The Impact of Aspirin on Ultrasound Markers of Uteroplacental Flow in Low-Risk Pregnancy: Secondary Analysis of a Multicenter RCT

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Am J Perinatol 2019;36:855–863.

Abstract

Objective This article evaluates the effect of low-dose aspirin on uterine artery (UtA) Doppler, placental volume, and vascularization flow indices in low-risk pregnancy.

Study Design In this secondary analysis of the TEST randomized controlled trial, low-risk nulliparous women were originally randomized at 11 weeks to: (1) routine aspirin 75 mg; (2) no aspirin; and (3) aspirin based upon the preeclampsia Fetal Medicine Foundation screening test. UtA Doppler, three-dimensional (3D) placental volume, and vascularization flow indices were assessed prior to and 6 weeks postaspirin commencement.

Results A total of 546 women were included (aspirin $n = 192$, no aspirin $n = 354$). Between first and second trimesters, aspirin use was not associated with a change in UtA Doppler, placental volume, or vascular flow indices. There was no significant difference in the change in UtA Doppler pulsatility index (PI) *Z*-scores or notching (PI *Z*-score −0.2 vs. −0.2, $p = 0.17$), nor was there a significant change in placental volume *Z*-score and vascular flow indices (volume *Z*-score change: 0.74 vs. 0.62, $p = 0.34$).

Conclusion Low-dose aspirin commenced at 11 weeks in low-risk women does not appear to improve uterine and placental perfusion or placental volume. Any perceived effect on uteroplacental vasculature is not reflected in changes in placental volume nor uteroplacental flow as assessed by two-dimensional and 3D ultrasound.

Keywords
- aspirin
- uteroplacental
- uterine artery Doppler
- placental volume
- 3D ultrasound
- three-dimensional power Doppler indices

received
June 24, 2018
accepted after revision
September 13, 2018
published online
November 5, 2018

DOI https://doi.org/10.1055/s-0038-1675208.
ISSN 0735-1631.

Preeclampsia is a leading cause of maternal morbidity and mortality.[1,2] Defective placentation has been proposed in its etiology, as characterized by absent or incomplete remodeling of the spiral arteries from high resistance vessels in the first trimester to low resistance vessels in the second trimester.[3,4] Multiple studies assessing the uteroplacental circulation have found an association between abnormal first trimester uterine artery (UtA) Doppler and preeclampsia.[5–8] There are temporal changes in UtA blood flow with increasing gestation and in normal pregnancies, impedance to flow typically decreases with advancing gestation.[9] The reduction in UtA pulsatility index (PI) between the first and second trimester is greater in those pregnancies with normal outcome than in those that develop preeclampsia,[8] with the persistence of an elevated PI associated with an adverse perinatal outcome.[10]

There is a significant correlation between three-dimensional power Doppler (3DPD) indices within the placental unit in in vivo models,[11] and placental vascular indices have been found to be related to the number of fetal capillary vessels per villus when samples were obtained from chorionic villus sampling.[12] 3DPD indices, both alone[13,14] and in conjunction with placental volume, are lower in pregnancies complicated by preeclampsia compared with normal pregnancies.[15–25] Previous research suggests that the lowest values of placental vascularization are associated with a significantly lower placental volume as well as an elevated UtA PI.[19,26–28]

Low-dose aspirin 50 to 150 mg initiated prior to 16 weeks' gestation can reduce the incidence of early-onset preeclampsia.[29–31] Little is known about the effect of aspirin, if any, on the uteroplacental vasculature. Hence, in the proposed study we sought to investigate if low-dose aspirin 75 mg administered from 11 weeks' gestation in low-risk women impacted upon: (1) UtA Doppler PI and (2) placental volume and placental vascular flow indices between the first and second trimesters of pregnancy.

Materials and Methods

This study is a secondary analysis of a multicenter randomized controlled *T*rial of feasibility and acceptability of routine low dose aspirin versus *E*arly *S*creening *T*est indicated aspirin for preeclampsia prevention (*TEST* Study), the methodology and findings of which have been previously published.[32,33] This trial sought to evaluate the feasibility and acceptability of the provision of routine aspirin in low-risk women, compared with screening test-indicated aspirin for preeclampsia prevention. Following randomization of 546 nulliparous women to one of three groups: Group 1–routine aspirin 75 mg from 11 until 36 weeks; Group 2–no aspirin; and Group 3–aspirin based on the Fetal Medicine Foundation (FMF) preeclampsia screening test. It was found that 51.8% of those approached were open to taking part in a trial where aspirin may be given routinely and that average aspirin adherence was 90%.[33] The average time to obtain a screening result was 7.6 days. Of those taking aspirin, the incidence of antenatal vaginal spotting and postpartum hemorrhage > 500 mL was greater.[33]

Nulliparous subjects over 18 years of age with a nonanomalous singleton pregnancy between 11 and 13 + 6 weeks' gestation without significant risk factors for preeclampsia (i.e., hypertension, chronic renal disease, autoimmune diseases [such as antiphospholipid syndrome], and diabetes mellitus) were recruited prospectively to one of two tertiary maternity units over 2 years. Ethical committee approval was obtained prospectively and participants gave written informed consent prior to enrolment. The trial was registered with the ISRCTN No. 15191778.

In the original trial, all participants underwent computerized randomization to one of three groups, as outlined. All participants underwent the FMF screening test at 11 to 13 + 6 weeks' gestation; the results of which were only prospectively calculated and revealed to those in the screen-and-treat group (Group 3). Screening test components included: (1) maternal risk factors, for example, ethnicity, and mode of conception; (2) mean arterial blood pressure (MAP); (3) UtA Doppler PI; (4) maternal serum plasma protein-A (PAPP-A) and placental growth factor (PLGF). Those women in the screen-and-treat group with a preeclampsia risk greater than 1:8 prior to 42 weeks' gestation were prescribed enteric-coated aspirin 75 mg every night which they commenced before 16 weeks' gestation and continued until 36 weeks.[33] The risk of preeclampsia was calculated for Groups 1 and 2 at the end of the study and was therefore not revealed to those study participants. Preeclampsia was defined as per the International Society for the Study of Hypertension in Pregnancy.[34]

First trimester 3D placental volumes and 3DPD indices were assessed in addition to the FMF screening test. All participants returned between 20 and 22 weeks' gestation where MAP, UtA Doppler, placental volume, 3DPD indices, PAPP-A, and PLGF were repeated. A fetal anatomy scan was also performed. A dose of aspirin 75 mg once daily was used in this study based upon currently clinically accepted practice in the United Kingdom and Ireland and National Institute for Health and Care Excellence guidelines for aspirin usage in at-risk women.[35] Study participants were advised to take the aspirin at night as evidence at the time of study design proposed a circadian effect of aspirin.[36] Aspirin adherence was assessed qualitatively by patient reporting with the use of a diary card and pill count at the 20- to 22-week scan and again at 36 weeks in addition to an objective measure of aspirin response; interval urinary B2-thromboxane2 thromboxane measurement. In the original TEST trial, the safest and lowest effective dose known to prevent preeclampsia based upon evidence at the time was selected, and in the absence of definitive data on adverse outcome when using a higher dose, it was a reasonable dosage to consider. Other recently published studies support the use of a higher 150 mg dosage.[37,38]

All ultrasound assessments were performed using a Voluson Expert 730, GE 2012 by one of two experienced operators (C.M. and F.C.) who were licensed by the FMF, London, UK. UtA Doppler acquisition was in line with published guidance.[39,40] For first and second trimester UtA values, an average of three consecutive automated indices was obtained and the PI measured. The mean PI of the right and left uterine arteries was then calculated. The presence or absence of UtA notching was

assessed subjectively. All prenatal and ultrasonographic data were contemporaneously transferred to an ultrasonography software system and uploaded onto a live Web-based central consolidated database.

The 4 to 8 MHz ultrasound transducer was used to acquire a 3DPD placental image using preset first and second trimester instrument setting (angio mode; sweep angle: 85°; density: 6; enhance: 16; smooth: 4/5; power Doppler quality: high or 16; frequency: low; actual power: 2 dB; pulse repetition frequency: 0.9 kHz; acquisition time of 10 seconds). The stored placental volume sets were manipulated offline using four-dimensional view (GE, Vienna, Austria) by the same two investigators (C.M. and F.C.). The placental volume was calculated using the VOCAL software with the contour mode set to manual. The rotation steps were set to 30 degrees and six contours of the placenta were drawn manually. The 3DPD histogram then calculated the vascularization index (VI), flow index (FI), and vascularization-FI (VFI). VI describes the overall perfusion or number of vessels in the tissue, FI represents the intensity of flow at the time of the 3D sweep, and VFI represents both flow and vascularization.[41,42] To determine inter- and intraobserver agreement for placental volume acquisition, sonographers analyzed the same five placental volumes each on three occasions, with a total of 15 readings, performed on five first and five second trimester randomly selected volume acquisitions. A random-effects analysis was used to determine the intraclass correlation coefficient (ICC), with a value greater than 0.75 demonstrating good reliability in consensus.[43]

An intention-to-treat analysis was performed for all cases where bilateral UtA Doppler, placental volume measurements, and vascular indices were available. UtA Doppler PI values were transformed to *Z* scores using the formula: mean measurement)/standard deviation, which acted as a standardized reflection of the mean PI result.[44] Placental volume measurements were transformed to *Z* scores using the same formula.[45] To compare the change in UtA Doppler PI, notching, and placental volume indices between aspirin and nonaspirin groups, a Wilcoxon rank-sum test was performed.

Results

Of the 546 women included in the study, there were 192 in the aspirin taking group and 354 in the nonaspirin taking group. Demographic characteristics are shown in ►**Table 1**. In total, the proportion of preterm preeclampsia < 34 weeks was 0.55% ($n = 3$) and of any preeclampsia < 42 weeks was 4.03% ($n = 22$).

Uterine Artery Doppler

Satisfactory first trimester UtA waveforms (either unilaterally or bilaterally) were obtained in 98% of participants ($n = 534$). Second trimester UtA Doppler was obtained in all but one of the study population (0.18%). Comparison of median UtA Doppler PI values to published references ranges found that median PI values in our study were similar between 11 and 13 + 6 weeks and 20 to 22 weeks of gestation.[44] Cases where only unilateral UtA waveforms were obtained were excluded from the analysis. *Z*-scores for UtA PI for aspirin and nonaspirin taking groups were calculated for the first and second trimesters and are presented in ►**Table 2** and ►**Supplementary Table S1** (available in the online version). In relation to change in *Z* score between the first and second trimesters, there was no difference between aspirin and non-aspirin taking groups. Similarly, no significant change was seen in the rate of decrease in PI centiles (►**Table 2** and ►**Supplementary Table S1**, available in the online version). There was a trend toward a higher median uterine PI in the first trimester in the screen-positive group for preeclampsia and a greater change in the UtA *Z* scores from the first to the second trimesters compared with the other groups (►**Supplementary Table S1**, available in the online version). However, the small numbers in this screen-positive group ($n = 13$) make it difficult to draw any firm conclusions. UtA Doppler notching (unilateral or bilateral) was present in 84% of the study population in the first trimester (►**Table 2**). Again, there was no significant difference in the reduction of UtA notching between the groups. The incidence of UtA notching from the first to the second trimester decreased in both groups from 84 to 24%.

Placental Volume and Power Doppler Indices

There was no observed increase in placental volume or placental vascular indices between the aspirin and nonaspirin groups (►**Tables 2** and **3**). Placental vascular indices remained constant in this study in both the groups between the first and second trimesters despite the increase in

Table 1 Demographics of aspirin and nonaspirin groups expressed as mean (SD) or *N* (%)

Characteristic	Aspirin $N = 192$	Nonaspirin $N = 354$
Gestation at visit 1 (wk)	13.0 (0.7)	12.6 (0.9)
Maternal age (y)	31.9 (5.0)	32.4 (4.9)
Body mass index (kg/m^2)	25.3 (4.9)	24.8 (4.3)
Smoker	16 (8.3%)	17 (4.8%)
Completion of secondary education	143 (74.5%)	280 (79.1%)
Type of conception		
Spontaneous	176 (91.7%)	322 (91.0%)
Ovulation induced	5 (2.6%)	12 (3.4%)
IVF	8 (4.2%)	14 (4.0%)
ICSI	3 (1.6%)	6 (1.7%)
Ethnicity		
Caucasian	186 (96.9%)	343 (96.9%)
African-Caribbean	1 (0.5%)	2 (0.56%)
Asian	5 (2.6%)	9 (2.54%)

Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; SD, standard deviation.

Table 2 Uterine artery Doppler pulsatility index (PI), notching, and placental volume

Biometric	Aspirin ($N = 192$)	Nonaspirin ($N = 354$)	p-Value
Uterine artery Doppler PI			
11–13 + 6 wk	1.5 (1.2–1.7)	1.5 (1.1–1.7)	0.05
20–22 wk	0.9 (0.7–0.9)	0.8 (0.7–1.1)	0.74
Change	−0.6 (−0.9 to 0.4)	−0.5(−0.8 to −0.3)	0.07
Uterine artery Doppler PI Z-score			
11–13 + 6 wk	−0.6 (−1.1 to 0.0)	−0.7 (−1.3 to −0.1)	0.04
20–22 wk	−0.8 (−1.2 to −0.3)	−0.9 (−1.3 to −0.2)	0.67
Change	−0.2 (−0.7 to 0.3)	−0.2 (−0.6 to 0.4)	0.17
Uterine artery Doppler PI centile			
11–13 + 6 wk	29 (13–50)	24 (10–46)	0.04
20–22 wk	22 (11–37)	18 (9–44)	0.67
Change	−4.6 (−18 to 6)	−2.6 (−17 to 10)	0.09
Uterine artery Doppler notching			
11–13 + 6 wk	167 (87%)	291 (83%)	0.15
20–22 wk	47 (26%)	85 (25%)	0.82
Placental volume (cm^3)			
11–13 + 6 wk	83 (64–117)	93 (69–121)	0.22
20–22 wk	222 (170–293)	235 (178–292)	0.73
Change	139 (84–195)	133 (88–194)	0.88
Placental volume Z-score			
11–13 + 6 wk	−0.3 (−0.9 to 0.6)	−0.02 (−0.7 to 0.9)	0.16
20–22 wk	0.4 (−0.3 to 1.3)	0.6 (−0.2 to 1.5)	0.22
Change	0.7 (−0.1 to 1.5)	0.6 (−0.3 to 1.4)	0.34

Note: Intention-to-treat population ($N = 546$). Median (interquartile range).

placental volume and gestational age. After adjustment for placental volume, there was a small but statistically significant increase in flow indices in both the groups but this small difference is unlikely to be of any clinical importance (►**Table 4**). In relation to change in indices between the first and second trimesters, the FI showed limited variability between groups, while VI showed the greatest variability, as supported by other studies.[18,23] When comparing the

Table 3 Placental vascularization and flow indices (median [IQR])

Biometric	Aspirin ($N = 192$)	Nonaspirin ($N = 354$)	p-Value
Vascularization index			
11–13 + 6 wk	8.0 (5.4–11.2)	8.1 (5.3–12.1)	0.57
20–22 wk	8.4 (5.6–11.1)	8.8 (6.0–11.7)	0.21
Change	0.4 (−3.6 to 3.6)	0.4 (−3.4 to 4.3)	0.84
Flow index			
11–13 + 6 wk	44.1 (40.0–48.6)	43.9 (39.7–48.9)	0.78
20–22 wk	44.0 (41.4–47.5)	44.6 (41.6–47.7)	0.46
Change	−0.3 (−3.1 to 4.6)	0.9 (−4.1 to 4.6)	0.61
Vascularization flow index			
11–13 + 6 wk	3.4 (2.3–5.5)	3.7 (2.1–5.9)	0.64
20–22 wk	3.7 (2.4–5.1)	4.0 (2.6–5.4)	0.16
Change	0.1 (−1.5 to 1.6)	0.2 (−1.8 to 2.0)	0.98

Abbreviation: IQR, interquartile range.

Table 4 Change in uterine artery (UtA) Doppler pulsatility index (PI), notching, placental vascularization, and flow indices from trimester 1 to trimester 2 (ITT population $N = 546$)

Biometric	Change between trimesters 1 and 2	95% confidence interval	*p*-Value
UtA Doppler PI (*Z*-score)	−0.1	−0.2, −0.0	0.03
Placental volume (cm^3)	146.0	139.6, 153.6	< 0.001
Vascularization index	0.1	−0.5, 0.6	0.83
Flow index	0.5	−0.1, 1.0	0.11
Vascularization flow index	−0.1	−0.34, 0.2	0.58
Adjustment for placental volume			
Vascularization index	1.9	0.6, 3.2	0.005
Flow index	2.1	0.8, 3.4	0.001
Vascularization flow index	0.8	0.2, 1.4	0.014

Abbreviation: ITT, intention-to-treat.

groups and adjusting for placental volume, results for the aspirin group remained nonsignificant (adjusted *p*-value for aspirin = 0.92 for VI; 0.98 for FI; and 0.88 for VFI). Several placental volumes and vascular indices were omitted from analysis ($n = 5$ first trimester and $n = 13$ in the second trimester) due to poor quality of the volume data set often secondary to poor tissue penetration and flash artifact due to fetal and maternal movement. More volumes ($n = 13$) were excluded in the second trimester as the sonographers encountered more difficulty acquiring the whole placental volume when the placenta was laterally located or when the length of the placenta exceeded the width of the volume sweep angle. Placental volumes were smaller and the VI was lower in the first trimester (►**Supplementary Tables S1** and **S2**, available in the online version) in the Group 3 screen-positive group for preeclampsia compared with other groups. The VI and FI were lower in this group also in the second trimester and there was a less significant increase in placental size from the first to second trimester when compared with Groups 1 (aspirin) and 3 (screen-negative group for preeclampsia). Again, the numbers were too small to draw firm conclusions.

Intra- and Interobserver Variability of Placental Volume and Vascular Indice Measurements

Interobserver variability of placental volume measurement was < 1% in both trimesters. Intraobserver variability was 2% for first trimester volume assessments (ICC = 98%) and < 1% for second trimester assessments (ICC = 99%). Both the VI and VFI were less variable in the second trimester compared with the first trimester (< 3%). FI was more variable when measured in the second trimester with an interobserver variability of 56% (►**Table 5**).

Uterine Artery Doppler PI and Placental Volume Changes in Preeclamptics

Study participants who developed preeclampsia and were taking aspirin ($n = 10$) showed a slightly smaller decrease in UtA Doppler *Z*-score from first to second trimester (►**Table 6**) than those women who developed preeclampsia and were not taking aspirin ($n = 11$). Interestingly, study participants who developed preeclampsia and were not prescribed aspirin ($n = 13$) had the largest increase in placental volume (►**Table 7**). Numbers were too small to determine statistical significance.

Table 5 Inter- and intraobserver reliability of placental volume and indices

Biometric	Trimester	Fetal % ICC	Sonographer % (interobserver)	Residual % (intra-observer)
Placental volume	1	98	< 1	2
	2	99	< 1	< 1
Vascularization index	1	37	34	29
	2	94	3	3
Flow index	1	82	5	12
	2	26	56	18
Vascularization flow index	1	47	24	30
	2	90	7	3

Abbreviation: ICC, intraclass correlation coefficient.

Table 6 Uterine artery Doppler pulsatility index *Z*-score change

Group	Preeclampsia	*N*	Median (IQR)
Aspirin	No	166	−0.2 (−0.8 to −0.3)
	Yes	10	−0.1 (−1.0 to 1.4)
No aspirin	No	315	−0.2 (−0.6 to 0.4)
	Yes	11	0.03 (−0.1 to 0.7)

Abbreviation: IQR, interquartile range.

Table 7 Placental volume *Z*-score change

Group	Preeclampsia	*N*	Median (IQR)
Aspirin	No	164	0.7 (−0.1 to −1.5)
	Yes	9	0.6 (−0.5 to 1.2)
No aspirin	No	316	0.6 (−0.3 to 1.4)
	Yes	13	0.9 (−0.3 to 2.1)

Abbreviation: IQR, interquartile range.

Discussion

The findings of this study do not support a significant effect of aspirin use in low-risk women on UtA Doppler PI, placental volume, or 3D-placental Doppler indices.

Studies evaluating the distribution of placental vascular indices in normal pregnancies from 12 to 40 weeks' gestation suggest that 3DPDs remain constant throughout gestation.[45,46] In relation to placental pathology in preeclampsia, vascular lesions and placental hypoplasia are strongly associated with early-onset preeclampsia (< 34 weeks), whereas hyperplasia or excessive placental growth is more related to late-onset disease.[47] This suggests that placental volume can be variable, representing differing degrees of placental involvement in the disease spectrum. It is likely that the premise of whether aspirin prevents the placenta-mediated disease or delays its onset by improving impaired placentation is very tenuous.[48]

Similar to our findings, previous studies have not found a significant difference in second trimester UtA Doppler PI in at-risk women when taking 150 mg of aspirin, compared with a nonaspirin taking group.[49,50] The high incidence of first trimester UtA Doppler notching is consistent with other studies.[51,52] By the second trimester, the incidence of notching may have decreased further if the UtA Doppler had been further interrogated between 23 and 25 weeks, after the second wave of trophoblastic invasion of the maternal spiral arteries had occurred. If bilateral UtA Doppler notching persists by this gestation (23–25 weeks), it is then typically considered an independent risk factor for early-onset preeclampsia and gestational hypertension.[53] Aspirin has been shown to modulate the production of cytokines, decrease apoptosis, and improve trophoblast function in in vitro models of early preeclampsia.[54] It also inhibits cyclooxygenase irreversibly, thus inhibiting prostaglandin and thromboxane synthesis.[55] It may be that the dose of aspirin used in our own study was too low to significantly change placental size and uteroplacental blood flow. Recent research has shown that aspirin has a dose-dependent effect in pregnancy, with 60 mg commenced before 16 weeks having no impact on preeclampsia outcome, compared with a 100-mg dosage.[56] Another possible explanation for our negative findings may be that there was "a failure to respond" or "aspirin resistance" within the study cohort. This is hypothesized to be pharmacokinetic (failure to achieve an adequate level of drug) or pharmacodynamic (failure to inhibit platelet function) in nature. Studies examining the effect of aspirin on platelet function suggest that up to 30% of women are resistant to aspirin therapy, which in most cases can be overcome by higher dosage regimes.[57,58] The enteric coating of aspirin (as used in our own study) may have also rendered it less bioavailable, notably in patients with an elevated body mass index (BMI).[59]

First trimester placental volume analysis is a well-described technique with good reproducibility.[27,60–64] While previous studies have found the intra- and interexaminer variability to be increased in the second trimester assessment, measurements in our study showed good reproducibility with high correlation coefficients across trimesters.[65] Alternatively, although several studies have demonstrated good reproducibility of 3DPD indices,[11,19,66,67] we found that 3DPD indices can be quite variable.[68] An advancing gestation, increased placental size and difficulty delineating the myometrial border from the placenta can lead to variation in placental volume and vascularity measurements using the VOCAL technique with means of vascular indices varying greatly in different studies.[69,70] This may be related to the depth of insonation of the Doppler signal which can be dependent on placental location, BMI, placental size, site of measurement within the placenta, and erythrocyte density; all of which can generate artifactual Doppler signals at greater depths leading to variability in measurement.[23,71] In addition, the footprint of the 3D probe in the second trimester limits the acquisition of acquiring all of the placenta in the volume acquisition when the ultrasound beam is swept in a fan-like shape.[25]

This study has multiple strengths: (1) it is novel in its approach and is one of the first studies to combine placental volume and vascular indices together with UtA Doppler between the first and second trimesters comparing aspirin and nonaspirin taking groups; (2) it is supported by robust published findings and methodology from a randomized controlled trial; (3) all assessments were performed by one of two trained sonographers, reflected in the low levels of intra- and interexaminer variability of placental volume measurement, thus optimizing the reliability of findings; and (4) high levels of aspirin adherence and close patient follow-up.

The limitations of our study are primarily threefold: (1) As it was a secondary analysis of a randomized controlled trial, it was not originally powered from the outset to detect differences between groups. (2) The demographic profile

of our study is a predominantly Caucasian, nonsmoking, well-educated population with a normal BMI, most of whom conceived spontaneously. From competing risk models for preeclampsia, one is aware that multiparity, smoking, assisted conception, Afro-Caribbean or South Asian ethnicity, and increased maternal weight are risk factors for preeclampsia.[61,62] Restricting the study to primiparous subjects and excluding multiparous, high-risk women with preexisting medical and obstetric complications may have attenuated the impact of aspirin on the findings. (3) Forming an aspirin-taking group from the routine aspirin group (Group 1) and screen-positive aspirin group (Group 3), although with low numbers ($n = 13$), may introduce bias in the aspirin-taking cohort as by principle, and although low risk at baseline, they may contain more women with a propensity to develop uteroplacental disease by virtue of the fact that they are now high-risk for preeclampsia following screening. This limitation has been somewhat accounted for through subanalysis.

In conclusion, this study has not found a significant impact of low-dose aspirin on ultrasound markers of uteroplacental flow in low-risk women. Further large prospective studies may be required to confirm the validity of these findings with consideration to using a higher dose of aspirin when robust safety data emerges to support its safety. Perhaps in future study, placental sonobiopsy may be more preferable for those situations where it is difficult to acquire the placenta volume in a single sweep without generating artifact leading to better reproducibility of vascular indices. Ultrasound at present may not be sensitive enough to detect the mechanisms of aspirin at this current dosage on placental development in the prevention of placental disease, supporting the belief that the mechanism of preeclampsia and its prevention is significantly more complex than we fully appreciate.

Funding

This trial was funded by Perinatal Ireland, HRB, and the Mother and Baby Clinical Trials Network, HRB.

Conflict of Interest

None.

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