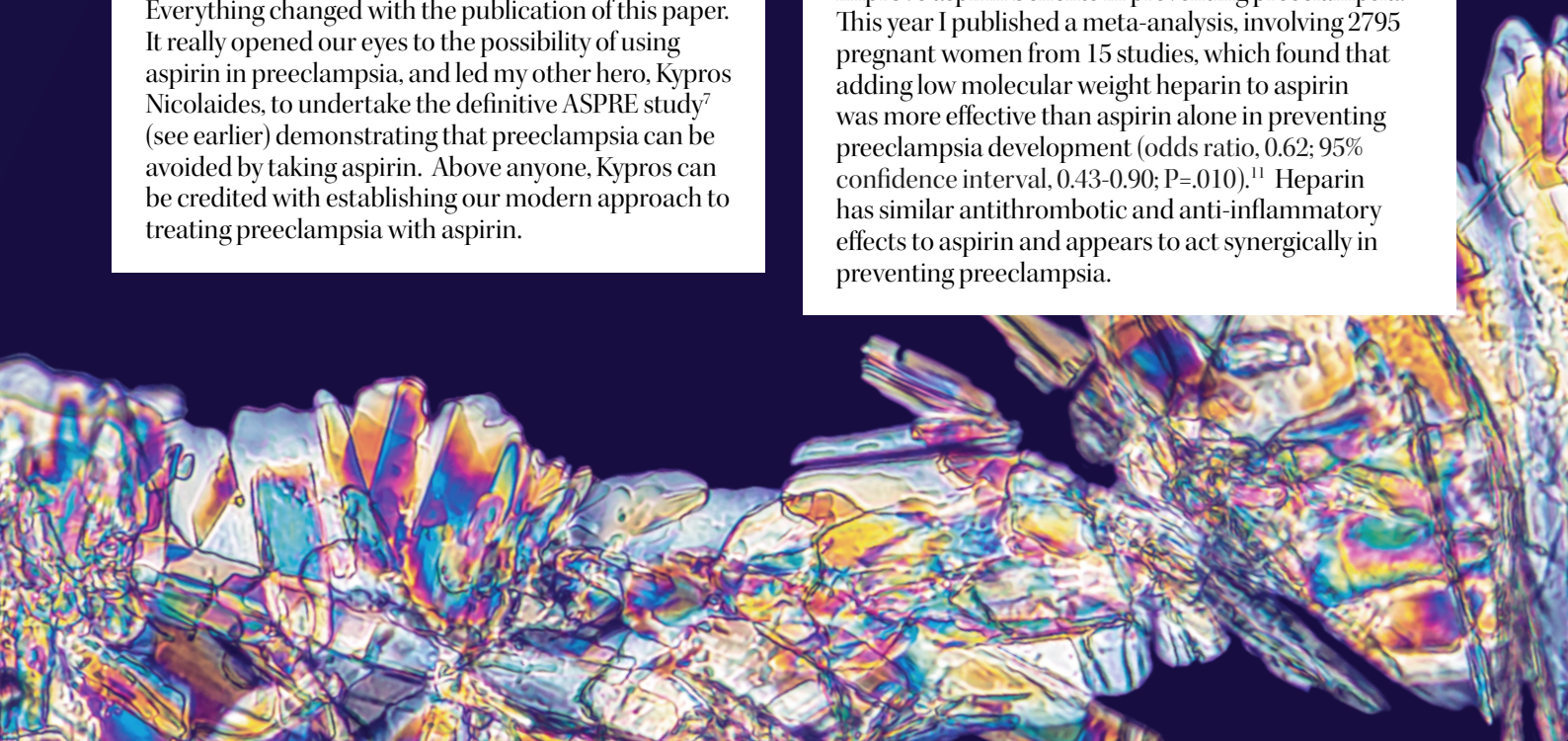
To me, the way aspirin has helped pregnant women avoid the devastation of preeclampsia has been nothing short of a miracle. In recent years aspirin has been responsible for one of the biggest reductions in maternal and foetal mortality ever. In fact, aspirin has proved so successful at preventing preeclampsia that we now struggle to find enough women with the condition to recruit to our clinical trials!

I've always supported the concept of prevention over cure, and to my mind aspirin represents the most important preventive drug in the history of medicine. I love the way aspirin can be used to avoid the development of a range of conditions including CVD, cancer, and preeclampsia. I think the reason for its wide-ranging effects comes down to the way aspirin tackles inflammation, a common root pathway for so many different pathologies.

I also like the fact aspirin is so cost effective and can be used in low-income countries where treatment resources are scarce. While it's unlikely health services in developing countries have the funds for preeclampsia screening, it would be cost effective for them to prescribe aspirin, a drug with few side effects, to all pregnant women as a precautionary measure to avoid preeclampsia. Although of course further studies would be needed in these settings to confirm this hypothesis.

What studies have you undertaken with aspirin?

I've been interested in exploring whether we can improve aspirin benefits in preventing preeclampsia. This year I published a meta-analysis, involving 2795 pregnant women from 15 studies, which found that adding low molecular weight heparin to aspirin was more effective than aspirin alone in preventing preeclampsia development (odds ratio, 0.62; 95% confidence interval, 0.43-0.90; P=.010).[11] Heparin has similar antithrombotic and anti-inflammatory effects to aspirin and appears to act synergically in preventing preeclampsia.



What studies are you now undertaking with aspirin and preeclampsia?

I'm interested in exploring whether giving aspirin prior to invitro fertilization (IVF) could improve the odds of achieving a successful pregnancy. In theory, aspirin given prior to pregnancy might have several benefits including preventing thrombosis, improving the microcirculation and maternal endothelium, and reducing inflammation and oxidative stress.

In our study, which started in early 2021, we are randomising women on our IVF waiting list to six months of aspirin or a placebo prior to implantation. As well as looking at outcomes such as achieving successful pregnancy, we'll also be following up women for preeclampsia as there have been observations women undergoing IVF are more prone to developing the condition. Ultimately, we want to see if aspirin taken prior to pregnancy makes a difference to the course of pregnancy and both maternal and foetal CV health.

I'm also got funding for a cohort study to explore the long-term health consequences of preeclampsia. I hope to enrol four thousand women to gain new insights into how aspirin might mitigate the long-term consequences of preeclampsia.

Are there any other studies you would like to do in aspirin?

The current practice is to discontinue aspirin at 36 weeks due to the possibility of bleeding risks associated with delivery. However, because most preeclampsia occurs after 36 weeks it's likely to be beneficial for women to continue taking aspirin right up to the time of the birth. I'd therefore like to perform a study randomising women at risk of preeclampsia into two groups, one treated with aspirin up to 36 weeks and the other up to delivery. The study would show whether the strategy of continuing aspirin could reduce incidence of late onset preeclampsia and whether there are any adverse effects.

Tell us a surprising fact about aspirin.

Our bodies appear to have circadian rhythms influencing the effectiveness of aspirin. People who take aspirin at bedtime, as opposed to in the morning, get better protection from heart attacks and strokes, and greater reductions in blood pressure, plasma renin activity and cortisol excretion compared to those taking it in the morning. Potential explanations for this effect include the possibilities that aspirin is better absorbed by the gastrointestinal tract at night, and that aspirin taken at bedtime is better placed to attenuate morning peaks of platelet reactivity. Whatever the reason, this appears to be a real effect and we routinely advise pregnant women at risk of preeclampsia to take aspirin at night.

References

1. Chappell LC, Cluver Ca, Kingdom J, et al. Pre-eclampsia. Lancet 2021;398:341-354.
2. Say L, Chou D, Gemmill A, et al.. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2:e323–e333.
3. Leon JL, McCarthy FP, Direk K et al. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records. Circulation. 2019;140:1050.
4. Tan MY, Syngelaki A, Poon LC, et al.Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound Obstet Gynecol. 2018; 52: 186- 195.
5. Mendoza M, Tur H, Garcia-Manau P, et al. Cut-off values for gaussian first-trimester screening for early-onset preeclampsia with maternal history, biochemical markers and uterine artery doppler. J Gynecol Obstet Hum Reprod. 2021;50:101827.
6. Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med 2016;374:13-22.
7. Rolnik DL, Wright D, Poon LC. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Pre-eclampsia. N Engl J Med 2017;377:613-22.
8. Crandon AJ, Isherwood DM. Effect of aspirin on incidence of pre-eclampsia. Lancet 1979;1:1356.
9. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 2007; 369:1791-8.
10. Roberge S, Giguère Y, Villa P et al. Early Administration of Low-Dose Aspirin for the Prevention of Severe and Mild Preeclampsia: A systematic Review and Meta-analysis. American Journal of Perinatology 2012; 29: 551-556.
11. Cruz-Lemini M, Va´zquez JC, Ullmo J, et al. Low-molecular-weight heparin for prevention of preeclampsia and other placenta-mediated complications: a systematic review and meta-analysis. Am J Obstet Gynecol 2022;b226(2S):S1126-S1144.e17.

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