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Prevention of preeclampsia using low dose Aspirin: A randomised controlled trial

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Summary

Objectives: To test the effectiveness of aspirin in low doses to prevention PE in high risk .
Study design: Prospective randomized controlled double blind trial.
Setting: Department of Obstetrics & Gynaecology, Al-Habobi teaching hospital, Thi-qar province/Iraq.
Patients and methods: 100 participants at high risk of developing preeclampsia were randomly divided into 2 groups. Group I involved 50 pregnant women who received acetyl salicylic acid 75 mg/ day. Group II included 50 pregnant women who received placebo. Primary outcomes included gestational hypertension and pre-eclampsia. Secondary outcomes included development of eclampsia, HELLP syndrome, placental abruption, IUGR, NICU admission, neonatal complications and congenital anomalies.
Results: The incidence of preeclampsia was 22% in the Aspirin group and 44% in the control group (P <0.001). A highly significant difference was found when comparing the two groups regarding gestational age at delivery (37.8±1.9 vs. 33.2±3.2), development of PE (22% vs. 44%) particularly early onset (14% vs. 34%) and severe form (8 vs. 22%) and occurrence of HELLP syndrome (4 vs. 16%) respectively (P <0.001) . There was a significant difference between cases and controls regarding the development of gestational hypertension (14% VS. 22%) (P 0.05) .There was a significant improvement of neonates delivered to mothers who received aspirin proved by the presence of significant higher birth weight (2989±815 vs. 2062±976), lower occurrence of IUGR (10% vs. 24%), neonatal ICU admission (34% vs. 78%) and respiratory distress syndrome (20% vs. 60%).
Conclusion: the use of low-dose aspirin is of significant importance in reducing the risk of gestational hypertension, pre-eclampsia and IUGR in high risk women.

Keywards: Preeclampsia, Aspirin

الوقاية من تسمم الحمل باستخدام جرعة صغيرة من الأسبرين: باختبار عينة عشوائية

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الخلاصة:

ألهدف: لاختبار فعالية الأسبرين بجرعات منخفضة لمنع PE تحت عوامل خطورة عالية.

طرائق ألعمل: اجريت الدراسة في قسم التوليد وألامراض النسائية في مستشفى الحبوبي التعليمي في محافظة ذي قار/ العراق. شملت الدراسة 100 مشاركة في خطر كبير من تسمم الحمل تم تقسيمهن عشوائيا إلى مجموعتين. المجموعة الأولى من 50 امرأة حامل حصلوا على أسيتيل الساليسيليك بجرعة 75 ملغ

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/ يوم. تضمنت المجموعة الثانية 50 امرأة من النساء الحوامل الذين تلقوا العلاج الوهمي. وشملت النتائج الأولية ارتفاع ضغط الدم الحملي وتسمم الحمل. وشملت النتائج الثانوية تطور تسمم ألحمل متلازمة هيلب، انفصال المشيمة ألباكر تأخر النمو داخل ألرحم وقبول نيكو , مضاعفات حديثي الولادة والتشوهات الخلقية.

ألنتائج: كان معدل حدوث تسمم الحمل 22٪ في مجموعة الأسبرين و 44٪ في المجموعة الضابطة تحت مستوى احتمالية (P <0.001). تم الحصول على فرق معنوي كبير للغاية عند المقارنة بين المجموعتين فيما يتعلق بعمر الحمل عند الولادة (37.8 ± 1.9 مقابل 33.2 ± 3.2)، وتطور PE (22٪ مقابل 44٪) ولادة مبكرة وخاصة (14٪ مقابل 34٪) و شكل حاد (8 مقابل 22٪) وحدوث متلازمة هيلب (4 مقابل 16٪) على التوالي (P <0.001). كان هناك فرق معنوي بين الحالات السريرية ومجموعة السيطرة فيما يتعلق بتطور وارتفاع ضغط الدم الحملي (14٪ مقابل 22٪) (P 0.05) كما حدث تحسنا كبيرا لحديثي الولادة الذين ولدوا للأمهات اللاتي حصلن على الأسبرين من خلال زيادة اوزان المواليد عند الولادة مقارنة بالمجموعة الاخرى (2989 ± 815 مقابل 2062 ± 976) مع قلة حدوث حالات تأخر النمو داخل الرحم (10٪ مقابل 24٪)، و دخول حديثي الولادة الى وحدة العناية المركزة (34٪ مقابل 78٪) ومتلازمة الضائقة التنفسية (20٪ مقابل 60٪) .

ألاستنتاج: استخدام جرعة منخفضة من الاسبرين له أهمية كبيرة في الحد من مخاطر ارتفاع ضغط الدم الحملي، تسمم الحمل وتأخر النمو داخل الرحم عند النساء اللاتي يتعرضن الى مخاطر عالية لتطور هذه الحالات.

Introduction

About 15 to 20 % of all pregnant women have hypertension in different forms. Hypertension associated with pregnancy is a main cause of perinatal hazards and deaths. **Preeclampsia** is a unique syndrome associating pregnancy with different severity of placental dysfuction and a general inflammatory response of the pregnant woman [Dekker, 2011].

Younger aged females and those with no previous parity are more susceptible to develop PE, while higher ages are more susceptible to hypertension in its chronic form with preeclampsia superimposed [Cunningham *et al.*, 2014]. Other factors include environmental, socioeconomic, and even seasonal influences [Lawlor *et al*., 2005 : Spenser *et al*., 2009].

Other risk factors are high body weight, twins and higher orders pregnancies, aging of the mother, hyperhomocysteinemia, and metabolic disorders [Scholten *et al*., 2013: Walker, 2000].

The cause of preeclampsia stills largely unknown, but inadequate placentation is a well known predisposing factor. The projected 2 stage module [Roberts and Hubel, 1999] with diminished perfusion of the placenta (1^{st} stage) causes the maternal disease (2^{nd} stage) gives simple but precise explanation for the syndrome in its early severe form , however its less applicable for the mild late forms [Redman and Sargent, 2000].

According to Redman and coworkers (2014), stage 1 is caused by defective endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome [Redman *et al*., 2014].

Prevention of PE using aspirin in low dose has been suggested depending on the disease and its coagulation abnormalities is related to faulty balance of prostaglandin between dilators and constricting types. Aspirin in low doses – being an inhibitor of cyclo-oxygenase enzymes – decreases production of thromboxane more than prostacyclin so defend against the pathological constriction of vessels and placental coagulation [Coomarasamy *et al*., 2003].

Our study aimed to effectiveness of aspirin in low doses to prevention PE in susceptible women.

Materials and methods

A prospective double blind case control randomized study was done on pregnant women in their first trimester that came to Al-Habobi teaching hospital during the period starting from January 2015 to march 2016.

After approval of local ethics committee, informed written consents from 100 high risk pregnant women with the following conditions: maternal age between 18 and 41 years, gestational age < 12 weeks (calculated from day LMP and confirmed by ultrasound), all were singleton living pregnancy.

High risk patients were defined by having any risk to develop PE. Those include hypertension in its chronic form, pregestational diabetes mellitus, body mass index (BMI) > 30kg/m² or preeclampsia in previous pregnancy. Women with twins and higher orders

gestation, antiphospholipid syndrome, rupture of membranes, fetal anomalies, patients taking preventive therapy, and those with known allergy to the used medications were barred from the trial.

Grouping of the participants' randomly using computer generated random numbers was done into 2 groups. Group I involved 50 pregnant women who received acetyl salicylic acid 75 mg/ day (Aspocid infantile, CID pharmaceutical. Egypt). Group II included 50 pregnant women who received placebo.

Full history was done followed by proper examination. Obstetric ultrasound examination to assess number of fetuses, vitality, morphology and confirmation of gestational age.

Blood pressure at randomization was measured with a mercurial sphygmomanometer blood pressure measuring instrument, GOH industries LTD, Tokyo, Japan. After five minutes of rest for the patient, two assessments of blood pressure separated by three minutes and calculation for their mean was done.

Follow up was done biweekly till gestational age of 30 weeks then weekly. Participants were asked during the follow up about appearance of any warning manifestations. Measuring of blood pressure and checking of urinary proteins using dipstick were also done and confirmation of proteinuria was done by evaluation of urinary protein : creatinine ratio. Ultrasound evaluation at gestational ages of 28, 32 and 36 weeks. PE was diagnosed with blood pressure higher or equal 140/90 mmHg measured twice with four hours between the measurements with more than 30 mg/mmol urine protein to creatinine ratio. Occurrence of PE before 34 weeks was considered early onset [Salimi *et al.*, 2014].Blood pressure higher than 160/110, occurrence of symptoms or the presence of biochemical or haematological impairment was used to define severe PE [NIHCE, 2011].

Primary outcomes included gestational hypertension and pre-eclampsia. Secondary outcomes included development of eclampsia, HELLP syndrome, placental abruption, IUGR, NICU admission, neonatal complications and congenital anomalies.

Incidence of PE among controls was suspected to be 43% and among high risk was 20 % [Zimmermann *et al.*, 1997] so using chi-squared statistic gives a sample size of 49 participants gives a power of 80% (α error 0.05). The PS Power and Sample Size Calculation software, version 3.0.11 for microsoft Windows

Description of data was done using mean, standard deviation (± SD), or frequencies and percentages as needed. Chi square (χ^2), Exact test or ANOVA were used as appropriate. P values smaller than 0.05 was used to define significance. SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006) program was used.

Results

There were no significant differences between the two study groups regarding age, parity, BMI, number of smokers, number of patients with prepregnancy hypertension or Diabetes and history of PIH in prior pregnancy (Table 1). There was no statistically significant difference between the two study groups regarding baseline systolic and diastolic blood pressure (Table 1).

Table (1): baseline characteristics of the study population

		Aspirin group (n= 50)	Control group (n= 50)	P value
Age (years)		28.9±6.7	29.3±7.1	0.348NS
BMI (kg/m2)		28.9±3.2	27.9±3.6	0.521NS
Parity		0.58±0.91	0.62±0.89	0.737NS
Smokers *		10 (20%)	9 (18%)	0.672NS
Previous history of PE*		12 (24%)	13 (26%)	0.77NS
Medical diseases	Chronic hypertension*	11 (22%)	11 (22%)	0.988NS
	DM*	9 (18%)	7 (14%)	0.654NS
SBP		121.45±15.8	119.9±19.6	0.434NS
DBP		79.8±10.9	76.82±10.1	0.581NS

Data are presented as mean ±SD

* Data are presented as number (percent)
BMI Body mass index ;PE Preeclampsia ;DM Diabetes Mellitus ;SBP Systolic blood pressure ;DBP Diastolic blood pressure ;NS Non significant

A highly significant difference was found when comparing the two groups regarding gestational age at delivery, development of PE particularly early onset and severe form and occurrence of HELLP syndrome (Table 2).

There was a significant difference between cases and controls regarding the development of gestational hypertension but no statistical difference between them regarding development of eclampsia or placental abruption (Table 2). Regarding neonatal outcome there was a significant improvement of neonates delivered to mothers who received aspirin proved by the presence of significant higher birth weight, lower occurance of IUGR, neonatal ICU admission and respiratory distress syndrome. However the number of neonatal deaths and

neonatal jaundice showed no significant difference (Table 2)

Table (2): Outcome parameter among study groups

		Aspirin group (n= 50)	Control group (n= 50)	P value
GA at delivery *		37.8±1.9	33.2±3.2	<0.001 HS
Gestational hypertension		7 (14%)	11 (22%)	0.05 S
Preeclampsia		11 (22%)	22 (44%)	<0.001HS
Early onset preeclampsia		7 (14%)	17 (34%)	<0.001HS
Severe preeclampsia		4 (8%)	11 (22%)	<0.001HS
Eclampsia		1 (2%)	1 (2%)	0.858 NS
HELLP		2 (4%)	8 (16%)	<0.001HS
Placental abruption		2 (4%)	3 (6%)	0.563 NS
IUGR		5 (10%)	12 (24%)	<0.001HS
Neonatal BW *		2989±815	2062±976	<0.001HS
NICU admission		17 (34%)	39 (78%)	<0.001HS
Neonatal deaths		1 (2%)	2 (4%)	0.535NS
Neonatal complications	RDS	10 (20%)	30 (60%)	<0.001HS
	Jaundice	7 (14%)	9 (18%)	0.594 NS

Data are presented as number (percent)

* Data are presented as mean ±SD
GA Gestational age; IUGR Intrauterine growth restriction; BW birth weight ; NICU neonatal intensive care unit; RDS Respiratory distress syndrome

Discussion

PIH can develop into pre-eclampsia, eclampsia or even HELLP syndrome; these are major causes of both of maternal and neonatal morbidity and mortality [Schutte *et al*., 2008]

In our study, we found a significant lower incidence of gestational hypertension and pre-eclampsia especially early onset and its severe form in women treated with low dose aspirin. Askie and colleagues in 2007 [Askie *et al.*, 2007] James and coworkers in 2008 [James *et al*., 2008] reported modest but sturdy reduction in preeclampsia in patients taking aspirin. Our findings were agreed with Hermida and colleagues in 2003 [Hermida *et al*., 2003] who reported a greatly statistically important blood pressure reduction in women getting aspirin in comparison with placebo group. However, the CLASP trial in 1994 failed to demonstrate a significant decrease in the occurrence of gestational hypertension but noted a significant decrease in the incidence of preeclampsia[CLASP, 1994].

Our study illustrated a significant diminish in the rate of IUGR, neonatal low birth weight and NICU admittance between the group taking aspirin and the control group. A systematic assessment done by Duley and others in 2001, showed that there was a significant difference in the risk of small for gestational age in the aspirin group, however, there were no significant difference between treatment and control groups in the risk of birth weight <2500 gm or admission to NICU [Duley *etal.*, 2001].

In this study, there was a statistically significant difference between the aspirin group and the control group as regards the GA at delivery, HELLP syndrome and RDS.

There was no significant difference between women taking aspirin and controls regarding development of eclampsia, placental abruption and neonatal deaths. That appear logic after the development of neonatal survival which helped to reduce conservative management and continuation of pregnancy in women who developed PE so they will not develop eclampsia and lowered incidence of complications asbplacental abruption

This result goes with what have been reported by Duley *et al*., 2001 that there was no significant difference between the aspirin group and the control group as regards the risk of eclampsia or placental abruption.

On the other hand, Souza *et al* grouped randomly a total of 49 pregnants suffering from chronic hypertension with abnormalities in the Doppler of uterine artery at gestational ages ranged from 20 to 27 weeks to take either aspirin and calcium or placebo . They found that women received aspirin and calcium have a 28.6% lower incidence of superimposed PE which was considered a non significant reduction by the authors [Souza *et al*., 2014].

Small sample size used by Souza and colleagues is not enough to detect significance and delayed introduction of prophylactic drugs till 27 weeks allow development and establishment of the disease. They also have different inclusion criteria as they involved only one of the risk factors named chronic hypertension and ignoring other factors. These facts can explain different findings between our study and their one.

YU *et al* grouped 560 pregnant women randomly at gestational age of 23 weeks with abnormal uterine artery Doppler (PI > 1.6) to take either 150 mg of aspirin daily or a placebo. Women with chronic hypertension or pregestational diabetes were excluded

from their study. They found a similar incidence of development of PE among both groups no significant differences between the aspirin (18.7% vs. 17.8%,P value 0.77) [YU *et al*., 2003].

Again this study excluded women with important risk factors as chronic hypertension and Diabetes. These women formed 42.5% of our participants. Also the higher dose of aspirin may have different effect on the thromboxane and prostacyclin balance when compared to the dose used in our study.

We concluded that the use of low-dose aspirin is of significant importance in reducing the risk of gestational hypertension, pre-eclampsia and IUGR in high risk women.

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