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ASPRE project

ASPRE QUESTIONS AND ANSWERS

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Liona Poon contributed to a pan-European multicentre randomised controlled trial of aspirin vs. placebo in the prevention of pre-term pre-eclampsia (ASPRE), which was funded by the EC FP7 scheme. In the past 10 years she has focused her research on establishing a programme for effective early prediction and prevention of pre-eclampsia, which is a major cause of maternal and perinatal morbidity and mortality.

Edited and reviewed by Dr. Liona Poon

Aspirin related questions

Q: What happens if the women are already on aspirin, when I screen – will this impact the risk?

A: If a woman is already on aspirin at 12 weeks, we should still screen as we aim to provide individualised risk for each pregnant woman. One of the most likely reasons for why someone would be on aspirin before 12 weeks is conception by *in vitro* fertilisation and there is a possibility that the woman is on 75 mg aspirin, which is a suboptimal dosage and it might not be continued till 36 weeks.

Q: How should a doctor manage high risk women who are sensitive or allergic to aspirin?

A: As there is no other proven intervention, then expectant management would be appropriate. This would include frequent BP measurements to ensure early diagnosis of pre-eclampsia.

Other potential prophylaxes, such as Heparin and Metformin, could be considered, depending on why she is categorised as high-risk.

Q: Is there an increase in vaginal spotting with 150 mg of aspirin?

A: No overall increase of vaginal spotting was observed in the ASPRE trial. There was no significant difference in the rate of vaginal bleeding between Placebo and aspirin groups. During the trial, we did not advise women to stop the trial drug based on vaginal spotting.[1]

Q: For those countries, where women are smaller than the women enrolled in the ASPRE study, would you recommend a lower dosage of aspirin?

A: The rates of side effects, in particular upper gastrointestinal symptoms and bleeding, were not significantly different in women with BMI ≤25 kg/m^2 and those with BMI >25 kg/m^2. We therefore do not have data to support the recommendation for a lower dosage of aspirin in smaller women. A study by Masotti et al (1979) demonstrated that doses of 3.5 mg/kg of aspirin seemed to be able to induce maximum inhibition of platelet aggregation without significantly affecting prostacyclin production.[2] Suggested aspirin dosages based on maternal weight are provided in Table 1.

Table 1. Suggested aspirin dosages

Maternal Weight	Required Dosage	Administration
< 40 kg	100 mg	1 x 100 mg
40–90 kg	150 mg	2 x 60 mg 2 x 75 mg 2 x 80 mg
> 90 kg	200 mg	2 x 100 mg

Q: Why can't we just offer aspirin to all women? Why do we need to implement a screening test?

A: If aspirin is effective and 'safe' it should be given to those that would benefit from it the most. As Prof. Zarco Alfirevic commented on the NEJM website "a word of caution to all enthusiasts out there who will now start to advocate (near) universal prescribing of low dose aspirin in pregnancy. The FMF algorithm has identified an interesting phenotype which appears to respond to aspirin very well. We cannot and should not assume that all screen negative women will respond equally well to aspirin. Furthermore, current safety data are reassuring but still limited."

The ASPRE screening algorithm, for the same screen positive rate as per NICE (The National Institute for Health and Care Excellence), identifies 75% of cases of pre-term pre-eclampsia. It identifies a group of at risk women that responds to aspirin in the prevention of pre-term pre-eclampsia.

In addition, we should consider the issue of compliance. A study (McNulty et al, 2011) found that compliance with Folic acid supplementation was only 19% and led to the recommendation of fortification of food in many countries.[3] Though aspirin is considered safe in drug trials, nonetheless, it is a drug with known side effects, and therefore high-risk women for pre-term pre-eclampsia should be identified and compliance with aspirin prophylaxis should be ensured throughout pregnancy.

This is an indication of the level of compliance that can be expected in a motivated high-risk group of women, who are being actively managed by their physicians. Adherence according to trial group is presented in Table 2.

Furthermore, if universal aspirin prophylaxis is to be implemented, in a screened population of 10,000 women, you would give aspirin to 10,000 women to prevent 33 cases of pre-term pre-eclampsia. This means you would give aspirin to more than 9,000 women unnecessarily.

Table 2. Adherence according to trial group

Adherence	Intake of tablet	Aspirin Group (N=798)	Placebo Group (N=822)
Good	≥85% no. (%)	633 (79.3)	661 (80.4)
Moderate	50 - 84.9% no. (%)	121 (15.2)	120 (14.6)
Poor	<50% no. (%)	44 (5.5)	41 (5.0)

Mann-Whitney test for difference in distribution of adherence p=0.89

Q: How do these results meta-analyse with the other studies using aspirin 150 mg vs. placebo?

A: A new meta-analysis (Roberge et al, 2017) including the results of ASPRE, has confirmed that aspirin <100 mg/day starting at any gestation, has no benefit. Aspirin ≥100 mg/day, started after 16 weeks has no benefit; whilst aspirin ≥100 mg/day, started before 16 weeks, has a major benefit.[4]

	Aspirin n/798 vc. Placebo n/822 (OR; 99% Confidence Interval)
Adverse outcomes at <34 weeks' gestation	
Pre-eclampsia	3 vs. 15 (0.18; 0.03 to 1.03)
Gestational hypertension	2 vs. 2 (1.02; 0.08 to 13.49)
Small for gestational age with pre-eclampsia	2 vs. 7 (0.29; 0.03 to 2.48)
Small for gestational age without pre-eclampsia	7 vs. 14 (0.53; 0.16 to 1.77)
Miscarriage or stillbirth without pre-eclampsia	14 vs. 19 (0.78; 0.31 to 1.95)
Placental abruption without pre-eclampsia	1 vs. 3 (0.36; 0.02 to 7.14)
Spontaneous delivery without pre-eclampsia	12 vs. 12 (1.07; 0.37 to 3.10)
Composite	**32 vs. 53 (0.62; 0.34 to 1.14)**
Adverse outcomes at <37 weeks' gestation	
Pre-eclampsia	13 vs. 35 (0.38; 0.16 to 0.91)
Gestational hypertension	8 vs. 7 (1.19; 0.31 to 4.56)
Small for gestational age with pre-eclampsia	5 vs. 13 (0.41; 0.10 to 1.63)
Small for gestational age without pre-eclampsia	17 vs. 18 (1.01; 0.42 to 2.46)
Miscarriage or stillbirth without pre-eclampsia	14 vs. 19 (0.78; 0.31 to 1.95)
Placental abruption without pre-eclampsia	2 vs. 4 (0.52; 0.06 to 4.91)
Spontaneous delivery without pre-eclampsia	40 vs. 49 (0.83; 0.47 to 1.47)
Composite	**79 vs. 116 (0.69; 0.46 to 1.03)**

Clinical implementation questions

Q: What happens if a woman has had pre-eclampsia previously, but now elects to be screened. What if her screening procedure indicates "low risk", but her previous history indicates she is at high risk. How would that patient be managed?

A: In essence the question is, what happens if the woman is screened positive by NICE guidelines, but screened negative by the FMF algorithm. We would manage her as a low risk case as a detail review of her biomarkers would indicate that they are normal. However, if the clinician feels strongly for aspirin prophylaxis, there is no harm in treating this woman with aspirin.

Q: What if UTPI (uterine artery Doppler) is not available, are prior history, serum biochemistry and MAP (mean arterial pressure) enough?

A: To achieve the best prediction and prevention of pre-term pre-eclampsia (<37wks), ideally screening should be done with evaluation of maternal history, measurement of uterine artery Doppler, mean arterial pressure and placental growth factor. In the absence of one or two of the biomarker(s), risk calculation can still be done but the detection rate for pre-term pre-eclampsia will be reduced, in turn leading to a reduction in the treatment effect size by the aspirin prophylaxis.

Q: What if patient presents at 14 weeks. Is there anything a physician can do concerning screening?

A: The algorithm has been validated for the 11–13+6 weeks gestation.

As a minimum a clinician could still use the NICE recommendation: if a woman is at high risk, she should be started on aspirin 150 mg/day.

Q: If a patient is screened as high risk at 11 weeks, you then scan her again at 22 weeks and she is at low risk. How would you manage that patient?

A: This is a hypothetical situation. In ASPRE trial, we did not observe normalisation of the biomarkers with the use of aspirin. Aspirin should be taken from 11–13+6 weeks till 36 weeks.

Q: Given that aspirin did not reduce the prevalence of pre-term pre-eclampsia in women with chronic hypertension, is there any value in screening those women and how would you manage those women clinically?

A: Chronic hypertension is a major risk factor for pre-term pre-eclampsia. The risk is increased by a factor of 15. Number of cases with chronic hypertension was small in the ASPRE study, therefore, it is too soon to draw a conclusion.

If the clinician feels strongly for aspirin prophylaxis, there is no harm in treating with aspirin. Appropriate management of blood pressure is also recommended.

Q: The differences in secondary outcomes were not significant, why was this?

A: The study was not powered for secondary outcomes. To account for comparisons for multiple outcomes, 99% confidence interval was reported, instead of 95% confidence interval. Interestingly, we have observed strong trends in the direction of benefit with the use of aspirin, which are consistent with earlier publications.

Q: How many women need to be screened, to prevent one case of pre-term Pre-eclampsia?

A: If you screen 10,000 women, we anticipate 70 cases of pre-term pre-eclampsia (<37wks). 53 of the 70 cases will be detected by the ASPRE screening algorithm and 33 cases of pre-term pre-eclampsia will be prevented by aspirin prophylaxis. Therefore, the number needed to screen to prevent one case of pre-term pre-eclampsia is 303.

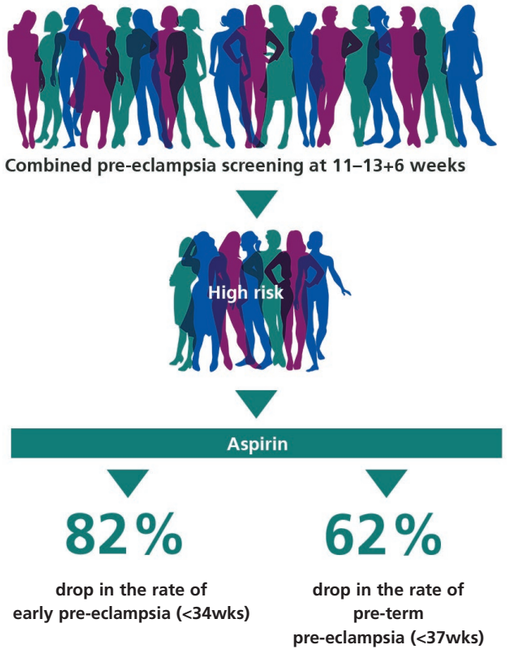
Q: Rates of term pre-eclampsia (≥37wks) and gestational hypertension were not reduced in this study. What value is there in a screening test and treatment, which only impacts on a small proportion of the pre-eclampsia cases?

A: Given pre-eclampsia is a heterogeneous syndrome, it is unrealistic to expect a single screening test and treatment, to identify and prevent all cases of pre-eclampsia.

It is clear that the ASPRE screening test identifies a specific phenotype of pre-eclampsia, which is linked to placental insufficiency. Though it focuses on a small proportion of pre-eclamptic cases, they are those that are associated with higher rates of maternal and perinatal morbidity and mortality.

In addition, these cases of Pre-eclampsia, constitute a significant cost burden to healthcare systems. This is illustrated by the analysis of Stevens et al, AJOG 2017 who reviewed the impact on the US Healthcare system[5] in Table 3.

Having now validated a screening test and confirmed a prophylactic option for women at risk of pre-term pre-eclampsia, future research will focus on identifying appropriate screening tests for term pre-eclampsia.



Estimated unit and total health care cost for pre-eclampsia patients in the United States, by gestational age at birth (2012) using California Office of Statewide Health Planning and Development and commercial claims data

Costs	<28 wks (3604)	28-33 wks (23,624)	34-36 wks (41,856)	37 wks or longer (87, 596)	All (156, 680)
Maternal cost per birth	$29,131	$24,063	$19,692	$17,021	$19,075
Infant cost per birth	$282,570	$59,803	$11,112	$6013	$21,847
Combined cost per birth	$311,701	$83,866	$30,804	$23,035	$40,922
Total health care cost	$1.2 billion	$2.0 billion	$1.3 billion	$2.0 billion	$6.4 billion
Total cost because of infant cost, %	91%	71%	36%	26%	

Table 3. Short-term costs of pre-eclampsia in the US by Stevens et al.[5]

Q: You have previously identified contingent models for cell free DNA test, to limit the number of women, who require this expensive test. Is there a similar contingent model for pre-eclampsia screening, for example first line screening by taking a comprehensive maternal history and identifying a very high risk group, to be given aspirin prophylaxis immediately and then an intermediate risk group, to be offered UTPI, MAP and serum biochemistry. Another option is maternal history and UPTI (as we have access to ultrasound machines) and then identify an intermediate group for PlGF (placental growth factor) and MAP.

A: To achieve the best prediction and prevention of pre-term pre-eclampsia, ideally screening should be done with evaluation of maternal history, measurement of uterine artery Doppler, mean arterial pressure and placental growth factor. In the absence of one or two of the biomarker(s), risk calculation can still be done but the detection rates for pre-term pre-eclampsia will be reduced, in turn leading to a reduction in the treatment effect size by aspirin prophylaxis.

Q: This test will now identify women without clinical risk factors as high risk. This may increase anxiety amongst this group.

A: The screen positive rate using the NICE guideline is the same as with combined screening in the ASPRE trial, 10%. This means that the number of women at potential risk of anxiety is equal with both approaches. The major difference is that the ASPRE algorithm will identify about 75% of women who will develop pre-term pre-eclampsia versus 39% only, with the NICE guideline.

Q: The ASPRE sites underwent training from the FMF. We are concerned that the performance will not be as good in non-expert centres.

A: A training course is available on the FMF website (fetalmedicine.org). This is a 1 hour course, which provides all of the information necessary to be able to implement this screening. Different options are described, which allow for local challenges in implementation, with minimal impact on performance. It is not necessary to start with the full protocol, if there are local challenges to be addressed. It is however important to start offering the new model of screening, since regardless of which option is adopted, it is clearly offering women a better clinical service than current guidelines.

Q: Twins were amongst the exclusion criteria. Would you offer this screening to women with twin pregnancies? Are twins included in the FMF algorithm?

A: Twin pregnancy is considered as a moderate risk factor, according to the NICE recommendation. The risk of pre-term pre-eclampsia is significantly higher in twin pregnancy, approximately 15%. The new FMF algorithm does include twin pregnancy as a risk factor. However, there is no data on the evidence of efficacy of aspirin in twin pregnancy.

If the clinician feels strongly for aspirin prophylaxis, there is no harm in treating these women with aspirin.

Q: Why did 10% of pregnant of women, withdraw from the trial? This is considered high.

A: The percentage of patients agreeing to participate was unexpectedly high and in some respects, it was not surprising, that 10% reconsidered their decision and decided not to participate in the trial.

Q: Abruption with pre-eclampsia: why were these not reported?

A: This outcome was not included in our Statistical Analysis Plan. However, the data is as followed:

In the aspirin group: 5 (0,6%) abruption, 1 with pre-eclampsia (not pre-term pre-eclampsia)

In the Placebo group: 10 (1,2%) abruption, 4 with pre-eclampsia (all pre-term).

Risk Assessment Questions

Q: It would appear that the screening performance of the risk algorithm in the ASPRE study was not as effective as reported in O'Gorman et al, 2017, is this correct?

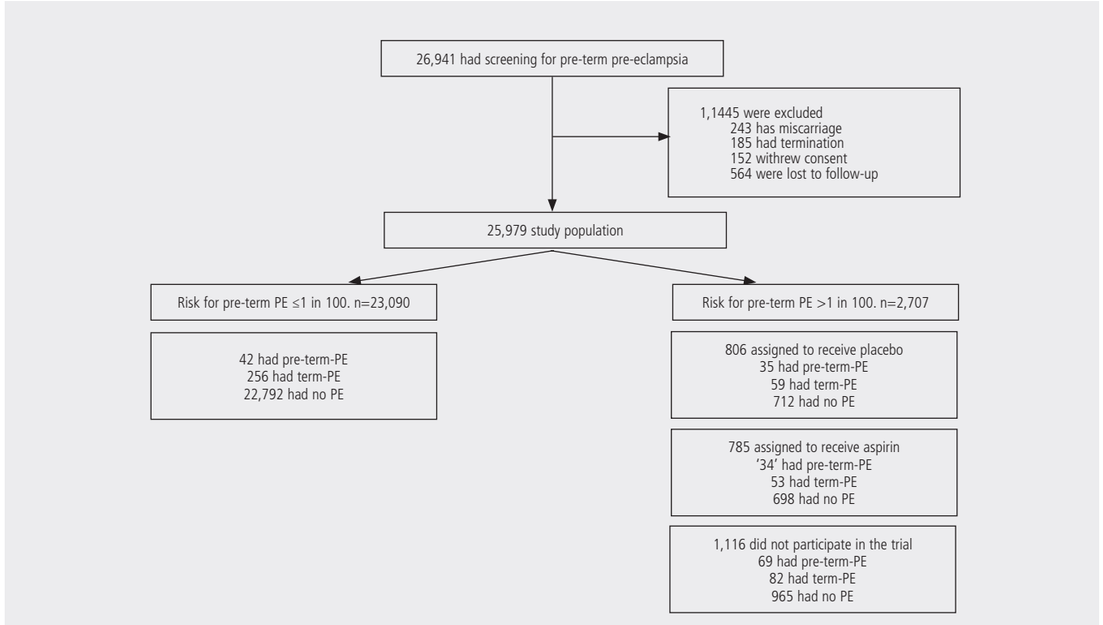
A: No, it is not correct.

In our prospective validation study including a study population of 25,797 pregnancies, with 180 (0.7%) cases of pre-term pre-eclampsia, 450 (1.7%) of term pre-eclampsia and 25,167 (97.6%) without pre-eclampsia. With a risk cut-off of 1 in 100, combined first-trimester screening for pre-term pre-eclampsia detected 76.7% (138/180) of pre-term pre-eclampsia and 43.1% (194/450) of term pre-eclampsia, at screen positive rate of 10.5% (2,707/25,797) and false positive rate of 9.2% (2,375/25,797). More detailed information is shown in the diagram below.

Conclusion:

Furthermore, the performance of screening during the ASPRE trial was compatible with that of a study[6] of approximately 60,000 singleton pregnancies used for development of the algorithm; reporting that combined screening detected 76.6% of cases of pre-term pre-eclampsia and 38.3% of term pre-eclampsia at false positive rate of 10%.

If you have further ASPRE questions, please contact your local PerkinElmer representative.



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