Aspirin delays the development of preeclampsia

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Condensation

Prophylactic use of aspirin may reduce the risk of both preterm and term preeclampsia by delaying the gestational age at delivery with the disease.

Short version of article title

Aspirin delays the development of preeclampsia.

Implications and Contributions

A. This is an unplanned secondary analysis of data from the ASPRE trial to explore the hypothesis that in women at high-risk of preeclampsia, use of aspirin delays the gestational age at delivery with the disease.

B. In the ASPRE trial treatment with aspirin reduced the incidence of early and preterm preeclampsia by about 80% and 60%, respectively, but had no significant effect on the incidence of term preeclampsia. We have developed and fitted a model which demonstrates that aspirin may prevent both preterm and term preeclampsia and the reduction of the latter is by about 40%. However, the overall incidence of term preeclampsia is not affected because cases of term preeclampsia prevented are countered by cases of preterm preeclampsia that are delayed by the effect of aspirin.

C. The ASPRE trial data are consistent with the hypothesis that aspirin reduces the risk of both preterm and term preeclampsia by delaying the gestational age at delivery with PE.

ABSTRACT

Background: In the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial risks of preterm preeclampsia (PE) were obtained from the competing risk model. Consenting women with risks of greater than 1 in 100 were randomised to treatment with aspirin or placebo. The trial showed strong evidence of an effect (odds ratio 0.38, 95% confidence interval 0.20 to 0.74) on the incidence of preterm-PE, which was the primary outcome of ASPRE. There was a small and insignificant effect on the incidence of term-PE which was one of the secondary outcomes (odds ratio 0.95, 95% CI 0.64 to 1.39). These differential effects on term and preterm-PE could reflect a mechanism in which the action of aspirin is to delay the delivery with PE thereby converting what would, without treatment, be preterm-PE to term-PE.

Objective: To examine the hypothesis that the effect of aspirin is to delay the time of delivery with PE.

Study design: This was an unplanned exploratory analysis of data from the ASPRE trial. The delay hypothesis predicts that in groups for which preterm-PE, without aspirin, were infrequent relative to term-PE, a reduction in term-PE would be expected because few cases of preterm-PE would be converted to term-PE. In contrast, in groups for which preterm-PE were frequent relative to term-PE, the conversion of preterm-PE to term-PE by aspirin would reduce or even reverse any effect on the incidence term-PE. This is examined using the ASPRE trial data by analysis of the effect of aspirin on the incidence of term-PE stratified according to the risk of preterm-PE at randomization. Given that women were included in ASPRE with risks of preterm PE > 1 in 100, a risk cut-off if 1 in 50 was used to define higher risk and lower risk

strata. A statistical model in which the effect of aspirin is to delay the gestational age at delivery was fitted to the ASPRE trial data and the consistency of the predictions from this model with the observed incidence was demonstrated.

Results: In the lower risk group (<1 in 50), there was a reduction in the incidence of term-PE (odds ratio 0.62, 95% confidence interval 0.29 to 1.30). In contrast, in the higher risk group (≥1 in 50) there was a small increase in the incidence of term-PE (odds ratio 1.11, 95% confidence interval 0.71 to 1.75). Although these effects fail to achieve significance, they are consistent with the delay hypothesis. Within the framework of the aspirin-related delay hypothesis, the effect of aspirin was to delay the gestational age at delivery with PE by an estimated 4.4 weeks (95% CI 1.4 to 7.1 weeks) for those that in the placebo group would be delivered at 24 weeks and the effect decreased by an estimated 0.23 weeks (95% CI 0.021 to 0.40 weeks) for each week of gestation so that at 40^{+0} weeks the estimated delay was by 0.8 weeks (95% confidence interval -0.03 to 1.7 weeks).

onclusions: The ASPRE trial data are consistent with the hypothesis that aspirin delays the gestational age at delivery with PE.

Key words: First trimester screening, Aspirin, ASPRE trial, Preeclampsia, Pyramid of pregnancy care, Competing risks model, Preterm delivery, Term delivery, Pregnancy

INTRODUCTION

In the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial, singleton pregnancies identified through screening at 11-13 weeks' gestation by a combination of maternal factors and biomarkers as being at high-risk of PE, were randomized to receive aspirin (150 mg per day) vs. placebo from 11 to 14 until 36 weeks' gestation.[1] Treatment with aspirin reduced the rate of preterm-PE, with delivery before 37 weeks' gestation, (odds ratio 0.38, 95% confidence interval 0.20 to 0.74), but there was no significant effect on the incidence of term-PE (odds ratio 0.95, 95% CI 0.64 to 1.39).

It is uncertain whether preterm-PE and term-PE have different pathogenetic mechanisms or are merely gradations of the same underlying condition.[2] Similarly, the mechanism of action of aspirin in preventing PE is uncertain. One explanation for the results of the ASPRE trial is that the pathophysiology of preterm-PE and term-PE is different and that only the former is susceptible to the preventative effects of aspirin. An alternative hypothesis is that aspirin reduces the risk of both preterm-PE and term-PE and its effect is to delay the gestational age at delivery with PE so that some cases of term-PE that are prevented are replaced by cases of preterm-PE; consequently, the incidence of term-PE is increased by shifts from preterm PE to term PE countering the effects of aspirin in preventing term-PE.

The objective of this study is to examine whether an aspirin-related delay in the gestational age at delivery with PE could explain the findings of the ASPRE trial.

MATERIALS AND METHODS

The ASPRE trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel.[1] In the 13 participating hospitals routine screening for preterm-PE was carried out at 11-13 weeks' gestation by an algorithm combining maternal demographic characteristics and medical and obstetrical history,[3-5] with the measurements of mean arterial pressure,[6] uterine artery pulsatility index[7] and serum pregnancy associated plasma protein-A and placental growth factor (PAPP-A and PlGF 1-2-3^{TM} kits, DELFIA® Xpress random access platform; PerkinElmer Inc. Wallac Oy, P.O.Box 10, 20101 Turku, Finland). The eligibility criteria for the trial were maternal age $\geq$18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11-13 weeks scan and estimated risk for preterm-PE of >1 in 100.[4] Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted.

Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy.[8] The systolic blood pressure should be >140 mmHg and/or the diastolic blood pressure should be >90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. Hypertension should be accompanied by proteinuria of >300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension.

Statistical analyses

This is an unplanned secondary analysis of data from the ASPRE trial. In ASPRE, the patient-specific risk for PE was estimated by the competing risks approach.[3,4] In this approach it is assumed that if the pregnancy was to continue indefinitely all women would develop PE and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE. The effects of variables from maternal demographic characteristics, medical history and biomarkers is to modify the distribution of gestational age at delivery with PE so that in pregnancies at low risk for PE the gestational age distribution is shifted to the right with the implication that in most pregnancies delivery will actually occur before development of PE. In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age the higher is the risk for PE.

Subgroup Analysis – Stratification by risk of preterm PE

The prevention of term-PE and the transition from preterm-PE to term-PE was explored by analysis of the effect of aspirin on the incidence term-PE stratified according to risk of preterm-PE at randomization. Given that women were included in ASPRE with risks of preterm PE > 1 in 100, a risk cut-off of 1 in 50 was used to define higher risk and lower risk strata. Estimates and confidence intervals for the effect on term-PE in the higher and lower risk groups were obtained by fitting separate mixed effects logistic regression models with fixed effects for treatment and for the logistic transformation of risk of preterm-PE and random effects for participating centre.

Aspirin-related shift model

The analysis explores the hypothesis that aspirin shifts the distribution time to delivery with PE. We postulate that, if T denotes the random variable representing the gestational age at delivery with PE in the placebo group, the effect of aspirin is a delay of δ shifting the distribution to that of T + δ. In randomized controlled trials, where there is no censoring, this model is used extensively with t-tests being applied to test the null hypothesis that $\delta = 0$. In applications to PE, the same model can be applied but the analysis needs to take account of censoring using a survival time model. In terms of the conventional classification of preterm-PE (T < 37 weeks) and term-PE (T ≥ 37 weeks), the effect would be to prevent some term-PE because birth for other causes would occur prior to PE. However, for some women delays to preterm-PE would lead to term-PE.

We fitted a model to reflect the hypothesis of an aspirin-related shift effect with δ decreasing with gestational age, so that the magnitude of the delay in gestational age at delivery with PE is greater at earlier than later gestational ages (Figure 1).

We assumed a Gaussian distribution for T in the placebo group with a mean dependent of the logit of the risk according to a linear regression model and a constant standard deviation σ. In the aspirin group, the same model was used but T was increased by the treatment effect $\delta = \beta_0+\beta_1(T -24)$. With this parameterisation β_0 represents the effect of aspirin at 24 weeks gestation. For every week of gestation after 24 weeks, this the effect is reduced by $-\beta_1$. The standard deviation in the aspirin group is $(1 +\beta_1) \sigma$.

Using a non-informative prior distribution for unknown parameters, the aspirin-related shift model was fitted within a Bayesian framework using Markov chain Monte Carlo (MCMC) implemented inWinBUGS.[9] Inferences for model parameters are presented in terms of posterior means, standard deviations and 95% credibility intervals. Samples from the posterior predictive distribution were used to simulate ASPRE outcome data as follows. Samples of 5,000 observations of the model parameters were taken from the MCMC iterations. For each of these, the gestational ages at delivery with PE were generated for the 1,620 trial participants for both the aspirin and placebo treatments. Gestational ages at births due to other causes were obtained by sampling with replacement from the gestational ages at birth due to other causes from the ASPRE trial. PE events were then defined according to whether the gestational age at delivery with PE was younger than the gestational age due to births from other causes. This provided 5,000 samples from the posterior predictive distribution of data from the ASPRE trial under the assumption of the model.

As described above WinBUGS[9] as used for model fitting, the statistical software R was used for data analyses.[10]

RESULTS

The distribution of gestational age at delivery with PE in the placebo and aspirin groups is shown in Figure 2, which demonstrates that in the aspirin group the incidence of early deliveries with PE is reduced.

A subgroup analysis of incidence of preterm-PE and term-PE is given in Table 1. The

higher risk group contains those with risks of preterm-PE of ≥1 in 50 and the lower risk group those with risks of <1 in 50. In the higher risk placebo group the ratio of term-PE to preterm-PE is 41 to 31 (1.3 to 1) compared to a ratio of 18 to 4 (4.5 to 1) in the lower risk group. Therefore, in the higher risk group there are relatively more cases of preterm-PE that could, with aspirin, convert to term-PE than in the lower risk group. These transitions from preterm-PE to term-PE would counteract cases of term-PE prevented by aspirin. In contrast, in the lower risk group, there are relatively few cases of preterm-PE that could be converted to term-PE. As expected under the hypothesis of the shift model, there was a larger decrease in incidence of term-PE in the lower risk group (Figure 3). In the lower risk group there was a reduction in the incidence of term-PE (odds ratio 0.62, 95% confidence interval 0.29 to 1.30), whereas in the higher risk group there was a small but insignificant increase in the incidence of term-PE (odds ratio 1.11, 95% confidence interval 0.71 to 1.75).

In the survival analysis, 90% of observations were censored, 92% in the aspirin group and 88% in the placebo group. Parameter estimates from the aspirin-related shift model are shown in Table 2. The effect of aspirin treatment was to delay the gestational age at delivery with PE by an estimated 4.4 weeks (95% credibility interval 1.4 to 7.1 weeks) for those that in the placebo group would be delivered at 24 weeks. This effect decreased by an estimated 0.23 weeks (95% credibility interval 0.02 to 0.40 weeks) for each week of gestation (Figure 4) and at 40^{+0} weeks, the estimated effect was a delay by 0.8 weeks (95% credibility interval -0.03 to 1.7 weeks). The observed number of cases of PE with delivery at <34, 34^{+0} to 36^{+6} and ≥37 weeks' gestation in the aspirin and placebo groups and summaries of samples from the posterior predictive distribution (mean, 2.5^{th} and 97.5^{th} percentiles) are shown in Table 3. The

data of samples from the posterior predictive distribution are consistent with the observed data and this provides support for the aspirin-related shift hypothesis.

COMMENT

In the ASPRE trial treatment with aspirin reduced the incidence of PE with delivery <32, <34, <37 weeks' gestation by about 90%, 80% and 60%, respectively, but had no significant effect on the incidence of term-PE.[1] The findings of this *post hoc* exploratory analysis of data from the ASPRE trial are consistent with the hypothesis that the mechanism of action of aspirin is to delay the gestational age at delivery with PE.

We have developed and fitted a model that reflects the hypothesis of an aspirin-related shift effect so that the magnitude of the delay in gestational age at delivery with PE is greater at earlier than later gestational ages and have demonstrated that this model predicts the incidence data in the ASPRE trial. According to this model, aspirin prevents both preterm-PE and term-PE and the reduction of the latter is by about 40%. However, much of term-PE prevented is replaced by term-PE that results from the effect of aspirin in delaying the need for preterm delivery with PE. This model therefore explains the findings from ASPRE that treatment with aspirin leads to substantial reduction in the incidence of preterm-PE but has little effect on the incidence of term-PE.

In contrast to previous approaches to prediction of PE which treat preterm-PE and term-PE as different conditions[11-14] we have developed and validated prediction

models for the gestational age at delivery with PE.[3-5] In this paper, we have applied the same logic to the analysis of the effect of aspirin and demonstrated that the data from ASPRE are consistent with the hypothesis that aspirin delays the gestational age at delivery with PE in a way that has a larger effect for deliveries that would, without treatment, occur at earlier gestations. Within the context of this model, the incidence of deliveries with PE at term is increased by the effects of delays to preterm-PE.

This hypothesis generating unplanned exploratory analysis of the ASPRE trial data does not have sufficient power for any firm conclusions to be drawn from the subgroup analysis of term-PE. All we would claim in this paper is that the delay hypothesis is an empirically valid and clinically plausible mechanism. In interpretation of studies such as ASPRE, it is important to recognize that reductions in preterm-PE might counter or even reverse any effects on the incidence of term-PE.

FIGURE LEGENDS

Figure 1: Effect of aspirin in delaying the gestational age at delivery with preeclampsia.

Figure 2: Distribution of gestational age at delivery with preeclampsia in the placebo and aspirin groups in the ASPRE trial. This demonstrates that in the aspirin group the incidence of early deliveries with PE is reduced.

Figure 3: Odds ratios (aspirin/placebo) and 95% confidence intervals for the effect of aspirin on term preeclampsia. As expected under the hypothesis of the shift model, there was a larger decrease in incidence of term preeclampsia in the lower risk group.

Figure 4: Fitted model for the effect of aspirin in delaying gestation at delivery with preeclampsia (black line) with 95% credibility intervals (black interrupted lines). The aspirin-related delay was greater for earlier than later preeclampsia.

Table 1: Incidence of preterm-PE and term-PE in the aspirin and placebo groups stratified by risk.

Risk of preterm-PE	Treatment group	PE < 37 w	PE ≥ 37 w	No PE	Total
		n	n	n	
≥1 in 50	Aspirin	11 (2.7%)	41 (8.8%)	412 (88.8%)	464
	Placebo	31 (7.1%)	41 (8.1%)	435 (85.8%)	507
<1 in 50	Aspirin	2 (0.6%)	12 (3.6%)	320 (95.8%)	334
	Placebo	4 (1.4%)	18 (5.7%)	293 (93.0%)	315
All	Aspirin	13 (1.8%)	53 (6.6%)	732 (91.7%)	798
	Placebo	35 (4.8%)	59 (7.2%)	728 (88.6%)	822

Table 2: Posterior means and 95% confidence interval for parameters from the aspirin-related shift model.

Coefficient	**Estimate (95% confidence interval)**
Constant	38.95 (37.43, 40.54)
logit(risk)	-2.35 (-2.912, -1.85)
Aspirin	4.4 (1.4, 7.1)
Aspirin*(gestational age – 24 weeks)	-0.23 (-0.02, -0.40)
Standard deviation	5.838 (4.973, 6.857)

Table 3: Observed number of cases of preeclampsia with delivery at <34, 34^{+0} to 36^{+6} and ≥37 weeks' gestation in the aspirin and placebo groups from the ASPRE trial and summaries of samples from the posterior predictive distribution (mean, 2.5^{th} and 97.5^{th} percentiles).

	Number of cases delivering with preeclampsia			
Aspirin group (n=798)	**< 34 w**	**34^{+0} to 36^{+6} w**	**≥ 37 w**	**None**
Observed	3	10	53	732
Predicted model	4.9 (1, 11)	16.4 (8, 26)	44.1 (29, 62)	732.5 (711, 752)
Placebo group (n=822)				
Observed	15	20	59	728
Predicted model	16.9 (8, 26)	27.6 (17, 39)	49.3 (34, 67)	728.3 (703, 751)

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