OBSTETRICS

Aspirin delays the development of preeclampsia

David Wright, PhD; Kypros H. Nicolaides, MD

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

OBJECTIVE: The objective of the study was to examine the hypothesis that the effect of aspirin is to delay the time of delivery in women who have preeclampsia.

STUDY DESIGN: This was an unplanned exploratory analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention trial. The delay hypothesis predicts that in groups for which preterm preeclampsia, without aspirin, were infrequent relative to term preeclampsia, a reduction in term preeclampsia would be expected because few cases of preterm preeclampsia would be converted to term preeclampsia. In contrast, in groups for which preterm preeclampsia were frequent relative to term preeclampsia, the conversion of preterm preeclampsia to term preeclampsia by aspirin would reduce or even reverse any effect on the incidence term preeclampsia. This is examined using the Aspirin for Evidence-Based Preeclampsia Prevention trial data by analysis of the effect of aspirin on the incidence of term preeclampsia stratified according to the risk of preterm preeclampsia at randomization. Given that women were included in Aspirin for Evidence-Based Preeclampsia Prevention with risks of preterm preeclampsia >1 in 100, a risk cutoff 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 Aspirin for Evidence-Based Preeclampsia Prevention 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 preeclampsia (odds ratio, 0.62, 95% confidence interval, 0.29—1.30). In contrast, in the higher risk group (≥1 in 50) there was a small increase in the incidence of term- preeclampsia (odds ratio 1.11, 95% confidence interval, 0.71— .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 preeclampsia by an estimated 4.4 weeks (95% confidence interval, 1.4—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% confidence interval, 0.021—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).

CONCLUSION: The Aspirin for Evidence-Based Preeclampsia Prevention trial data are consistent with the hypothesis that aspirin delays the gestational age at delivery with preeclampsia.

Key words: aspirin, Aspirin for Evidence-Based Preeclampsia Prevention trial, competing risks model, first-trimester screening, preeclampsia, pregnancy, preterm delivery, pyramid of pregnancy care, term delivery

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 preeclampsia (PE), were randomized to receive aspirin (150 mg/d) 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 [CI], 0.20—0.74), but there was no significant effect on the incidence of term PE (odds ratio, 0.95, 95% CI, 0.64—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 was to examine whether an aspirin-related delay in the gestational age at delivery

Cite this article as: Wright D, Nicolaides KH. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019;220:580.e1-6.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.02.034

AJOG at a Glance

Why was this study conducted?

This is an unplanned secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention (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.

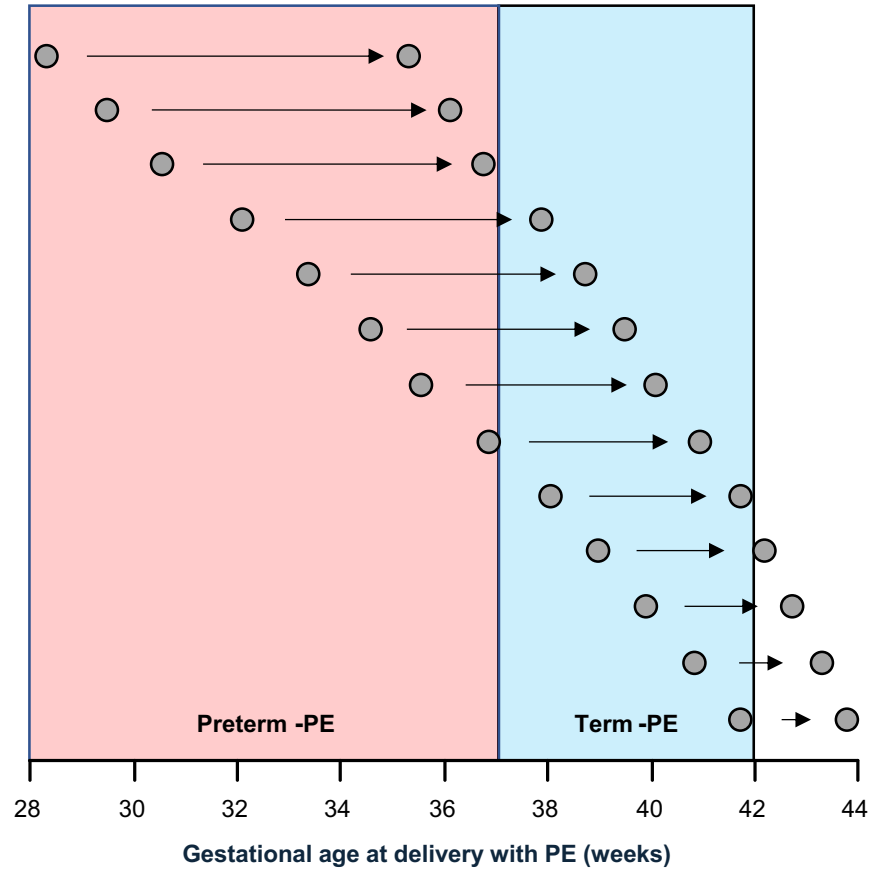
Key findings

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 that 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.

What does this add to what is known?

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 preeclampsia.

FIGURE 1
Effect of aspirin in delaying gestational age at delivery with PE



PE, preeclampsia.

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

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 kits; DELFIA Xpress random access platform; PerkinElmer Inc, Wallac Oy, Turku, Finland).

The eligibility criteria for the trial were maternal age ≥18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11−13 week scan, and an estimated risk for preterm PE of >1 in 100.[1] Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted.

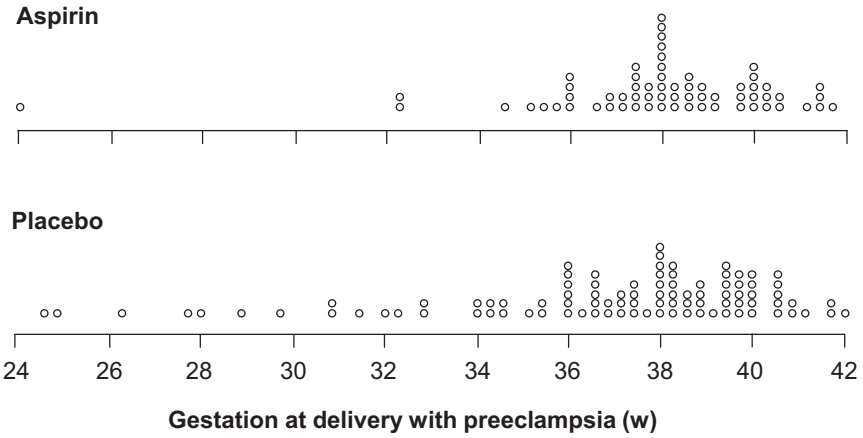
Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy.[8] The systolic blood pressure should be >140 mm Hg and/or the diastolic blood pressure should be >90 mm Hg on at least 2 occasions 4 hours apart, developing after 20 weeks of gestation in previously normotensive women.

Hypertension should be accompanied by proteinuria of >300 mg in 24 hours or 2 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,

FIGURE 2
Distribution of gestational age at delivery with preeclampsia



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 preeclampsia is reduced.

ASPRE, Aspirin for Evidence-Based Preeclampsia Prevention.

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

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 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 the analysis of the effect of aspirin on the incidence 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 cutoff 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 center.

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 $T + \delta$.

In randomized controlled trials, in which there is no censoring, this model is used extensively with Student 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).

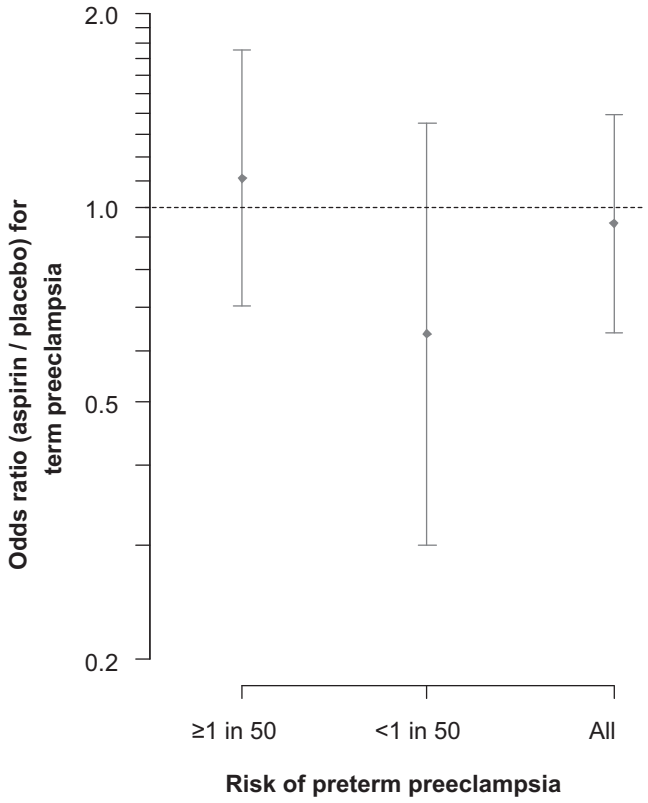
We assumed a Gaussian distribution for T in the placebo group with a mean dependent of the logit of the risk according to a linear regression model and a constant standard deviation σ. In the aspirin group, the same model was used but T was increased by the treatment effect $\delta = \beta_0 + \beta_1(T, -24)$. With this parameterization, β_0 represents the

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 wks n	PE ≥37 wks n	No PE n	Total
≥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

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

FIGURE 3
Odds ratios and confidence intervals for aspirin effect on term preeclampsia



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.

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

effect of aspirin at 24 weeks' gestation. For every week of gestation after 24 weeks, the effect is reduced by $-\beta_1$. The standard deviation in the aspirin group is $(1 + \beta_1)\,\sigma$.

Using a noninformative prior distribution for unknown parameters, the aspirin-related shift model was fitted within a Bayesian framework using Markov chain Monte Carlo implemented inWinBUGS.[9] Inferences for model parameters are presented in terms of posterior means, SDs, and 95% credibility intervals.

Samples from the posterior predictive distribution were used to simulate ASPRE outcome data as follows. Samples of 5000 observations of the model parameters were taken from the Markov chain Monte Carlo iterations. For each of these, the gestational ages at delivery with PE were generated for the 1620 trial participants for both the aspirin and placebo treatments.

Gestational ages at births from other causes were obtained by sampling with replacement from the gestational ages at birth from 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 from births from other causes. This provided 5000 samples from the posterior predictive distribution of data from the ASPRE trial under the assumption of the model.

WinBUGS[9] was used for model fitting and the statistical software R[10] was used for data analyses.

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

Coefficient	Estimate (95% credibility interval)
Constant	38.95 (37.43 to 40.54)
Logit(risk)	−2.35 (−2.91 to −1.85)
Aspirin	4.4 (1.4 to 7.1)
Aspirin×(gestational age − 24 wks)	−0.23 (−0.40 to −0.02)
SD	5.84 (4.97 to 6.86)

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

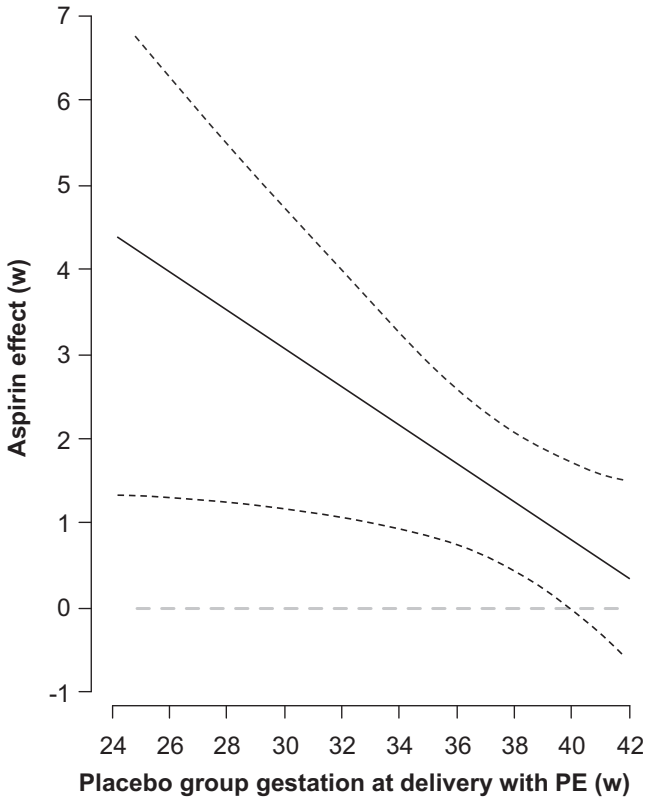
Results

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 with 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% CI, 0.29 to 1.30),

FIGURE 4
Model for aspirin effect in delaying gestation at delivery with preeclampsia



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.

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

whereas in the higher-risk group, there was a small but insignificant increase in the incidence of term PE (odds ratio, 1.11, 95% CI, 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 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, 2.5th and 97.5th 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, and <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 unplanned 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.

TABLE 3
Observed number of cases of preeclampsia and summaries of samples from the posterior predictive distribution

	Number of cases delivering with preeclampsia			
Groups	<34 wks	34^{+0} to 36^{+6} wks	≥ 37 wks	None
Aspirin group (n=798)				
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)

The predicted model is presented as mean (2.5^{th} and 97.5^{th} percentiles).

Wright et al. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019.

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 a 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 that 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. ■

Acknowledgment

The study was registered with the clinical trial identification number ISRCTN13633058 (http://www.isrctn.com/ISRCTN13633058).

References

1. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–22.

2. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol 2014;10:466–80.

3. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 2015;213:62.e1–10.

4. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. Am J Obstet Gynecol 2016;214:03.e1–12.

5. Wright D, Tan MY, O'Gorman N, et al. Predictive performance of the competing risk model in screening for preeclampsia. Am J Obstet Gynecol 2019;220:199.e1–13.

6. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11–13 weeks' gestation. Fetal Diagn Ther 2012;31:42–8.

7. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2007;30:742–9.

8. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertens Pregnancy 2001;20: IX–XIV.

9. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput 2000;10:325–33.

10. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria: R Development Core Team; 2011 (http://www.R-project.org/).

11. Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH. Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks. Ultrasound Obstet Gynecol 2010;35:662–70.

12. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks. Prenat Diagn 2011;31:66–74.

13. Scazzocchio E, Figueras F, Crispi F, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. Am J Obstet Gynecol 2013;208:203.e1–10.

14. Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. Am J Obstet Gynecol 2014;211:514.e1–7.

Author and article information

From the Institute of Health Research, University of Exeter, Exeter (Dr Wright), and the Harris Birthright Research Centre for Fetal Medicine, King's College, London (Dr Nicolaides), United Kingdom.

Received Nov. 19, 2018; revised Feb. 14, 2019; accepted Feb. 15, 2019.

The financial supporters of this work had no involvement in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

The study was supported by grants from the Fetal Medicine Foundation (Charity number 1037116) and by the European Union 7th Framework Programme—FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project number 601852).

The authors report no conflict of interest.

Corresponding author: Professor KH Nicolaides, MD. kypros@fetalmedicine.com