

# Effect of regular oral intake of aspirin during pregnancy on pregnancy outcome of high-risk pregnancy-induced hypertension syndrome patients

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**Abstract. – OBJECTIVE:** The aim of this study is to analyze the effect of 100 mg/d regular oral intake of aspirin during pregnancy on high-risk pregnancy-induced hypertension syndrome patients.

**PATIENTS AND METHODS:** We consecutively selected 98 cases high-risk pregnancy-induced hypertension syndrome patients. After obtaining the informed consent of the patients, we randomly divided the patients into aspirin group (50 cases) and placebo group (48 cases). The oral intake of aspirin lasted from the final diagnosis of pregnancy to antepartum time, and was taken before sleep. The bleeding index was closely detected and we stop taking aspirin when necessary.

**RESULTS:** The comparison of clinical outcome showed that the incidents of pregnancy-induced hypertension syndrome, pre-eclampsia and eclampsia of aspirin group were significantly lower than that of the placebo group ( $p < 0.05$ ). Comparing the complications of fetus perinatal period, the difference was not statistically significant ( $p > 0.05$ ).

**CONCLUSIONS:** 100 mg/d regular oral intake of aspirin during pregnancy is safe, effective and worthy of generalization to high-risk pregnancy-induced hypertension syndrome patients.

Key Words:

Aspirin, High-risk pregnancy-induced hypertension syndrome, Eclampsia, uterine-incision delivery, Bleeding volume.

## Introduction

We showed that pregnancy-induced hypertension syndrome might be related to an anomaly of the placenta<sup>1</sup>. Placenta nurse cells undergo autophagy which leads to ischemia and anoxia, and further releases multiple inflammatory factors

and damages vascular endothelial cells, and then starts endogenous and extrinsic clotting mechanism<sup>2</sup>. Thrombus A2 (TXA2) secreted by platelet increases, and prostacyclin (PGI2) decreases, which finally leads to a change of hemodynamics and hypertension. Aspirin can interrupt the transformation from arachidonic acid to TXA2 by inhibiting the activity of cyclooxygenase, thus to reduce platelet accumulation and thrombosis<sup>3</sup>. On the basis of this, it is conjectured theoretically that aspirin can prevent pregnancy-induced hypertension syndrome to some extent. It was pointed out in 2010 (NICE) guidebook that all gravid with one middle or a high-risk factor for pre-eclampsia should orally intake small dose of aspirin (75 mg) every day from 12 weeks pregnancy to labor<sup>4</sup>. Large-sampled clinical randomized controlled trials are lacking in our country. So far there is not a final conclusion whether regular oral intake is needed, and how are the dose, applied population and clinical outcome<sup>2,5</sup>. This study analyzed the application experience suitable for Chinese pregnant women by single-centered, small-sampled clinical research.

## Patients and Methods

### Patient

115 cases of pregnancy-induced hypertension syndrome patients were consecutively selected in our Guaranteed Center from October 2012 to October 2015, in which the diagnostic criteria of pregnancy-induced hypertension syndrome was according to “2010 NICE guide” (3), by including age  $\geq 40$ , BMI  $\geq 35$  kg/m<sup>2</sup>, pre-eclampsia fa-

mily history, multiple pregnancy history, previous hypertensive disease, chronic nephrosis, autoimmune disease like systemic lupus erythematosus; systemic lupus erythematosus and antiphospholipid syndrome, type 1 or type 2 diabetes, chronic hypertension well controlled. Select standard: (1) 50 > Age ≥ 18; (2) Single birth; (3) No abortion history. Rule out standard: (1) Coagulation disorder; (2) Need oral intake of anticoagulants like Warfarin or vein application of heparin; (3) Have hypertension before pregnancy and fail to control up to standard with drug; (4) Being allergic to aspirin, low compliance. This study was approved by the Ethics Committee of our Department and the informed consent of patients and/or family members was obtained.

According to the order of admission to hospital of the patients, we used random number method to divide them into aspirin group (58 cases) and placebo group (57 cases), in which gestational week of aspirin group is 4-15 weeks, average (8.7±3.4) weeks; age 23-34, average age (26.6±5.2); BMI 26.7-34.2 kg/m<sup>2</sup>, average (31.5±4.7) kg/m<sup>2</sup>; systolic pressure 72-146 mmHg, average (103.6±24.7) mmHg; diastolic pressure 62-88 mmHg, average (72.6±16.9) mmHg. Gestational week of placebo group is 3-14 weeks, average (8.2±3.7) weeks, average 21-36, average (25.3±5.8); BMI 24.5-36.3 kg/m<sup>2</sup>, average (31.7±4.8) kg/m<sup>2</sup>; systolic pressure 70-148 mmHg, average (102.8±25.5R) mmHg; diastolic pressure 60-86 mmHg, average (70.5±15.7) mmHg. The differences of gestational week, age, BMI, systolic pressure and diastolic pressure between the two groups do not have statistical significance ( $p > 0.05$ ).

**Methods**

After dividing the groups, patients in aspirin group were given 100 mg/d aspirin (Bayer Co., Leverkusen, Germany), which was orally intaken before sleep until labor. Patients in the placebo group were given 100 mg/d drug with basically

the same characteristics, color and tastes (provided by the Biopharmaceutics Center of our Department), which was orally intake before sleep until labor. Regularly test routine blood and coagulation function (once per month), and stop the drug to observe if there was abnormal condition.

**Observation Index**

The differences of occurrences of pregnancy-induced hypertension syndrome, pre-eclampsia, eclampsia, uterine-incision delivery, bleeding volumes before, in and after labor, occurrence of complications of fetus perinatal period were compared between the two groups.

**Statistical Analysis**

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Measurement data was expressed by mean average ± standard deviation. Comparison between groups is tested by t-test. Enumeration data is expressed by (%). Comparison between groups is tested by X<sup>2</sup>-test or precise probabilistic method.  $p < 0.05$  is regarded to have statistical significance.

**Results**

**Comparison of Occurrences of Pregnancy-Induced Hypertension Syndrome, Pre-Eclampsia and Eclampsia**

In the aspirin group, 2 cases stopped treatment, 2 cases lost following-up, 4 cases having abnormal tested index. Hence, in the aspirin group, there were 50 cases at the end. In the placebo group, there were 4 cases which stopped treatment, 5 cases lost following-up and, at the end, 48 cases were in the group. Incidents of pregnancy-induced hypertension syndrome, pre-eclampsia and eclampsia of aspirin group were significantly lower than that of placebo group ( $p < 0.05$ ) as shown in Table I.

**Table I.** Comparison of occurrences of pregnancy-induced hypertension syndrome, pre-eclampsia and eclampsia [cases(%)]

Group	Cases	Incidences of pregnancy-induced hypertension syndrome		
		Pre-eclampsia	Eclampsia	
Aspirin	50	6 (12.0)	3 (6.0)	1 (2.0)
Placebo	48	14 (29.2)	10 (20.8)	6 (12.5)
X <sup>2</sup>		4.443	4.683	4.071
p		0.035	0.030	0.044

**Table II.** Comparison of occurrence of uterine-incision delivery, labor gestational week, and bleeding volumes before, in and after labor.

Group	Cases	Occurrence of uterine-incision delivery [cases (%)]	labor gestational week (weeks)	Bleeding volumes before labor (ml)	Bleeding volumes in labor (ml)	Bleeding volumes after labor (ml)
Aspirin group	50	5 (10.0)	38.4±4.6	67.3±15.2	142.5±24.3	125.8±26.9
Placebo group	48	13 (27.1)	37.6±5.5	92.5±16.8	235.4±25.7	193.6±25.8
<i>t</i> ( <i>X</i> <sup>2</sup> )		4.767	4.927	4.628	4.639	5.203
<i>p</i>		0.029	0.022	0.031	0.031	0.017

**Comparison of Occurrences of Uterine-incision Delivery, Labor Gestational Week, and Bleeding Volumes before, in and after Labor**

In aspirin group, occurrence of uterine-incision delivery significantly reduces, labor gestational week significantly prolongs, bleeding volumes before, in and after labor reduced significantly (*p* < 0.05) as shown in Table II.

**Comparison of Occurrence of Fetus Perinatal Period Complications**

The difference of occurrence of fetus perinatal period complications was not statistically significant (*p*>0.05) as shown in Table III.

**Discussion**

It has been found that there are different effects of oral aspirin intake at different gestational weeks<sup>4</sup>. It was found in a research on 100 cases of pregnant women with possibility of developing pre-eclampsia that with oral aspirin intake from 20 gestational weeks to 36 gestational weeks, the occurrence of late-pregnancy pre-eclampsia is 4%, which is significantly lower than that of the control group (24%)<sup>5</sup>. While comparing post-labor bleeding, abruptio placentae, abruptio placentae and premature birth, there was no statistically significant difference. In 2010, Bujold<sup>6</sup> did a meta-analysis of 11,348 cases of pregnant women and found that low dose aspirin oral

intake before 16 gestational weeks can reduce the incidence of pregnancy-induced hypertension syndrome, the incidence of pre-eclampsia and severe pre-eclampsia. In 2011, Rossi et al<sup>7</sup> found in a study of effectiveness of low dose aspirin on prevention of pregnancy-induced hypertension syndrome that for the population without risk factors of pregnancy-induced hypertension syndrome, low dose aspirin oral intake does not change the incidence of pregnancy-induced hypertension syndrome. While for population with the risk factors, with a low dose aspirin oral intake from 16 gestational weeks, though incidence of pregnancy-induced hypertension syndrome (8%) is slightly reduced compared with the placebo group (9%), but the difference does not have statistical significance, and there was no statistical significance of neonatal mortality and perinatal mortality. Considering the reasons, placenta ischemia and anoxia caused by placentation abnormality is the main cause of a series of symptoms including platelet aggregation, placental infarction and pregnancy-induced hypertension syndrome. Therefore, only if the aspirin intake is before complete placentation, it can effectively reduce the occurrence of pregnancy-induced hypertension syndrome.

It has been found that compared to intake when getting up, aspirin intake before sleep has a better effect of preventing pregnancy-induced hypertension syndrome<sup>9,10</sup>, and around 30% pregnant women have drug resistance to aspirin, which can be confirmed by platelet aggregation test<sup>11</sup>. There is an evident prevention effect of using the drug before

**Table III.** Comparison of occurrence of fetus perinatal period complications [cases(%)]

Group	Cases	Intracalvarium and intraventricle hemorrhage	Ischemiac and anoxia	Others	Complications incidence
Aspirin group	50	1	1	1	3 (6.0)
Placebo group	48	0	2	2	4 (8.3)
<i>X</i> <sup>2</sup>					0.003
<i>p</i>					0.955

16 gestational weeks, thus besides high-risk factors, more investigation is needed on the aspects of drug intake time, applied population and beginning gestational week<sup>12</sup>. This study points out that occurrences of pregnancy-induced hypertension syndrome, pre-eclampsia and eclampsia of aspirin group were all significantly lower than that of the placebo group, the gestational week significantly prolongs, the bleeding volumes before, in and after labor were all significantly decrease. The difference of the occurrence of perinatal fetus complications does not have statistical significance. Aspirin general dosage for preventing cardiovascular and cerebrovascular diseases (100 mg/d) was higher than that of European and American countries (50-75 mg/d), needing aspirin dosage for achieving 80% inhibitory rate of acute myocardial infarction within 6h is 300 mg, which was higher than that of European and American countries (125-225 mg), suggesting the diversity of anti-thrombotic activity of aspirin among different ethnics<sup>13</sup>. This study took 100 mg/d as oral intake dose, with aspirin treatment right after final diagnosis of pregnancy and being incorporated in the group. The drug intake time significantly advanced (average 8.7 weeks), the total course of treatment significantly prolonged (average 30 weeks), and it was safe and effective to gravidity women and fetus.

Few shortcomings of this study were small sample size, more evaluation to distinguish effect of aspirin, e.g. whether pre-pregnancy combined hypertension and pregnant combined diabetes have influence on the outcome, or whether oral intake dose can further reduce (like whether 76 mg is effective), whether starting time can further delays (like from 12 gestational week), whether it is still effective to low and medium risk pregnancy-induced hypertension syndrome patients and whether stopping drug in the middle process and fetus perinatal period complications are related with aspirin oral intake. Further investigation is needed to solve these questions.

## Conclusions

100 mg/d regular oral intake of aspirin during pregnancy is safe and effective to pregnancy-induced hypertension syndrome patients, and is worthy of application and generalization.

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## Conflicts of interest

The authors declare no conflicts of interest.

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