CONTROLLING PROGRESS OF INTRA UTERINE GROWTH RETARDATION BY MATERNAL MEDICATION

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SUMMARY

The role of medication, aspirin and isoxsuprine hydrochloride in restricting the process of growth retardation was studied in these small number of cases by a double blind controlled method. Objective was to determine the role of low dose aspirin/isoxsuprine in the management of pregnancies with intrauterine growth retardation.

The incidence of emergency caesarean section and instrumental vaginal delivery for fetal distress was 20% in the low dose aspirin group compared to 36.66% in the isoxsuprine and 43.33% in placebo group. The difference was statistically significant (P<0.01). The mean birth weight in the aspirin treated greater than is the isoxsuprine (2150 gms) and the placebo group 2100 gms) (P<0.01).

The number of babies weighing greater than the 10 th percentile was higher at 33.33% in aspirin treated group compared to 20% in the isoxsuprine and 13.33% in the placebo growth. However, this difference was found to be statistically significant. P>0.05 Mean head circumference was 33.1 cms in the aspirin treated group compared with 31.7 cms in the Isoxsuprine treated group and 31.8 cms in the placebo group. This reference in the head circumfernce was significant statistically.

The clinical significance of growth retardation is based on the fact that birth weight is the single most importan factor that affects neonatal mortalit in addition to being a significant deter minant of infant and childhood morbidit

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(Mc Cormick 1985). Recent findings suggest that ischaemic heart disease, stroke and other associated conditions like hypertension and non-insulin dependent diabetes originate through impaired growth and development during fetal life and infancy (Lucas 1991, Barket 1989, 1990, Hales 1991). Perinatal mortality is 4-8 times higher for growth retarded fetuses and serious short or long term sequlae are noted in one half of the surviving infants (Battalgia 1970, Diakokau et al, 1979, Galbraith et al 1979).

Though many attemps have been made during the past 30 years to classify and resolve the reproductive problems associated with impaired foetal growth, confusion and impricision persists regarding appropriate care of a pregnancy suspected of intrauterine growth retardation (IUGR), we should prevent its occurence and when present control its further progress.

MATERIAL AND METHODS

The present study was conducted in the Department of Obstetrics and Gynaecology of Mahatma Gandhi Institute of Medical Sciences, Sevagram. A total number of 110 women admitted to the obstetric wards with intrauterine growth retardation were selected for the study. The diagnosis of intrauterine growth retardation was based on four weeks lag on clinical measurement of the fundal height. In these women previous menstrual cycles wer regular and they were sure of last menstrual period. They had single live foetus in longitudenal lie. The exclusion criteria were unknown dates, infrequent periods, twin pregnancy, hydramnios, obvious uterine malformation, renal disease and secondary hypertension. Gestation was determined with the help of Baillard scoring system Baitjaral et al(1991) and birth weights were classified as percentile for age (Lubchencho 1966). Finally growth retardation was diagnosed if baby weight was less than 10th percentile. Neonatal Mortality and morbidity if any, were recorded.

The role of aspirin and isoxsuprine hydrochloride in restricting the process of growth retardation was studied in these small number of cases by a double blind controlled method. Objective was to determine the role of low dose Aspirin Isoxsuprine in the management of pregnancies with intrauterine growth retardation. Contraindications to these drugs were kept in mind. Randomization was carried out in a double blind controlled manner. The patient, obstetrician and paediatrician were blind to the exact medication received by the patient. These 110 women were divided into three groups.

S1, in this group low dose aspirin was given 60 mg daily from the day of admission till they delivered.

S2, this group were given isoxsuprines Hydrochride 10 mg three times a day.

S3, in this group a placebo was given.

Those women who delivered within 15 days of hospital admission (within 2 weeks of medication) were excluded while finally analysing the role of short term use of these drugs in the management of intra uterine growth retardation. Finally, each group S1, S2, and S3 consisted of 30 women each.

OBSERVATIONS

There was no significant difference in

the mean age, height weight, past gestational complications and present gestational, complications in all the three groups (Table I). The mean gestational age at delivery was not significantly different in all the 3 groups.

The mean platelet count at entry was 1.59 lac/mm3 in l, 1.62 lac/mm3 in S2 and 1.68 lac/mm3 in S3.By the time of delivery the platelet counts in S2 and S3 were nearly same but increased, (receiving aspirin) in S1. However the difference was statistically not significant (P7 0.05).

The average duration of medication was 22 days in S1, 27 days in S2 and 24 days in S3. This difference was statistically not significant. The incidence of emergency caesarean section and instrumental vaginal delivery for fetal distress was 20% in the low dose aspirin group compared to 36.66% in the isoxsuprine and 43.33% in placebo group. This difference was statistically significant (P<0.01) (Table I). There was a difference in the placental weight with the mean placental weight being 430 gms in the low dose aspirin group and 370 and 377 gms in the isoxsuprine and placebo groups respectively. The difference was found to be statistically significant (P<0.05). The mean birth weight in the aspirin treated group was 2510 gms and was statistically significantly greater than that in the isoxsuprine (2150-gms) group and the placebo groups (2100 gms) (p<0.01).

The number of babies weighing greater than the 10th percentile was higher 33.33% in aspirin treated group compared to 20% in the isoxsuprine and 13.33% in the placebo groups. However this difference was not found to be statistically significant (p>0.05).

Mean head circumference was 33.1 cms in the aspirin treated group compared with 31.7 cms in the isoxsuprine treated group and 31.8 cms in the placebo group. It was found to be statistically significant difference (p<0.05). The length of the foetus was 46.1 cms for the aspirin treated group as compared to 45.2 cms of the isoxsuprine

Table I

Characteristics of Patients in all Groups (S1, S2 & S3)

Particulars	S1 (n=30)		S2 (n=30)		S3 (n=30)	
	Mean	%	Mean	%	Mean	%
Age (years)	25.2	4.2	24.5	3.9	25.5	4.3
Height (cms)	152.1	5.9	151.5	5.4	152.0	6.1
Weight (kg)	43.1	3.8	42.5	4.2	44.0	3.7
BOH	4	-	3	-	3	-
Systolic BP (mm Hg)	120.2	17.18	119.4	15.	121.1	16.4
Diastolic BP (mm Hg)	80.6	10.99	78.4	10.1	77.3	9.8

Table II

Characteristics of Labour in all Groups (S1 S2 & S3)

Type of delivery	S1 (n=30)		S2 (n=30)		S3 (n=30)	
	No.	%	No.	%	No.	%
Caeserian section						
Elective	4	13.33	3	10.00	3	10.00
Emergency	2	6.67	4	13.33	5	16.66
Instrumental Vaginal Delivery	4	13.33	7	23.33	8	26.67
Normal Vaginal Delivery	20	66.67	16	53.34	14	46.67
Total	30	100.00	30	100.00	30	100.00

treated and 44.8 cms of the placebo group. This difference was not found to be statistically significant (P>0.05).

There were less number of infants with low apgar at 5 minutes in aspirin group. However the difference wan not found to be statistically significant (p>0.05). There was one intrapartum death in the isoxsuprine and 1 neonatal death in the placebo group and no death in Aspirin treated group. There was decrease in the neonatal morbidity and lesser admissions to NICU in the aspirin treated group. There was no increase in major and minor bleeding complications in the newborns in any of the groups.

DISCUSSION

The platelets and vasoactive peptides released by the endothelium play an important role in maintaining the lumen of the vessel wall. Increased platelet aggregation has been reported in normal pregnancy using platelet rich plasma (Leuschen et al 1986 and Andrews Broughton - Pipkin 1985). Louden and Broughton-Pipkin (1990) studied eight women longitudnally and found that platelet aggregation was increased in response to some aggregating agents. Norris (1992) demonstrated increased platelet reactivity in third trimester of normal pregnancy particularly in response to collagen AA which disappears within 24-48 hours of delivery. Jogee et al (1983) found that production of prostacyclin PGI2 in vitro by human placental cells from pregnancies complicated by fetal growth retardation was significanctly reduced as compared with that in placental cells from normal pregnancies at term. Aspirin is an irreversible inhibitor of the cyclooxygenase by acetylating the active site of the enzyme invloved in the prostaglandin synthesis. The effect on platelets is long lasting, effectively maintaining inhibition for its life span. Low

dose aspirin can selectively inhibit thromboxane production by umbilical vessels in vitro (Makila et al 1981). More recent studies by Fitzerald et al (1987) indicate that the dose of aspirin which effectively and selectively inhibits platelet cyclo-oxygenase is much lower in the range of 40 mg/kg. Throp et al (1988) demonstrated that low dose aspirin significantly decreases production of thromboxane in placental arteries but not of prostaglandin by irreversibly acetylating and inactivating fatty acid cyclooxygenase. Platelets unlike endothelial cells, that have a nucleus, are incapable of resynthesizing the enzyme.

Edler et al (1988) studied the effect of low dose aspirin 75mg/ day from first or second trimester until delivery in patients at very high risk of losing the pregnancy due to inadequate uteroplacental blood flow. They observed improvement without maternal or fetal complications. Trudinger et al (1988) carried a placebo controlled blind trial in women with elevated umbilical artery wave form (systolic/diastolic ratio) to evaluate the fetal benefits of low dose aspirin (150mg/day) as a treatment of placental insufficiency in the last trimester of pregnancy. Aspirin was associated with restoration of a more normal fetal growth velocity attributable to an improvement in the placental function. Aspirin does not increase the overall risk of congenital malformations and cardiac defects are not associated with aspirin use (Werler et al 1989). Incidence of intraventricular haemorrhage, gastro-intestinal bleeding, cephalhaematoma, petechaie, were not found to be increased in Uzan's study (1991). Expistaxis and other minor feeding problems have been reported in patients receiving aspirin, but the incidence was not significant (Uzan 1991). Unusally profuse bleeding during delivery or caesarean section and post partum haemorrhage were not more frequent in this study. Platelet cyclo-oxygenase is more sensitive to inhibition by low dose aspirin (80mg) than vascular endothelial cyclo-oxygenase. The biochemical selectivity of low dose aspirin in portal circulation alters balance between prostacyclin and thromboxane, leading to dominance of prostacyclin and reduced thrombosis.

The primary challenge is to identify the fetus who is inappropriately growing in utero. Maximum safe retention in utero should be the goal of management as long as some growth is noted and acute fetal distress is not seen. There is as yet no evidence of a definite risk associated with low dose aspirin in pregnant women. However, data are still scarce and great caution remains necessary.

From this pilot study in small group of women, it seems low dose aspirin treatment even for short phase does help women with intrauterine growth retardation. Only large clinical trials, starting aspirin in the second trimester are necessary to know the effectiveness of low dose aspirin in the prevention and management of foetal growth retardation.

REFERENCES

1. *Andrews N.P., Broughton-Pipkin F., Heptinstall S. Thrombo Haemostatt 53:426:1985.*
2. *Ballard J.L., Khoury J.C., Wedig K, Wang L, Walsman E, Lipp R., J.Paediatrics, 119:417:1991.*
3. *Barker DJP : Brit J. Obstet. & Gynec 99:275: 1992.*

4. *Battalgia F.C. : Am. J. of Obstet. & Gynec 106:1103 1970*
5. *Daikakou J.N., Johnson JWC, Graf C., Kearoy K. Tyson J.E., Kind T.T.*
6. *Edler M.G., Desweit M. Robertson a. Eler M.A., Flloyed E., Howking D.F.,*
7. *Fitzgerald D.J., Mayo G. Catella F., Entmanns S. and Fitzgerald G.A. : Am.J.Obstet & Gynec 157:325:1987*
8. *Galbraith R.S., Karchmer E.J., Piercy W.N. AM.J. Obstet. & Gynec 133:281:1979.*
9. *Hales C.N., Barker DJP., Clark PMS., Cox L.J., Fall C., Osmond C., Winter P.D. : B.M.J. 303:1019:1991*
10. *Jogee M., Myatt L., Elder M.G. : Brit J. Obstet. & Gynec 90:247:1983*
11. *Leuschen M.P., Davis R.B., Boyd D., Goodlin R.C. : Am. J.of Obstet. & Gynec 155:1276-1986*
12. *Louden K.A., Broughton-Pipkin F., Heptinystall S., Fox S.C., Mitchell JRA., Symmonds E.M.: Brit J. Obstet. & Gynec 97:1108:1990*
13. *Lubchenco L.O. : Paediatrics, 37:403:1966,*
14. *Lucas A : The childhood Environment and Adult Disease. Ciba Foundation 156. John Wiley Chichester 38-1991*
15. *Makila U.M., Kokkonen E., Vinikka L. Ylirkorkala O.: 25:1981.*
16. *MC Cormick M.C. : The New Eng 312:1985*
17. *Norris L.A., Sheppared B.L., Bonnar J. : Brit J. of Obstet and Gynaec 99 : 253-1992*
18. *Seeds J.W. : Obstet & Gynec 64:577:1984*
19. *Throp J.a., Walsh E.W., Brath P.C. : Am. J. Obstet. and Gynaec 159:1381:1988*
20. *Trudinger B.J., Cook C.M., Thompson R.S., Giles W.B., Connelly A. : Am. J.Obstet & Gyneco 159:681:1988*
21. *Uzan S., Beaufils M., Breart G., Bazin B., Capitant C. Paris J. Lancet 337:1427:1991*
22. *Werler M., Mitchel A.A., Shapino : N. Eng.J.Med., 321:1639-1989.*