The study of role of aspirin and antioxidants in prevention of hypertensive disorders in a primigravida

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Abstract
Aim: To observe the effect of aspirin and other antioxidants in prevention of hypertension and thereby the outcome of pregnancy in terms of maternal and perinatal morbidity and mortality.
To evaluate the role of aspirin and antioxidants in decreasing systolic blood pressure (SBP) and diastolic blood pressure (DBP) and thereby on the severity of hypertensive disorders of pregnancies.
To evaluate the role of aspirin and antioxidants in prevention of oligohydramnios, fetal growth restriction (FGR).

Material and Method: This is a prospective randomized controlled study for evaluation of role of aspirin and antioxidants in prevention of hypertensive disorders of pregnancy in primigravida. It was carried out at department of Obstetrics and Gynaecology in NHL Municipal Medical College, Ahmedabad between October 2008 and September 2010. 80 women attending antenatal OPD were included in this study.

Results: Gestational hypertension occurred in 5% of the case group while in 10% of the control group. Incidence of preeclampsia is nil in case group while its 5% in control group. It shows that the severity of the hypertensive disorders is also less in the case group, even if it occurs at all. Mean arterial Blood pressure – both systolic and diastolic – are less in case group compared to the control group. Incidence of oligohydramnios is 2.5% in case group while 10% in control group, indicating the role of aspirin and antioxidants in prevention of oligohydramnios. Incidence of meconium staining of liquor is nil in case group while it is 7.5% in the control group indicating the preventive role of low dose aspirin and antioxidants against MSL. Incidence of low birth weight babies is nil in case group while it is 25% in control group and Mean birth weight is 2.96 Kg in case group while 2.63 kg in control group indicating the importance of aspirin and antioxidants in preventing low birth weight babies.

Conclusion: It was noted in the present study that low dose aspirin and antioxidants may have beneficial effect in the prevention of hypertensive disorders of pregnancy in the high risk primigravida subjects. Reduction in the severity of hypertension was also noted, even if it develops, in the women taking low dose aspirin and antioxidants. Overall improvement of the perinatal outcome was observed in the form of reduction in the incidence of oligohydramnios, meconium stained liquor and low birth weight babies.

Keywords: aspirin and antioxidants, hypertensive disorders in a primigravida

1. Introduction
Hypertensive disorders are one of the commonest medical problems, encountered during pregnancy. It complicates around 7-10% of all pregnancies. Moreover the incidence of hypertension is higher in primigravida and in developing countries, compared to multigravida.

Hypertension during pregnancy is defined as sustained systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mmHg or more on two occasions, at least 6 hours apart but within 7 days. When the hypertension is accompanied by proteinuria or convulsions it is called as preeclampsia / eclampsia respectively.

To correctly define the etiology of hypertension during pregnancy has always been a challenging task. It remains amongst the significant and intriguing unsolved problems in obstetrics.

Hypertension is a human pregnancy specific disorder that adversely affects the health of the mother as well as the fetus. Ultimately it is a major contributor of perinatal mortality.

There is imbalance between lipid peroxidation and antioxidant defence mechanism in preeclampsia which results in endothelial dysfunction. Vasoconstrictor substances like Thromboxane A2 are increased and vasodilator substances like Prostacyclins and Nitric Oxide are decreased in preeclampsia.

So far many studies have been done to evaluate the role of aspirin and antioxidant substances in prevention of preeclampsia. Aspirin is a cyclooxygenase inhibitor and it has a positive effect on correcting the imbalance between TXA2 and PGI2 in preeclampsia when started in second trimester. Many antioxidant substances like calcium, Magnesium, Zinc, β-Carotene, lycopene, vitamin C and vitamin E can be used to correct the imbalance between antioxidant defence and lipid peroxidation mechanism. It has been suggested that, supplementation of women with abnormal flow velocity waves in the uterine arteries, with aspirin and antioxidants, diminishes the frequency of proteinuria hypertension and delays the appearance of severe end-stage disease; hence screening will help identify such women.

With all these references, I was inspired to study the role of aspirin and antioxidants in prevention of hypertensive disorders in primigravida.

1.1 Risk factors for development of hypertension during pregnancy
- Extremes of age (higher in teenage)
- Nulliparity
- Obstetric
  - Hypertension in previous pregnancy
  - Multiple pregnancies
  - Hydrops fetalis
  - Hydatidiform mole
- Abnormal uterine doppler flow at 18-24 weeks
- Preexisting medical disorders
- Hypertension
- Diabetes mellitus
- Renal disease
- Autoimmune disease
- Thrombophilias
- Genetic
- Family history
- Environmental
- Smoking

The working group of NHBPEP (National High Blood Pressure Education Programme – 2000) classifies the hypertensive disorders of pregnancy into 4 categories.16

1.2 Diagnosis of hypertensive disorders complicating pregnancy

1.2.1 Gestational Hypertension
- Systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg for first time during pregnancy
- No Proteinuria
- BP returns to normal before 12 weeks postpartum
- Final diagnosis made only postpartum
- May have other signs or symptoms of preeclampsia, for example, epigastric discomfort or thrombocytopenia

1.3 Preeclampsia

1.3.1 Minimum criteria
- BP ≥ 140/90 mm Hg after 20 weeks’ gestation
- Proteinuria ≥ 300 mg/24 hours or ≥ 1 + dipstick

1.3.2 Increased certainty of preeclampsia:
- BP ≥ 160/110 mm Hg
- Proteinuria 2.0 g / 24 hours or ≥ 2 + dipstick
- Serum creatinine > 1.2 mg/dL unless known to be previously elevated
- Platelets <100,000 / µL
- Microangiopathic hemolysis - increased LDH
- Elevated serum transaminase levels - ALT or AST
- Persistent headache or other cerebral or visual disturbance
- Persistent epigastric pain

1.4 Eclampsia
- Seizures that cannot be attributed to other causes in a woman with preeclampsia.

1.5 Superimposed preeclampsia on chronic hypertension:
- New onset proteinuria ≥ 300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks’ gestation.
- A sudden increase in proteinuria or blood pressure or platelet count < 100,000 / µL in women with hypertension and proteinuria before 20 weeks’ gestation.

1.6 Chronic hypertension:
- BP ≥ 140/90 mm Hg before pregnancy or diagnosed before 20 weeks’ gestation not attributable to gestational trophoblastic disease. Or
- Hypertension first diagnosed after 20 weeks’ gestation and persistent after 12 weeks postpartum.

2. Materials and Methods

This is a prospective randomized controlled study for evaluation of role of aspirin and antioxidants in prevention of hypertensive disorders of pregnancy in primigravidas. It was carried out at department of Obstetrics and Gynecology in my institute between October 2008 and September 2010. 80 women attending antenatal OPD were included in this study.

2.1 Criteria for inclusion in the study

Normal healthy primigravidas with gestational age between 13 and 24 weeks. The subjects should not have any medical disorders that can affect the result of the study, like anaemia, chronic hypertension, renal disease, cardiovascular disorders, diabetes or any major illness.

All the subjects were screened at 24 weeks of gestation, on the basis of uterine artery doppler wave forms. Those, who were having persistance of diastolic notch were labelled as case group and those who were having no notch were classified in the control group. Case group was the study group, the subjects of which received the tablet of aspirin 75 mg once a day and a multivitamin capsule containing vitamin C 150 mg, vitamin E 50 mg, lycopene 5 mg, omega 3 fatty acids 300 mg along with routine therapy of iron and calcium. The other group was control group, the subjects of which did not receive any additional medication apart from iron and calcium therapy. Thus number of subjects was 40 in each group. Routine antenatal care was explained to the subjects and on each visit their vitals including pulse, BP, proteinuria, weight were recorded. BP was taken in left arm in sitting position after the subjects have taken rest of 15 minutes. The disappearance of Korotkoff sound was taken as the measurement of diastolic BP. On each visit, they were prescribed medicines till next visit and explained accordingly. Hypertension was defined as systolic blood pressure more than or equal to 140 mm Hg and / or diastolic blood pressure of more than or equal to 90 mmHg. Proteinuria is defined as more than or equal to 0.3 gm of protein in urine in 24 hours, but for convenience it was taken as ≥ +1 dipstick on two samples atleast 6 hours apart in the present study.

When the subjects arrived in labour ward for the delivery, all their details of current pregnancy were taken into consideration including their OPD and indoor registration number, their vital statistics including pulse, BP, Proteinuria, mode of delivery, status of liquor, baby sex, weight and others.

3. Discussion

This study includes 80 subjects, out of which 40 are in case group and 40 are in control group. Case group included 40 subjects, who were given Tablets of Aspirin and Antioxidants, who were having persistant end-diastolic notch at 24 weeks uterine artery doppler. Control group included 40 subjects, who were not given Tablets of Aspirin and Antioxidants, who were having normal uterine artery doppler wave forms at 24 weeks of gestation.
Pregnancy is for case and control ilic those of 32 indicates role intrapartum period. So, the negative IJBAR (201 are having no direct impact on the mode of delivery. Moreover the LSCS performed here are for the obstetric indications mainly.

Table 1: Distribution of mean age of subjects in years in each group

<table>
<thead>
<tr>
<th></th>
<th>Case group (Years)</th>
<th>Control group (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>22.2</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Table 2: Distribution of number of subjects, exhibiting hypertension during the course of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Gestational HT</th>
<th>Preeclampsia</th>
<th>Eclampsia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE GROUP</td>
<td>02</td>
<td>00</td>
<td>00</td>
<td>02</td>
</tr>
<tr>
<td>CONTROL GROUP</td>
<td>04</td>
<td>02</td>
<td>05</td>
<td>00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>06</td>
<td>02</td>
<td>05</td>
<td>08</td>
</tr>
</tbody>
</table>

Gestational HT: Case - 5 % Control – 10%; Preeclampsia: Case - 00 % Control – 5%; Eclampsia: Case - 00 % Control - 00%

Here, the relative risk is 0.33. So, there is 66% reduction in risk of PIH. So, the incidence of hypertensive disorders of pregnancy is quite lower in case group.

There was no case of preeclampsia recorded in the case group, where 2 cases were noted in the control group (5%). So, the negative predictive value of uteroplacental Doppler screening studies for the prediction of preeclampsia in the subjects having normal uterine artery doppler at 24 weeks is 95%. The same value is ranging between 94% and 99% in various studies.

In the study conducted by Bujold, the incidence of preeclampsia was 9.3% in the case group and 21.3% for control group. Rumiris D also showed the incidence of preeclampsia of 6.8% in case group and 29% in control group. The study by Kumar and Sharma showed the results of preeclampsia and Eclampsia of 8% and 17.7% respectively in the case and the control group.

Moreover, no case of preeclampsia has been recorded in any of the group in this study. So, even if the hypertension develops in the subjects taking aspirin and antioxidants, its severity is less compared to the subjects not taking them.

Table 3: Distribution of mean blood pressure in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean SBP Antepartum</th>
<th>Mean SBP Intrapartum</th>
<th>Mean DBP Antepartum</th>
<th>Mean DBP Intrapartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>121.0</td>
<td>124.5</td>
<td>77.7</td>
<td>77.6</td>
</tr>
<tr>
<td>Control Group</td>
<td>129.1</td>
<td>131.4</td>
<td>81.5</td>
<td>82.8</td>
</tr>
</tbody>
</table>

The table shows the distribution of the mean systolic BP and mean diastolic BP during antepartum and intrapartum period in both the case and the control groups. This data shows the reduction of mean systolic BP and mean diastolic BP during antepartum and intrapartum period. The value of mean DBP in mmHg is 77.7 and 77.6 for case group, while those of control group are 81.5 and 82.8. The study by Kumar and Sharma indicated value for mean DBP in mmHg of 86.7 and 92.2 for case and control groups respectively. Here, P is <0.05 and so the comparison data is significant. So, aspirin and antioxidants help in reducing mean BP.

Table 4: Distribution of number of subjects, developing oligohydroamnios during the course of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Oligohydroamnios</th>
<th>No Oligohydroamnios</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>01</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Control Group</td>
<td>04</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>05</td>
<td>75</td>
<td>80</td>
</tr>
</tbody>
</table>

The table shows the distribution of subjects in each group, developing oligohydroamnios. The value is 1 for case group and 4 for control group. So relative risk for developing oligohydroamnios is 25% (0.25). So it can be concluded that low dose aspirin and antioxidants are helpful in preventing oligohydroamnios.

Table 5: Distribution of subjects exhibiting meconium stained liquor at the time of delivery

<table>
<thead>
<tr>
<th>Group</th>
<th>MSL</th>
<th>Clear liquor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>00</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Control Group</td>
<td>03</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>03</td>
<td>77</td>
<td>80</td>
</tr>
</tbody>
</table>

The table shows distribution of subjects exhibiting meconium stained liquor at the time of delivery. There were no subjects in the case group having MSL but there were 3 (7.5%) subjects in the control group exhibiting MSL. Here the odds ratio is 0.13 and it indicates role of low dose aspirin and antioxidants in reducing the incidence of MSL.

Table 6: Distribution of mode of delivery in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaginal</th>
<th>Abdominal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>36</td>
<td>04</td>
<td>40</td>
</tr>
<tr>
<td>Control Group</td>
<td>36</td>
<td>04</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>08</td>
<td>80</td>
</tr>
</tbody>
</table>

The table shows distribution of mode of delivery in each group. Both the groups are exhibiting the same percentage of the subjects, being delivered vaginally as well as abdominally via lower segment caesarian section. Hence we conclude that low dose aspirin and antioxidants are having no direct impact on the mode of delivery. Moreover the LSCS performed here were for the obstetric indications mainly.

Table 7: Distribution of no of subjects, delivering low birth weight babies

<table>
<thead>
<tr>
<th>Group</th>
<th>BW&lt;2.5 Kg</th>
<th>BW&gt;= 2.5 Kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Control Group</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

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The table show the distribution of subjects delivering low birth weight babies that is <2.5 Kg. There were no such subjects in case group while the number was 10 for control group, the value is significantly different. So it could be concluded that low dose aspirin and antioxidants are helpful in preventing low birth weight babies. The study by Duley et al. also showed that there is 20% reduction in risk of low birth weight babies.

### Table 8: Distribution of mean birth weight of babies at the time of delivery

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean birth Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group</td>
<td>2.96</td>
</tr>
<tr>
<td>Control Group</td>
<td>2.63</td>
</tr>
</tbody>
</table>

The table shows the distribution of the subjects in each group according to their mean birth weight at the time of delivery. The value was 2.96 Kg for the case group and 2.63 Kg for the control group, suggesting a significant difference of the comparison. P is < 0.05. So it is suggested that low dose aspirin and antioxidants are helpful in preventing low birth weight babies.

### 4. Summary

In this study there are 40 subjects in the case group and 40 subjects in the control group were enrolled. The case group subjects were having persistence of end diastolic notch in the uterine artery at 24 weeks doppler study, while the control group were having normal uterine artery doppler waveforms at 24 weeks of gestation.

The case group subjects received the additional medication in the form of low dose aspirin and antioxidants as a prophylaxis of hypertension, in addition to routine drugs of iron and calcium. The control group subjects did not receive this additional prophylaxis.

There were no significant differences in the occurrence of hypertension as regard to the age, occupation, education, religion, residence, weight and hemoglobin level of the subjects at the start of the study in both the groups. Moreover the subjects were enrolled in the study at approximately the same mean gestational age.

Gestational hypertension occurred in 5% of the case group while in 10% of the control group. Incidence of preeclampsia is nil in case group while its 5% in control group. It shows that the severity of the hypertensive disorders is also less in the case group, even if it occurs at all.

Mean arterial Blood pressure – both systolic and diastolic – are less in case group compared to the control group. Incidence of oligohydroamnios is 2.5% in case group while 10% in control group, indicating the role of aspirin and antioxidants in prevention of oligohydroamnios.

Incidence of meconium staining of liquor is nil in case group while it is 7.5% in the control group indicating the preventive role of low dose aspirin and antioxidants against MSL.

Incidence of low birth weight babies is nil in case group while it is 25% in control group and Mean birth weight is 2.96 Kg in case group while 2.63 kg in control group indicating the importance of aspirin and antioxidants in preventing low birth weight babies.

### 5. Conclusion

It was noted in the present study that low dose aspirin and antioxidants may have beneficial effect in the prevention of hypertensive disorders of pregnancy in the high risk primigravida subjects. Reduction in the severity of hypertension was also noted, even if it develops, in the women taking low dose aspirin and antioxidants.

Overall improvement of the perinatal outcome was observed in the form of reduction in the incidence of oligohydroamnios, meconium stained liquor and low birth weight babies.

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