Prediction and prevention of early onset pre-eclampsia: The impact of aspirin after first trimester screening

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Abstract

Introduction:

Pre-eclampsia continues to be a significant cause of maternal and fetal mortality. Several recent studies have shown that the early onset form of disease (ePET), leading to delivery on maternal grounds <34 weeks gestation, can often be predicted at 11-13^{+6} weeks' gestation. We examined **the effect of the combination of screening and treatment with low dose aspirin on the rate of ePET.**

Study Design:

This study involved retrospective analysis of two consecutive cohorts of women screened for ePET. The first cohort was observed, to determine whether algorithms developed to screen for pre-eclampsia at 11-13^{+6} weeks' gestation could be applied to our population. High-risk women in the second cohort were advised of their risk and offered aspirin (150mg **at night**) with treatment starting immediately after screening. The prevalence of ePET and PET at 34-37 weeks' gestation was compared between these cohorts.

Results:

3066 and 2717 women were screened respectively in the observational and interventional cohorts. There were twelve cases (0.4%) of ePET in the observational cohort and one (0.04%) in the interventional cohort (p=0.01). For all preterm PET (<37 weeks) there were 25 cases (0.83%) in the observational cohort and 10 (0.37%) in the interventional cohort (p=0.03).

Conclusions:

A strategy of first trimester screening for ePET coupled with prescription of aspirin to the high-risk group appears to be effective in reducing the prevalence of ePET.

Introduction:

Pre-eclampsia continues to be a significant cause of maternal and fetal mortality and morbidity in both developed and developing societies.[1-3] A number of approaches that aim to reduce the impact of this disease have been suggested, based either on prediction and prevention or modulation of disease. Although no isolated marker has been identified as an effective screening tool, multivariate analysis has been shown to be of value in developing predictive models that can be applied as early as 11-13^{+6} weeks gestation.[4-8] These models are predictive for pre-eclampsia that develops at an early gestation and subsequently leads to delivery, on maternal grounds, prior to 34 weeks gestation (ePET).

We recently validated an algorithm that predicts the risk of developing ePET using a combination of maternal demographic, biophysical (maternal mean arterial pressure (MAP) and uterine artery Doppler pulsatility index (PI)) and biochemical (pregnancy associated placental protein A (PaPP-A) parameters.[6] The original algorithm included a second biochemical marker, placental growth factor (PlGF), that was not available to us for routine clinical practice.[7] In this observational study, we confirmed that this algorithm predicted 92% of women that developed ePET with a 10% screen positive group.[6]

A number of groups have investigated the value of low dose aspirin (LDA) as a therapeutic intervention. The value of this treatment remains controversial. Whilst some individual randomized controlled trials showed no, or minimal benefit from this intervention,[10-15] recent meta-analyses have suggested that, provided treatment is started at an early (<16 weeks') gestation, there is a reduction in early onset pre-eclampsia and that this is associated with a reduction in prevalence of perinatal death and morbidity.[16,17] A number of national and international agencies now recommend that women deemed to be at high risk of pre-eclampsia should be offered aspirin therapy.[18,19] We aimed to demonstrate the value of LDA intervention following first trimester prediction of ePET in an unselected population.

Methods:

We report the retrospective analysis of two consecutive cohorts screened for ePET. Both cohorts included women **with a singleton pregnancy** who were screened, and later delivered, in a tertiary obstetric hospital in Sydney. Women were primarily referred by their family doctor for screening for chromosomal abnormality, a test offered to all pregnant women booking for antenatal care in our health district. The first cohort, screened between 16 April 2010 and 9 March 2012, were observed and used to validate the Fetal Medicine Foundation (FMF) ePET algorithm; there was no therapeutic intervention. Women were screened by combination of demographic history, mean arterial pressure, uterine artery Doppler and PaPP-A.[6] The second cohort of women were screened, using the same

algorithm, between 1 April 2012 and 5 June 2013. Those defined as being 'high-risk' (with a risk ≥2% for ePET) were told of their risk and advised to take aspirin (150mg **at night**) to 34 weeks' gestation. The audit of this change in clinical practice, defining a high-risk cohort based on the first trimester predictive model rather than on this basis of demographic history alone, was approved by our local ethics committed (Ethics No: RPA 11-0305). The validation of the screening algorithm has been reported previously.[6]

Data related to risk assessment at the $11\text{-}13^{+6}$ week scan were collated with data describing pregnancy outcome. These data were available through the fetal medicine (Viewpoint version 5.6.9.483, GE Healthcare, Germany) and general obstetric and neonatal (Cerner Powerchart, Kansas City, Missouri, USA) service databases. The general obstetric and neonatal databases collect a variety of information related to antenatal, intrapartum and postnatal care as mandated by the NSW State health service. The medical records were also reviewed for all women delivering <37 weeks' gestation or in circumstances where the computerized data were found to be incomplete to ensure accuracy of registry information.

Pre-eclampsia was defined as de novo hypertension arising after 20 weeks' gestation, returning to normal postpartum, with proteinuria (24hr urine protein ≥300 mg or spot urine protein/creatinine ratio ≥30 mg protein/mmol creatinine) according to the criteria of the International Society for the Study of Hypertension in Pregnancy.[19] Chronic hypertension was defined by a history of hypertension prior to conception or of hypertension diagnosed <20 weeks' gestation. Women with chronic hypertension were not categorized as having hypertensive disease of pregnancy unless they subsequently developed pre-eclampsia. Sub-groups of women being delivered prematurely due to pre-eclampsia <34 weeks' and between 34^{+0} and 36^{+6} weeks' gestation were identified.

The demographic features of the two (observation and intervention) groups were compared using a Mann-Whitney U test for non-parametric data, t-test for continuous data that was normally distributed and Chi-squared test for categorical data. The prevalence of ePET and PET at 34-37 weeks' gestation were compared using a Chi-squared test. The statistical software package SPSS version 22 (IBM, Chicago, USA) was used for all data analyses.

Results:

3066 women were screened for ePET in the observational cohort; 2717 women were screened in the therapeutic cohort. 3014 (98.3%) and 2668 (98.2%) of women in the observation and interventional cohorts had a live birth and were included in the analysis. There were two women in the observational cohort and one woman in the therapeutic cohort who experienced an early neonatal death (<34 weeks). None of these women developed pre-eclampsia. The woman in the therapeutic cohort had screened low risk for pre-eclampsia and was not given aspirin. These women were excluded from further analysis. Rates of termination of pregnancy, intrauterine fetal death and neonatal death were the same in both cohorts (Table 1). The demographic characteristics of the two cohorts are shown in Table 2. There was a significant difference in the age of the women with the interventional cohort being slightly younger. The parity of women also differed between the two groups with more nulliparous women in the interventional cohort. There were less Caucasian women and more East Asian women in the interventional cohort. The rate of smoking was lower in the interventional cohort and the rate of previous pre-eclampsia in multiparous women was significantly higher in the interventional group. MAP MoM, UtAPI MoM and PAPPA MoM were all slightly higher in the interventional cohort. No other demographic factors were significantly different. The rates of pre-eclampsia for women who screened positive are outlined in Table 3.

11 (92%) of the 12 (prevalence 0.4%) women in the observational cohort who developed ePET were in the screen positive cohort with a calculated risk >90th centile.[6] 264 (9.9%) women in the interventional cohort had a risk of ePET $\geq$2% and were advised to take aspirin. One (prevalence 0.04%) developed ePET (Chi-squared: p=0.01). There were no cases of ePET reported in women who were low risk in the interventional cohort. Based on the prevalence of ePET seen in the observational cohort, we would have expected 10 cases of ePET in the interventional cohort. For every 29 **(95% CI 18-82)** women advised to take aspirin because they were high risk for ePET, one case of ePET was prevented. For every 296 **(95% CI 179-852**) women who were screened at 11-13^{+6} weeks, one case of ePET was prevented. In the observational cohort nine of the women who developed ePET were nulliparous and three were multiparous. In the intervention cohort the only woman to develop ePET was multiparous and had previously delivered <34weeks due to ePET.

13 (0.4%) of the women that were not delivered for ePET in the observational cohort were delivered at 34-36^{+6} weeks' gestation due to maternal symptoms and signs of pre-eclampsia, 6 of these women screened positive for ePET. Nine (0.3%) women in the interventional cohort were delivered at this late preterm gestation, 6 of these women screened positive for ePET. There was no significant difference between these two groups (p=0.57). Considered in combination 25 (0.83%) women were delivered for pre-eclampsia prior to 37 weeks in the

observational cohort. 10 (0.37%) women were delivered for the same indication in the interventional cohort showing a significant reduction (p=0.03).

71 (2.36%) women in the observational cohort were delivered due to pre-eclampsia at any gestation. 38 (1.42%) women in the interventional cohort were delivered due to pre-eclampsia at any gestation. The intervenional cohort showed a significant reduction in delivery for pre-eclampsia at any gestation (p=0.01).

Five (0.2%) women in the interventional cohort had a placental abruption. One was high risk for ePET at 12 weeks and was recommended to commence aspirin. The other four women were low risk for ePET at 12 weeks' gestation and did not take aspirin during their pregnancy. Although the cohorts are not large enough to be powered for statistical comparison there is no obvious increase in the rate of abruption in the cohort of women advised to start aspirin at 12 weeks' gestation.

Discussion:

We have demonstrated that the combination of a program that screens and identifies women at high risk for ePET at 11-13^{+6} weeks gestation followed by provision of aspirin as a therapeutic intervention reduces the prevalence of ePET significantly, with a 90% reduction in prevalence of disease. Aspirin needs to be prescribed to 29 high-risk women to prevent one case of ePET. 296 women need to be screened to prevent one case of ePET. The impact of screening and prevention is similar to many other interventions routinely used in obstetric management. Aspirin given to women on the basis of having a high-risk for ePET did not appear to impact on the prevalence of disease leading to delivery at 34-36^{+6} weeks' gestation however the numbers are small. When all preterm pre-eclampsia was considered there was a significant reduction in the number of women requiring delivery for pre-eclampsia prior to 37 weeks. The overall number of women requiring delivery for pre-eclampsia at any gestation was also lower in the interventional cohort.

The two groups demonstrated significant differences in some of the baseline characteristics. The interventional cohort included more nulliparous women and more multiparous women with a history of preeclampsia. There were less smokers in the interventional group. All of these are recognized risk factors for pre-eclampsia. The interventional cohort did include slightly younger women and more East Asian women than the observational group. It is possible that the affect of low dose aspirin is greater than demonstrated here.

Reviewing the use of low dose aspirin as a therapeutic agent to reduce the prevalence of pre-eclampsia reveals a tortuous path littered with periods of excitement and disappointment. Beaufils *et al*. (1985) first randomized 102 patients at high risk of pre-eclampsia and/or intrauterine growth restriction (IUGR) to a combination of Dipyridamole (300mg) and aspirin (150mg) or no treatment from 12 weeks' gestation: 15% of pregnancies in the non-treatment

group had an adverse outcome compared to none in the group treated with Dipyridamole and aspirin.[21] A second group treated primigravida women deemed to be high risk through an Angiotensin II challenge test from 28 weeks' gestation with aspirin (60mg) or placebo and reported a significantly lower rate of pre-eclampsia in the treatment arm.[21] This stimulated further interest leading to the report of the large Italian, US and predominantly UK-based CLASP studies that recruited >13,000 high risk patients, used 50-60mg aspirin for treatment and started therapy through a wide gestational age range, predominantly >16 weeks' gestation. The main outcome measure was prevention of all types of hypertensive disease (i.e. *not* only ePET). None of these trials demonstrated an obvious benefit from aspirin therapy.[10-12] Other large trials examined the use of aspirin in cohorts of primigravida patients, once again using lower doses of aspirin for treatment and enrolling most patients >16 weeks gestation.[13,14] These studies showed no benefit and raised concerns that aspirin may be associated with an increased risk of bleeding and of placental abruption. An alternative means of defining a high-risk group – through analysis of uterine artery blood flow at 22-24 weeks' gestation was coupled to randomised prescription of aspirin (150mg) or placebo.[15] This also failed to show any benefit in the use of aspirin and described a non-significant increase in rates of placental abruption (the study was not powered for this endpoint).

Despite the findings of these studies, meta-analysis of all relevant randomised controlled trials does show a small, but modest benefit in using aspirin to prevent pre-eclampsia.[23] Further analysis suggests that it is early intervention (<16 weeks gestation) that is of most benefit, resulting in a 50% reduction (RR 0.47, 95% CI, 0.34–0.65) in pre-eclampsia at all gestations and a 90% reduction (RR 0.11; 95% CI, 0.04–0.33) in ePET.[16,24] This data also supports a significant reduction (RR 0.41; 95% CI, 0.19–0.92) in perinatal morbidity related to this disease.[17] The value of aspirin is accepted by a number of national and international institutions who recommend prescription to high risk groups. This provides the rationale for our current practice; having determined that first trimester (11-13^{+6} weeks) screening was a better predictor for ePET than maternal history alone,[6] we decided to couple this screening process to intervention, rather than prescribing aspirin to women deemed to be high risk at the time of their obstetric medical booking visit – that would typically occur at 16-22 weeks' gestation. It is important to acknowledge that our understanding of the mechanism of action of aspirin is incomplete and further work is needed to investigate the hypothesis that its value in the first trimester includes a direct effect on placentation.[25,26]

Due to the heterogeneity of data and the relatively small number of cases that can be included in meta-analyses limited to treatment <16 weeks' gestation, some researchers have suggested that the combination of first trimester screening and early low dose aspirin intervention should be tested in a randomised controlled trial.[24] Such trials are ongoing, with published protocols; our data potentially help inform sample size calculations for these

studies.[27] The dose and timing of low dose aspirin is also controversial. Most of the randomised controlled trials performed to date have used lower doses (<80mg) of aspirin. In studies focusing on the effect aspirin has on platelet function, there is evidence that up to 30% of women are resistant to low dose therapy.[28,29] Similarly, previous trials have failed to define a specific time at which aspirin should be taken whilst there is good evidence that it is more effective when taken at night.[30,31] For these reasons, we chose to treat women with 150mg aspirin – using a generic non-enteric coated formulation – to be taken at night.

There are a number of limitations to this study. The cohorts of women were not concurrent, rather collected serially; although there was only a short time interval between these two groups and no other changes in management were made during this time. We discussed high-risk results with women directly at the time of first trimester screening and the advice to start / maintain aspirin was reiterated during subsequent antenatal visits but we did not measure patient compliance. A handful of women reported that they had either not started, or had subsequently stopped aspirin; either because they were allergic to aspirin, did not want to take tablets in pregnancy or reacted to aspirin in some way. Although we found no evidence of an increased prevalence of placental abruption in women taking aspirin, the study is not large enough to demonstrate this conclusively. We did not collect data in relation to risk of maternal postpartum or neonatal intra-cerebral haemorrhage.

A strategy of screening women with a first trimester algorithm for risk of developing ePET and advising high-risk women to take aspirin to 34 weeks' gestation does appear to be effective in reducing the prevalence of ePET. The reduction in prevalence of pre-eclampsia is consistent with recent meta-analyses focusing on women treated <16 weeks' gestation and on outcomes <34 weeks' gestation. These findings may better inform those who remain in equipoise in designing corroborative randomised controlled trials.

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Table 1: Pregnancy outcomes for women in observational and interventional cohorts.

	Observational cohort (n (%))	Interventional cohort (n (%))	Significance
Number screened at 11-13^{+6} weeks	3066	2717	
Termination of pregnancy	27 (0.88%)	36 (1.32%)	P=0.11
Intrauterine fetal death <24 weeks	14 (0.46%)	9 (0.33%)	P=0.45
Intrauterine fetal death ≥24 weeks	9 (0.30%)	3 (0.11%)	P=0.13
Neonatal death (Delivered <24 weeks)	1 (0.03%)	0 (-)	P=0.35
Neonatal death (Delivered 24-34 weeks)	1 (0.03%)	1 (0.04%)	P=0.93
Neonatal death (Delivered >34 weeks) *	1 (0.03%)	2 (0.08%)	P=0.49
Overall perinatal death rate	26 (0.85%)	15 (0.55%)	P=0.18
Live births	3013 (98.27%)	2666 (98.12%)	P=0.67
All PET	71 (2.36%)	38 (1.42%)	P=0.01
PET >37 weeks	46 (1.53%)	28 (1.05%)	P=0.11
All PET <37 weeks	25 (0.83%)	10 (0.37%)	P=0.03
PET between 34-36+6	13 (0.43%)	9 (0.34%)	P=0.57
PET < 34 weeks	12 (0.40%)	1 (0.04%)	P<0.01

* Included in Live Births risk analysis of early preeclampsia

Table 2: Characteristics of women in observational and interventional cohorts.

Maternal characteristics		**Observational cohort (no treatment) N=3066**	**Interventional cohort (Rx Aspirin 150mg nocte) N=2717**	**Significance**
Age (years)	Median (IQR)	33.34 (30-36.3)	32 (29-35)	P < 0.01
Parity (n (%))	Nulliparous	1610 (52.5%)	1699 (62.5%)	P < 0.01
	Multiparous	1457 (47.5%)	1018 (37.5%)	
Ethnicity (n (%))	Caucasian	2073 (67.5%)	1722 (63.4%)	P < 0.01
	East Asian	635 (20.7%)	659 (24.3%)	P < 0.01
	South Asian	309 (10.1%)	297 (10.9%)	P = 0.29
	African	32 (1.04%)	18 (0.7%)	P = 0.12
	Other	19 (0.62%)	21 (0.8%)	P = 0.48
Body mass Index (kg/m^2)	Median (IQR)	23.5 (21.4 - 26.4)	23.4 (21.4 – 26.5)	P = 0.74
Smoking (n (%))	Non-smoker	2973 (97.4%)	2657 (97.8%)	P = 0.07
	Smoker	93 (2.6%)	60 (2.2%)	
Previous PET (n (% of multiparous patients)	No	1401 (96.2)	954 (93.7)	P < 0.01
	Yes	55 (3.8)	62 (6.1)	
CRL at screening (mm)	Median (IQR)	64.75 (60 – 69.3)	64.9 (59.99 – 70.68)	P = 0.054
Mean arterial pressure (MoM)	Median (IQR)	0.98 (0.92 – 1.04)	1.07 (1.01 – 1.13)	P < 0.01
Uterine artery PI (MoM)	Median (IQR)	1.00 (0.79-1.26)	1.06 (0.87 – 1.305)	P < 0.01
PaPP-A (MoM)	Median (IQR)	1.05 (0.72 – 1.51)	1.17 (0.8 – 1.67)	P < 0.01

Table 3: Pregnancy outcomes for women with a live birth who screened high risk for ePET in the observational and interventional cohorts.

	Observational cohort (n (%))	Interventional cohort (n (%))	Significance
Number screened high risk at 11-13^{+6} weeks	301	264	
Neonatal death (>34 weeks)	1 (0.33%)	1 (0.38%)	P=0.93
No PET	269 (89.5%)	247 (93.56%)	P=0.08
All PET	31 (10.3%)	17 (6.44%)	P=0.10
PET ≥37 weeks	14 (4.65%)	10 (2.75%)	P=0.61
All PET <37 weeks	17 (5.65%)	7 (2.65%)	P=0.08
PET between 34-36+6	6 (1.99%)	6 (2.27%)	P=0.82
PET < 34 weeks	11 (3.65%)	1 (0.38%)	P<.0.01

* Included in Live Births risk analysis of early preeclampsia