OBSTETRICS

When to give aspirin to prevent preeclampsia: application of Bayesian decision theory

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BACKGROUND: There is good evidence that first-trimester assessment of the risk for preterm preeclampsia and treatment of the high-risk group with aspirin reduces the incidence of preterm preeclampsia. Furthermore, there is evidence that aspirin is associated with an increased risk of maternal and neonatal hemorrhagic complications. Against this background, there are ongoing debates whether aspirin should be recommended for all women or to a subpopulation of women predicted to be at increased risk of developing preeclampsia. Moreover, if a strategy of the prediction and prevention of preterm preeclampsia is to be used, what method should be used for the prediction, and what risk cutoff should be used to decide on who to treat?

OBJECTIVE: This study aimed to compare the policies of universal treatment, stratified treatment, and no treatment with aspirin.

STUDY DESIGN: Decisions about aspirin prophylaxis were considered from the perspective of the Bayesian decision theory. Using this approach, the treatment policies were evaluated for risks of preterm preeclampsia, effects of aspirin, and trade-offs between the harms and benefits of the treatment. Evidence on the risk of preterm preeclampsia was taken from the Screening programme for pre-eclampsia study, which was a first-trimester screening study for the prediction of pre-eclampsia. Evidence of the effect of aspirin was taken from the Aspirin for Evidence-Based Preeclampsia Prevention trial, which was a trial of aspirin vs placebo in the prevention of preterm preeclampsia. The trade-off between the benefits and harms of aspirin was specified by addressing the question, "What is the maximum number of women that should be treated to prevent 1 case of preterm preeclampsia?" The number can be considered as an exchange rate between the harms and benefits of using aspirin to prevent preterm PE. Given the uncertainty about the harms associated with aspirin, the treatment policies were compared across a wide range of exchange rates.

RESULTS: For exchange rates between 10 and 1000 women treated with aspirin to prevent 1 case of preterm preeclampsia, the net benefit achieved from the risk assessment and targeted treatment of women at high risk of preterm preeclampsia was higher than that from women with no treatment or women with universal treatment with aspirin.

CONCLUSION: Universal treatment with aspirin should be avoided. Risk-based screening should be used, and the cutoff for taking aspirin should be determined from the consideration of the trade-off between the benefits and harms and detection, false-positive, and screen-positive rates.

Key words: aspirin, competing risks model, first-trimester screening, preeclampsia, Aspirin for Evidence-Based Preeclampsia Prevention trial, Screening programme for pre-eclampsia study

Introduction

There is good evidence that first-trimester assessment of the risk of preterm preeclampsia (PE) and treatment of the high-risk group with aspirin reduces the rate of preterm PE by more than 60%, provided the daily dosage of the drug is >100 mg and the gestational age at onset of therapy is <16 weeks.[1–7] Against this background, there are ongoing debates about the prediction and prevention of preterm PE centered on 2 questions: (1) whether aspirin should be recommended for all women[8–10] or to a subpopulation of women predicted to be at increased risk of developing PE and (2) what method should be used for prediction if a strategy of prediction and prevention is to be used.[3–5,11–13]

The arguments in favor of recommending aspirin to all women are that it avoids the need for risk assessment and the whole population benefits from prophylactic treatment with aspirin. Arguments against this are that compliance is likely to be worse when aspirin is applied to the whole population than when recommended to a subpopulation selected and counseled based on risk and there is a need to balance the benefit from aspirin in the prevention of preterm PE with harm from aspirin because of hemorrhagic and other adverse effects. A recent study by Hastie et al,[14] involving 313,624 pregnancies, provided evidence that aspirin use in pregnancy was associated with an increased risk of bleeding during labor and the postpartum period; furthermore, the study showed that aspirin was associated with an increased risk of neonatal intracranial hemorrhage. This was consistent with studies in nonpregnant populations that reported that aspirin prophylaxis increases the risk of hemorrhagic complications.[15]

This study considered policies of using aspirin to prevent preterm PE from the perspective of the Bayesian decision theory,[16] assuming a trade-off between the potential harms and benefits of using aspirin to prevent preterm PE quantified by the maximum number of women that should be treated to determine the risks of using aspirin to avoid 1 case of preterm PE. This can be considered as the exchange rate between the harm and benefit of using aspirin to prevent preterm PE. At one extreme, the potential harm from aspirin might be considered so great that no woman would be treated to prevent preterm PE and the exchange rate would be zero. At the other extreme, any number of women would be treated to prevent 1 case of preterm PE. Between

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2021.10.038

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AJOG at a Glance

Why was this study conducted?

This study considered the policies for treatment with aspirin from the perspective of the Bayesian decision theory. This study assumed a trade-off between the potential harms and benefits of using aspirin to prevent preterm preeclampsia (PE), which is quantified by the number of women we are prepared to subject to the harms from treatment with aspirin to avoid one case of preterm-PE. The number can be considered as an exchange rate between the harms and benefits using aspirin to prevent preterm PE.

Key findings

For the exchange rates between 10 and 1000 women treated with aspirin to prevent 1 case of preterm PE, the net benefit achieved from the risk assessment and targeted treatment of women at high risk of preterm PE was higher than that from women with no treatment or women with universal treatment with aspirin.

What does this add to what is known?

Universal treatment with aspirin should be avoided. Risk-based screening should be used, and the cutoff for taking aspirin should be determined from the consideration of the trade-off between the benefits and harms and detection, false-positive, and screen-positive rates.

these two extremes, for example, an exchange rate of 100 would reflect the position where aspirin would be given to 100 women to prevent 1 case of preterm PE.

Materials and Methods

Study populations

Evidence on the effect of aspirin in the prevention of preterm PE was taken from the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial.[6] This was a multicenter, double-blind, placebo-controlled trial, in which women at high risk of preterm PE were randomly assigned to receive aspirin, at a dosage of 150 mg per day, or placebo from 11 to 14 to 36 weeks' gestation. The primary outcome was delivery with PE at <37 weeks' gestation, which occurred in 13 of 798 participants (1.6%) in the aspirin group vs 35 of 822 participants (4.3%) in the placebo group (odds ratio, 0.38; 95% confidence interval, 0.20−0.74; P=.004).

For the comparison of different treatment policies, we used data from the Screening programme for pre-eclampsia (SPREE) study.[5,17] This was a prospective multicenter study of 16,747 women recruited from 7 National Health Service maternity hospitals in England. The study compared the performance of screening by the prespecified competing risk model, which combines maternal risk factors with biomarkers at 11 to 13 weeks' gestation,[2] with that of the method of risk scoring based on maternal characteristics advocated by the National Institute for Health and Care Excellence (NICE).[11] The results from screening were not made available to the patients or their obstetricians and were produced blinded to outcome. This study demonstrated the superiority of screening using the competing risk model to the application of the NICE guidelines or the American College of Obstetricians and Gynecologists criteria.[11−13]

Exchange rate between benefit and harm from use of aspirin

For a specific exchange rate, the net benefit is defined as the number of cases of preterm PE prevented from using aspirin minus the harm resulting from the treatment. For example, an exchange rate of 100 would reflect that the harm from treating 100 women equates to that from 1 case of preterm PE. If 100 women were treated and 3 cases of preterm PE were prevented, the benefit from prevention of preterm PE would be 3. However, the harm from treating the 100 women would equate to 1 case of preterm PE. Therefore, the net benefit would be 3−1=2 cases of preterm PE. If the exchange rate were 10 instead of 100, then for every 10 treated, the harm would equate to 1 case of preterm PE. Consequently, treating 100 women would equate to 10 additional cases of preterm PE. The net benefit would be 3−10=−7. With this exchange rate, the treatment with aspirin is worse than no treatment that has zero net benefit.

The policies of no treatment, universal treatment, and selective treatment of a high-risk group were compared in terms of their expected net benefit. For screening strategies based on risks, the optimal risk cutoff, which maximizes the expected net benefit, was obtained from the exchange rate and relative risk reduction (RRR). For exchange rates between 10 and 10,000 women treated with aspirin to prevent 1 case of preterm PE, we obtained the net benefit from screening the SPREE population using the risks obtained from the prespecified competing risk model,[2] using maternal risk factors in combination with mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor. For a given exchange rate, the risk cutoff was determined, and the expected net benefit was computed by applying the RRR to the preterm PE events for those who screened positive in the SPREE population. Statistical analysis was performed using the R statistical software.[18]

Results

Net benefit

For the SPREE[5] population, the incidence of preterm PE was 0.8% or 80 per 10,000. From the ASPRE[6] study, if we assume that aspirin produces an RRR of 0.62, then the benefit from treating 10,000 is 80×0.62=49.6 cases of preterm PE prevented. The harm associated with treating 10,000 women with aspirin depends on the exchange rate. If we assume an exchange rate of 100 women treated with aspirin equates to 1 case of preterm PE, then the harm would be 10,000/100=100. With such an exchange rate, the net benefit would be

TABLE 1
Risk cutoffs for preterm preeclampsia above which the net benefit from the treatment with aspirin is positive

	RRR				
Exchange rate	0.2	0.4	0.6	0.8	1
10	1 in 2	1 in 4	1 in 6	1 in 8	1 in 10
50	1 in 10	1 in 20	1 in 30	1 in 40	1 in 50
100	1 in 20	1 in 40	1 in 60	1 in 80	1 in 100
500	1 in 100	1 in 200	1 in 300	1 in 400	1 in 500
1000	1 in 200	1 in 400	1 in 600	1 in 800	1 in 1000

Exchange rate is defined as the number of women treated with aspirin to prevent 1 case of preterm PE. The RRR is calculated as $(risk_{no\ aspirin} - risk_{aspirin})/risk_{no\ aspirin}$.

PE, preeclampsia; *RRR*, relative risk reduction.

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49.6−100=−50.5. The policy of universal treatment has a negative net benefit and is worse than no treatment. In contrast, if an exchange rate of 1000 women treated with aspirin equates to 1 case of preterm PE prevented, then the harm from treating 10,000 women with aspirin equates to 10 cases of preterm PE. With such an exchange rate, the net benefit would be 49.6−10=39.6.

The lowest exchange rate at which universal treatment is better than no treatment is inversely related to the incidence and RRR and is given by 1/incidence×RRR. For populations with a prevalence of preterm PE of 0.8%, such as the SPREE population,[5] the exchange rate would need to be 202. In relatively low-risk populations with a prevalence of preterm PE of 0.4%, half that of the SPREE population,[5] and assuming an RRR of 62%,[6] the exchange rate would have to be ≥403 women treated with aspirin to prevent 1 case of preterm PE. For a high-risk population with a prevalence of preterm-PE of 1.6%, double that of the SPREE population,[5] the exchange rate would need to be ≥101.

Determination of risk cutoffs

Denoting the risk (as a fraction: 0.1 for 1 in 10) of preterm PE by p, exchange rate by E and RRR, the expected net benefit for an individual woman is p×RRR−1/E. This is positive if $P>1/(E\times RRR)$ and negative if $P<1/(E\times RRR)$. For a given exchange rate and RRR, the risk cutoff above which there is benefit in the treatment with aspirin is RRR×E as shown in Table 1.

Many existing screening tests are based on a fixed risk cutoff. For example, the ASPRE trial used a risk cutoff of 0.01 (1 in 100) to define a high-risk group. Table 2 shows the exchange rates given specific RRRs.

Net benefits for a screening program

Consider now a screened population of size n. For a fixed exchange rate (E) and RRR, women with risks greater than 1/(E×RRR) would screen positive. The expected net benefit for the population is given as follows:

$$\text{Net benefit} = \text{true positive count} \times \text{RRR} - \text{screen positive count}/E$$

Per 10,000 women screened, the expected net benefit is as follows:

$$\text{Net benefit} = 10,000 \times (\text{true positive count} \times \text{RRR} - \text{screen positive count}/E)/n$$

TABLE 2
Screening performance and net benefit using maternal characteristics, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor for 3 exchange rates

					Per 10,000			
Scenario	Exchange rate E	Risk cutoff	SPR (%)	DR (%)	Treated	Prevented	Net benefit	NNT
1	10	0.1613 (1 in 6)	0.5	20	89	17.36	5.1 (−947.4)	5.1
2	150	0.0108 (1 in 93)	11.6	83	1945	73.16	35.9 (−14.1)	26.6
3	1000	0.0016 (1 in 620)	47.9	99	8027	86.80	47 (42.6)	92.5

DR, detection rate; *NNT*, number needed to treat to prevent one case of preterm preeclampsia; *SPR*, screen-positive rate.

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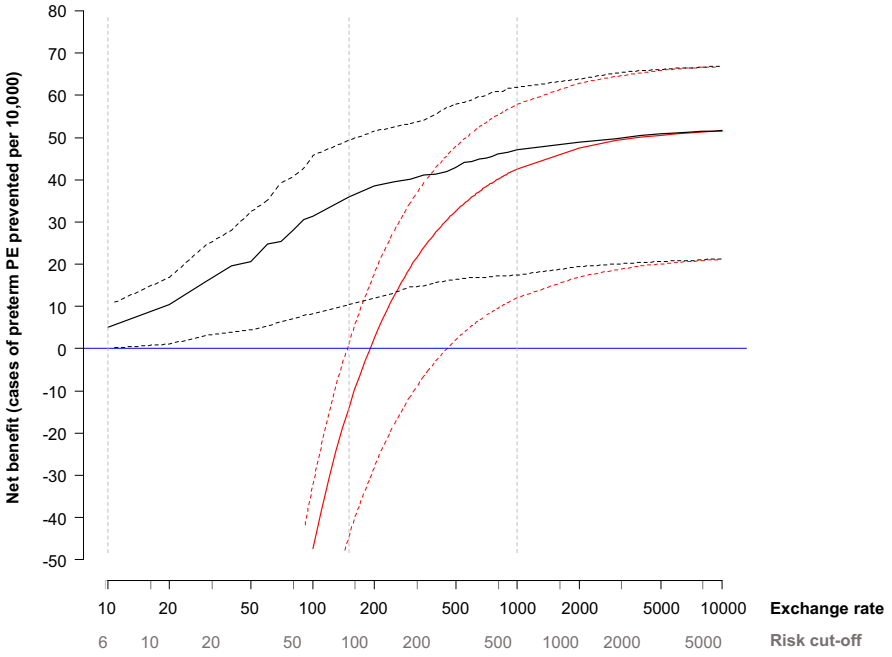
This can be compared with net benefits of zero for no screening and 10,000×(true positive count×RRR/n−1/E) for universal screening.

Assuming an RRR of 0.62, as found in the ASPRE trial,[6] the net benefit curves for different combinations of markers using the SPREE[6] data are shown in the Figure. For exchange rates of <202 women treated with aspirin to prevent ≤1 case of preterm PE, the net benefit is negative, and universal treatment is worse than no treatment. The net benefit decreases very rapidly, and for an exchange rate of 100 women treated with aspirin to prevent 1 case of preterm PE, the net benefit equates to an additional 50 cases of preterm PE. For all exchange rates between 10 and 1000 women treated with aspirin, screening is superior to universal treatment and no treatment.

The choice of the exchange rate was challenging. In Table 2, 3 scenarios are presented, and these scenarios correspond to the 3 vertical broken lines shown in the Figure. The first scenario reflected a position where there was serious concern about the harm from aspirin treatment; the exchange rate was 10 women treated with aspirin, which meant that the harm from treating 10 women with aspirin equated to the benefit of preventing 1 case of preterm PE. Only 0.5% of the population with risks >0.1613 (1 in 6) were treated. The detection rate (DR) was only 20%, and approximately 17 cases of preterm PE were prevented. After accounting for the harm from the treatment, the net benefit equated to the prevention of 5.1 cases. Universal treatment with aspirin equated to 947 cases of preterm PE. In the second scenario, an exchange rate of 150 corresponded to a risk cutoff close to 1 in 100 as used in the ASPRE trial.[6] Notably, 11.6% of the population were treated, and the DR was 83%. The net benefit equated to 35.9 cases prevented. Universal treatment in this situation equated to 14.1 cases of preterm PE and was worse than the policy of no treatment. The third scenario reflected a position where the harm associated with aspirin was very small relative to the benefits in terms of the prevention of preterm PE; the exchange rate was 1000 women treated with aspirin to prevent 1 case of preterm PE. This led to screening with a risk cutoff of 1 in 620 for which almost half of the population were treated with aspirin, and the DR was 99%. The net benefit was 47 with treatment with aspirin compared with 42.6 with universal treatment.

FIGURE
Net benefit curves for treatment of preeclampsia



The graph shows the net benefit curves for no treatment with aspirin (blue), universal treatment (red), and treatment of the high-risk group identified by first-trimester screening by a combination of maternal risk factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor (black). The *dashed lines* show the net benefit at the 95% confidence limits for the RRR owing to aspirin. This implies that at the lower limit, the point where universal treatment is better than no treatment is at an exchange rate of 450 treated to prevent 1 case of preterm preeclampsia. The *vertical lines* (left to right) correspond to scenarios 1 to 3 in Table 2. The risk cutoff values shown on the horizontal axis correspond to a benefit of 0 assuming the RRR of 0.62.

RRR, relative risk reduction.

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Comment

Main findings

The risk threshold above which aspirin treatment was preferable to no treatment was dependent on the exchange rate between the harm and benefit of using aspirin to prevent preterm PE, the RRR from using aspirin (Table 1). For an exchange rate of 10 women treated with aspirin to prevent 1 case of preterm PE and an RRR of 0.62, the risk threshold was 1 in 6. For an exchange rate of 1000 women treated with aspirin to prevent 1 case of preterm PE and the same RRR, the risk threshold was 1 in 620. If aspirin were 100% effective, then the risk thresholds are the same as the exchange rates: 1 in 10 and 1 in 1000, respectively, for the above.

Using the SPREE[5] data, we have compared the net benefit from screening with that from universal treatment with aspirin and that from no treatment. Across a wide range of exchange rates (Figure) this shows that screening is preferable to no-treatment and to universal treatment. Table 1

shows the performance of screening in terms of net benefit, screen-positive rate (SPR), and DR. With an exchange rate of 10 women treated with aspirin to prevent 1 case of preterm PE (scenario 1), the risk threshold for treatment with aspirin was 1 in 6. With such a threshold, only 0.5% of women were treated, and only 20% of those who, without aspirin, would get preterm PE would be treated. The net benefit from screening 10,000 women was 5.1 cases of preterm PE prevented. This should be compared with a net benefit of zero for no treatment and −947.4 from universal treatment. For this exchange rate, the harm from universal treatment far outweighed the benefit from the prevention of preterm PE, and the net benefit from universal treatment was 947.4 cases of preterm PE. For an exchange rate of 150 women treated with aspiring to prevent 1 case of preterm PE (scenario 2), the risk threshold was 1 in 90 with an SPR of 11.6%. Moreover, 83% of those women who, without aspirin, would develop PE would be treated. The net benefit from screening was 35.9 cases of preterm PE prevented compared with zero for no treatment and −14.1 for universal treatment. For an exchange rate of 1000 women treated with aspiring to prevent 1 case of preterm PE (scenario 3), the risk threshold for treatment with aspirin was 1 in 620, and nearly half of women were treated with aspirin, including 99% of those who, without aspirin would develop preterm PE. The net benefit from screening was 47 cases of preterm PE prevented compared with 42.6 with universal treatment and zero for no treatment.

Comparison with previous studies

The decision theory approach adopted in this study illustrated how to determine the risk thresholds for screening from the consideration of the balance between the harms and benefits of the treatment to prevent preterm PE. Previous studies have focused on screening using a prespecified SPR[5] or a fixed risk threshold.[6] Although this study presented a principled way of choosing a risk cutoff, because of the uncertainty about the harm from aspirin, the choice of an appropriate exchange rate was problematic. Consideration of exchange rates along with SPRs and DRs was useful in determining a suitable risk threshold for screening programs, evaluation of the performance of screening, and making comparisons among different policies for treatment with aspirin.

Limitations

The main limitation of the approach used in this study was the choice of the exchange rate. There was considerable uncertainty about the harm from aspirin during pregnancy. Studies in adult populations and pregnant populations showed evidence of an increased incidence of maternal and neonatal intracranial bleeding, respectively. Moreover, there was a well-understood mechanism to explain this increase. Long-term effects on babies born to women taking aspirin are less well understood. Clinical trials, such as the ASPRE trial,[6] are woefully underpowered for assessing rare but serious side effects. For example, to demonstrate "no harm" with a baseline incidence rate of 0.2% (1 in 500) and a boundary for the difference of 0.1% (RR, 1.5) with a power of 90%, a randomized controlled trial of 84,000 participants would be needed. Cohort studies, such as that of Hastie et al,[14] are difficult to interpret. For instance, the analysis of neonatal intracranial bleeding was adjusted for gestational age at delivery. Given that intracranial bleeding is very strongly associated with prematurity, the possibility that aspirin reduces it, by delaying the need for early deliveries in pregnancies at high risk of PE,[19] cannot be ruled out.

The monetary cost associated with the screening of patients and treatment of the high-risk group has not been considered as it has been in a health economic analysis.[20] Generally, the health economic analyses focused on the benefits of preventing PE without consideration of the potential harm. This study focused on the trade-off between the benefits and harms associated with aspirin treatment regardless of monetary costs.

Conclusion

Universal treatment with aspirin should be avoided. Risk-based screening should be used, and the cutoff for using aspirin should be determined from the consideration of the trade-off between the benefits and harms and DRs, false-positive rates, and SPRs. ■

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Received Aug. 15, 2021; revised Oct. 17, 2021; accepted Oct. 20, 2021.

The authors report no conflict of interest.

The study was supported by a grant from the Fetal Medicine Foundation (UK charity number: 1037116). The funding body was not involved in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the article for publication.

This paper is part of a supplement.

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