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Usefulness of Aspirin Therapy in High-risk Pregnant Women with Abnormal Uterine Artery Doppler Ultrasound at 14-16 Weeks Pregnancy: Randomized Controlled Clinical Trial

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Aim To assess the effectiveness of low-dose aspirin in the prevention of preeclampsia and intrauterine growth restriction (IUGR) in high-risk pregnant women with abnormal findings at uterine artery Doppler velocimetry performed at 14-16 weeks.

Design Randomized controlled clinical trial.

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Methods The trial enrolled 139 women at risk of preeclampsia or IUGR, with abnormal uterine artery Doppler findings that included the presence of unilateral or bilateral diastolic notch, high resistance index (RI), or high pulsatility index (PI) at 14-16 weeks of gestation. The women were randomly allocated into two groups, one receiving aspirin since admission to hospital (n = 74) and the other serving as control (n = 65). All women were followed up until delivery to assess maternal and perinatal outcomes. T-test was used for comparison of quantitative variables, and categorical variables were compared by χ^2 test.

Outcome Criteria Development of mild or severe preeclampsia, time of onset of preeclampsia, preterm delivery, and the development of IUGR.

Results Preeclampsia developed in 35% of women receiving aspirin and 62% of women in the control group ($P = 0.003$), with severe preeclampsia developing in 8% and 23% of women ($P = 0.215$), respectively. Preeclampsia before 37 weeks of gestation was recorded in only 4% of women receiving aspirin as opposed to 83% of controls ($P < 0.001$). In the group of women receiving aspirin, 19% of newborns suffered from IUGR as opposed to 32%of newborns in the control group ($P = 0.106$). There was no significant difference between the two groups in the rate of preterm delivery ($P = 0.080$), mode of delivery ($P = 0.971$), Apgar score < 5 after one minute ($P = 0.273$) and after 5 minutes ($P = 0.941$), maternal or neonatal bleeding (P = 0.948), and neonatal birth weight (P = 0.399).

Conclusion Low-dose aspirin administered as early as 14-16 weeks of gestation to pregnant women at high risk of preeclampsia with abnormal uterine Doppler findings may reduce or modify the course of severe preeclampsia. Its effects on the prevention of IUGR need further evaluation.

Preeclampsia and intrauterine growth restriction (IUGR) are important causes of perinatal morbidity and mortality. Preeclampsia is characterized by an imbalance between prostacyclin and thromboxane production, as well as failure of the second wave trophoblastic invasion of the endometrial-myometrial vasculature with the resultant abnormal uteroplacental blood flow (1,2). The uterine artery Doppler ultrasound emerged as a good test for preeclampsia prediction being simple to perform, reproducible, and non invasive (3-5). The presence of diastolic notch in uterine artery waveforms at 24 weeks of gestation increases the relative risk of preeclampsia 68

times (6). Low dose aspirin is considered to be an intervention to prevent or to modify the course of preeclampsia (7). Collaborative Low dose Aspirin Study in Pregnancy trial (CLASP, ref. 8) was the largest randomized controlled trial. The study concluded that aspirin was generally safe for the mother and fetus and the routine use of aspirin in all women at increased risk of preeclampsia and growth retardation was not justified. Aspirin does not appear efficacious among low or moderate risk populations. However, it also emphasized it may have an effect in women liable to severe early onset preeclampsia (8). In literature, there is more than one trial that tested aspirin administration against a placebo with abnormal uterine artery Doppler ultrasound results (7, 9,10). In almost all the trials, the aspirin therapy was commenced late in pregnancy.

The aim of our study was to determine the effectiveness of aspirin in reducing the risk of preeclampsia or even change its course from severe to mild, as well as reducing the incidence of IUGR in women defined as being at high risk for preeclampsia or IUGR, when this therapy is commenced as early as 14-16 weeks of pregnancy based on abnormal uterine artery Doppler ultrasound.

Subjects and Methods

Subjects

During the period from August 2002 to October 2004, 156 pregnant women were enrolled in the study. All participants were attending the antenatal clinic in Kasr El-Aini Maternity Hospital. Criteria for inclusion were gestational age between 14 and 16 weeks, and a high risk factor for preeclampsia or IUGR, such as previous history of the disease, essential hypertension, positive family history or underlying vascular disorder, maternal age <20 years or >40 years, and gestational diabetes mellitus. Cases with a known history of salicylate allergy, present or past peptic ulcer, past use of prostaglandin inhibitors within 10 days before the beginning of the study, as well as cases with other medical disorders such as chronic renal disorders, thyroid diseases, and hepatic and cardiac disorders were excluded from the study.

Method

In addition to the routine ultrasound (US) done in all participants to evaluate the pregnancy at the time of booking, all patients had Doppler velocimetry of the uterine artery either by transabdominal or transvaginal route. Velocimetry was performed by means of pulsed Doppler, with angle adjusted to 60°, filter adjusted to minimum, and gate adjusted to obtain five consecutive waveforms. The outcome measures were the presence of the uterine artery diastolic notch (bilateral or unilateral), the resistance index, and pulsatility index of the uterine artery. We used the ultrasound machine Elegra (Siemens, Munich, Germany).

Randomization and Intervention

Patients shown to have normal Doppler findings were excluded (12 cases), whereas those with abnormal results (the presence of unilateral or bilateral diastolic notch, uterine artery resistance index higher than the 90th percentile for age) were explained the whole procedure. Five patients refused to participate. The remaining 139 patients agreed to sign a consent and they were randomly divided into two groups: group 1 (74 patients) was treated with acetylsalicylic oral tablets (Aspocid 75 mg per tablet, CID Pharmaceuticals, Egypt) one tablet per day after lunch, and the control group (65 patients) was not given any treatment. Randomization was done using random number generated through a computer program (100 numbers were generated for each group). The numbers were put in similar envelops and after obtaining the abnormal Doppler results, the whole procedure was explained to the patient and if agreed, she was allowed to choose only one envelop. The randomization process, drug prescription, and allocation key were kept by one author (MI) who did not have any role in the patient follow-up or assessing the outcomes. Allocation key was opened after obtaining the statistical results.

Follow-up and Outcome

All women were examined at three-week intervals throughout pregnancy for fetal growth, and amniotic fluid assessment. Uterine Doppler study was also done at 24 weeks and umbilical, as well as middle cerebral Doppler follow-up, was done in the patients who developed preeclampsia. They were also monitored for blood pressure and proteinuria on regular basis. The primary outcome criteria were the development of preeclampsia, time of onset, criteria of severity, the IUGR, and the duration of pregnancy at time of termination. The neonatal birth weight was docu-

mented for the IUGR. Preeclampsia was defined as development of hypertension (140/90 mm Hg or more) plus proteinuria (>300 mg protein in 24-hour urine sample). Severity was diagnosed when systolic blood pressure reached 160 mm Hg, diastolic blood pressure reached 110 mm Hg, proteinuria reached 2 g in 24 hours urine sample, urine output was <500 mL per day, platelet count was <100,000 per mm^3, and liver enzymes were increased (11). Intrauterine growth restriction was diagnosed when the fetal weight was below the 10th percentile for gestational and also when the neonatal birth weight fell below the 10th percentile (12). Maternal and neonatal bleeding was also recorded as a secondary outcome.

Dropouts

One hundred thirty-six cases succeeded to complete the follow-up period, whereas 3 cases were lost. All patients were analysed in the group to which they were allocated (intention-to-treat analysis) and lost patients were analysed, using either the last follow-up report or applying the worst patient scenario (patients given aspirin had the worst outcomes and those with no treatment had the best outcomes). Only one patient was lost from the aspirin group, whereas the other 2 patients were from the control group. For all patients, the follow-up was lost after 37 weeks (Fig. 1).

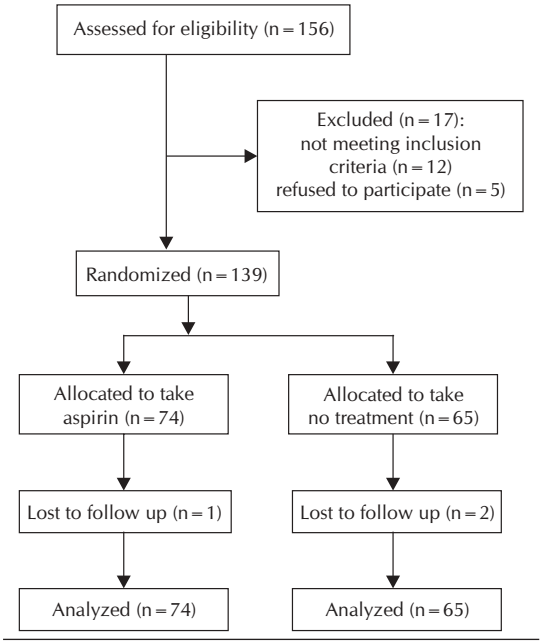

Figure 1. Flow diagram of the progress through the study.

Statistical Analysis

Data were presented as mean ± standard deviation (SD), frequency, and percentage whenever appropriate. Comparison of the different variables between the study groups was done using *t* test for independent samples in case of continuous data and χ^2-test with Yates correction equation for comparing categorical data. *P* values <0.05 were considered statistically significant. Absolute risk reduction (ARR), number needed to treat (NNT), and the 95% confidence interval for both were calculated to measure the clinical effect of aspirin in preventing preeclampsia, severe preeclampsia, and IUGR.

Results

A total number of 139 patients showed abnormal Doppler finding of the uterine artery at the time of recruitment and agreed to participate. The base line patient characteristics are shown in Table 1.

The results of maternal and neonatal outcomes of the study groups based on the intention-to-treat and worst patient scenario concepts (one dropout patient in the aspirin group and 2 patients in the control group) are shown in Table 2. In the aspirin group, 26 out of the randomized 74 patients, developed preeclampsia (35.1%) with two severe cases of disease (7.7%), and one patient developed the disease before 37 gestational weeks (3.9%). Intrauterine growth restriction was diagnosed in 14 neonates (18.9%), 3 delivered preterm (4.1%), 8 had Apgar score <5 at one minute, and only one had score <5 at 5 minutes. In the control group, 40 patients developed preeclampsia (61.5%), with 9 severe cases, (22.5%) and 33 patients developed the disease before 37 gestational weeks. Intrauterine growth restriction was diagnosed in 21 patients (32.3%), 9 (13.9%) were delivered preterm, 11 had Apgar score <5 at one minute, and only one maintained did not improve at 5 minutes. No maternal or neonatal hemorrhage was recorded. According to the worst patient scenario, the lost to follow-up patient in the aspirin group was recorded as developed severe preeclampsia before the 37th gestational week, delivered preterm, and the neonate showed IUGR with Apgar score <5 at 1 as well as 5 minutes, and both maternal and neonatal hemorrhage occurring. In the control group, the 2 lost to follow-up patients were recorded as with no preeclampsia

Table 1. Baseline patients' characteristics

Parameter*	Aspirin group (n=74)	Control group (n=65)	*P*
Maternal age (mean±SD, years)	28.5±5.9	29.1±5.5	0.529†
Maternal age <20 years (No., %)	8 (10.8)	6 (9.2)	0.979‡
Maternal age >40 years (No., %)	12 (16.2)	9 (13.9)	0.879‡
Primipara (No., %)	43 (58.1)	37 (56.9)	0.975‡
Multipara (No., %)	31 (41.9)	28 (43.1)	
Multifetal pregnancy (No., %)	18 (24.3)	12 (18.5)	0.528‡
Systolic blood pressure at randomization (mean±SD, mm Hg)	130.3±14.9	131.3±13.8	0.683†
Diastolic blood pressure at randomization (mean±SD, mm Hg)	79.5±11.7	81.1±10.9	0.397†
Maternal weight at randomization (mean±SD, kg)	71.1±11.7	68.9±13	0.286†
Gestational age at randomization (mean±SD, weeks)	15.2±0.8	15.5±0.9	0.053†
Previous history of preeclampsia (No., %)	21 (28.4)	20 (30.8)	0.903‡
Chronic hypertension (No., %)	25 (33.8)	23 (35.4)	0.985‡
Family history of hypertension (No., %)	15 (20.3)	14 (21.5)	0.980‡
Diabetes mellitus (No., %)	6 (8.1)	3 (4.6)	0.624‡

*SD – standard deviation.
†*t* test for independent samples.
‡χ^2-test.

Table 2. Intention to treat analysis of maternal and perinatal outcomes of the study groups

Outcome	Aspirin group (n=74)	Control group (n=65)	*P**
Development of preeclampsia (No. of positive/No. of all cases, %)	26/74 (35.1)	40/65 (61.5)	0.003
Severe preeclampsia (No. of positive/No. of all cases, %)	2/26 (7.7)	9/40 (22.5)	0.215
Onset of preeclampsia <37 weeks (No. of positive/No. of all cases, %)	1/26 (3.9)	33/40 (82.5)	<0.001
Intrauterine growth restriction (No. of positive/No. of all cases, %)	14/74 (18.9)	21/65 (32.3)	0.106
Preterm delivery (No. of positive/No. of all cases, %)	3/74 (4.1)	9/65 (13.9)	0.080
One minute Apgar score <5 (No. of positive/No. of all cases, %)	8/74 (10.8)	11/65 (16.9)	0.424
Five minutes Apgar score <5 (No. of positive/No. of all cases, %)	1/74 (1.4)	1/65 (1.5)	0.534
Maternal bleeding (No. of positive/No. of all cases, %)	1/74 (1.4)	0/65 (0.0)	0.948
Neonatal bleeding (No. of positive/No. of all cases, %)	1/74 (1.4)	0/65 (0.0)	0.948

*χ^2-test.

was developed and no maternal or neonatal complications.

The results are recalculated after excluding the dropouts (per-protocol analysis) and shown in Table 3.

After calculating the absolute risk reduction and the number needed to treat for the main maternal and neonatal outcomes, it was evident that aspirin was more effective in delaying the onset of preeclampsia (NNT=1; 95% CI, 1-2), than in preventing preeclampsia (NNT=4; 95% CI, 2-10). Its effect on preventing preterm delivery is doubtful (NNT=10; 95% CI, 5-372) and no effect was proved in preventing severity or the development of IUGR (Table 4).

Discussion

Our study showed that by detecting abnormal uterine artery Doppler indices (high RI or the presence of diastolic notch either bilateral or unilateral) between 14-16 weeks pregnancy, we can identify women at risk for development of preeclampsia. Also by commencing treatment of low dose aspirin to these patients in such early time of pregnancy we can reduce the incidence of preeclampsia. It also showed that the incidence of severe preeclampsia and the incidence of preeclampsia developing before 37 weeks were lower in the aspirin group than in the control group. Our results showed no significant impact of low dose aspirin therapy on the birth weight and no significant effect on preventing IUGR. When we compared our results with that in the literature we found considerable disparities which may be attributed to many factors like the time of recruitment of patients, the risk level of the pregnant woman (low or high risk), and the outcome measures. A multicenter randomized controlled trial (13) showed that there was no justification for screening with uterine artery Doppler in a low risk population, even if abnormal results were followed by aspirin treatment and increased prenatal surveillance. This was also documented by an overview on 27 studies involving 12,994 subjects (14). Also a recent study (15) of 3,324 of low risk women at 11-14 weeks demonstrated bilateral notching in 55% and concluded that this was unlikely to be useful in screening for pregnancy complications. However, if we only select high risk pregnant women, the results will be different. There were five randomized trials (7,9,10,16,17)

Table 3. Per protocol analysis of maternal and perinatal outcomes of the study groups

Outcome	Aspirin group (n=74)	Control group (n=65)	*P**
Development of preeclampsia (No. of positive/No. of all cases, %)	25/73 (34.3)	40/63 (63.5)	<0.001
Severe preeclampsia (No. of positive/No. of all cases, %)	1/25 (4.0)	9/40 (22.5)	0.079
Onset of preeclampsia <37 weeks (No. of positive/No. of all cases, %)	0/25 (0.0)	33/40 (82.5)	<0.001
Intrauterine growth restriction (No. of positive/No. of all cases, %)	13/73 (17.8)	21/63 (33.3)	0.059
Preterm delivery (No. of positive/No. of all cases, %)	2/73 (2.7)	9/63 (14.3)	0.032
One minute Apgar score <5 (No. of positive/No. of all cases, %)	7/73 (9.6)	11/63 (17.5)	0.273
Five minutes Apgar score <5 (No. of positive/No. of all cases, %)	0/73 (0.0)	1/63 (1.6)	0.941
Maternal bleeding (No. of positive/No. of all cases, %)	0/73 (0.0)	0/63 (0.0)	
Neonatal bleeding (No. of positive/No. of all cases, %)	0/73 (0.0)	0/63 (0.0)	
Spontaneous vaginal delivery	39/73 (53.4)	32/63 (50.8)	0.893
Induced vaginal delivery	25/73 (34.3)	24/63 (38.1)	0.774
Cesarean section	13/73 (17.8)	12/63 (19.1)	0.971
Neonatal birth weight (g)	3,065.4±798	2,948.3±812	0.399

*χ^2-test or *t* test.

Table 4. Analysis of treatment effect of maternal and perinatal outcomes of the study groups (based on intention to treat analysis)*

Parameter	ARR (95% CI)	NNT (95% CI)
Development of preeclampsia	0.26 (0.10 to 0.43)	4 (2 to 10)
Severe preeclampsia	0.15 (-0.02 to 0.31)	7 (3 to -59)
Onset of preeclampsia <37 weeks	0.79 (0.65 to 0.93)	1 (1 to 2)
Preterm delivery	0.01 (0.01 to 0.19)	10 (5 to 372)
IUGR	0.13 (-0.01 to 0.28)	7 (4 to -94)

*Abbreviations: ARR – absolute risk reduction, CI – confidence interval, NNT – number needed to treat, IUGR – intrauterine growth restriction.

which evaluated the aspirin therapy in high risk patients. Four trials (7,9,10,17) showed a tendency towards benefit, but in three (7,9,17), the sample size was not large enough to produce significant *P* values. These findings were consistent with a recent meta analysis of aspirin therapy in preventing preeclampsia following uterine artery Doppler studies in the second trimester and also showed tendency towards benefit (18). Vainio et al (19) reached the same conclusion as we did concerning the benefit of low dose aspirin in high risk patients. They started Doppler study of the uterine artery as early as 12-14 weeks and depended on the presence of bilateral diastolic notch to select the cases justified for receiving aspirin therapy. Harrington et al (20,21) reported in two studies that there were differences in uterine and umbilical artery Doppler blood flow indices at 12-16 weeks in pregnancies with normal or complicated outcome, and bilateral notching was associated with a 22-fold increase in the odds of developing preeclampsia. If bilateral notches alone were used to predict preeclampsia, the test achieved a sensitivity of 93%, but specificity was only 69%. The problem with most Doppler screening studies is its low positive predictive values and, as gestational age advances, the specificity and positive predictive value increase significantly, and the sensitivity decreases (22). In our study, we preferred to postpone the study of the uterine artery to 14-16 weeks, because we believe that placental implantation is completed by 14-18 weeks (23,24), so the expected changes in the uterine artery (from high resistant to a low resistant vessel) should occur within this time and not before, in this way we can have better selection of the patients and increase the specificity of the screening test. We can conclude that Doppler US study of the uterine artery at 14-16 weeks in high risk pregnant women appears to be useful as a screening test for development of preeclampsia. Commencing low dose aspirin therapy for such selected cases in the early stage of pregnancy may decrease the incidence of severe preeclampsia and also delay its onset. Its impact on reducing or eliminating the possibility of IUGR is questionable, therefore, this test and treatment combination should now be considered for incorporation into clinical practice in high risk pregnant women.

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