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Research Article

Role of dydrogesterone in the treatment of idiopathic IUGR

Leena Wadhwa[1,2]*, Swaraj Batra[1], Anjali Tempe[1]

[1]Work carried out together at Department of Obstetrics and Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi- 110002, India
[2]Presently working as Associate Professor at Department of Obstetrics and Gynecology, ESI-PGIMSR, Basaidarapur, Delhi- 110015, India

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***Correspondence:**
Dr. Leena Wadhwa,
E-mail: drleena_123@yahoo.co.in

ABSTRACT

Background: a) To evaluate the therapeutic efficacy of dydrogesterone in the treatment of pregnant women with idiopathic fetal growth restriction. b) To compare the outcome with the control group receiving conventional treatment in the form of rest and high protein diet.
Methods: Pregnant women with idiopathic IUGR between 28-34 weeks gestation were randomized to either
Group 1: Control group receiving conventional treatment in the form of rest and high protein diet (n=41).
Group 2: Study group receiving dydrogesterone (n=43)
Primary outcome were compared in terms of fetal birth weight, apgar at birth, perinatal morbidity and mortality. Secondary outcomes in terms of changes in Doppler indices, gestational age at delivery, requirement for inductions, need for cesarean sections for IUGR, fetal distress in labour were compared.
Results: Average fetal birth weight in kg were (1.71± 0.37 vs 2.03 ± 0.4, p=S), poor apgar scores (29.3% vs 20.9%, p=NS), nursery admissions (46% vs 18.6%, p=S), perinatal mortality (7.3% vs 4.7%, p=NS) in the control and study group respectively. Average gestational age at delivery was 36.4± 2.34 vs 36.9 ± 1.93 weeks (p=NS) in the control and study group respectively. Labour inductions were similar and cesarean section rates were significantly more in the control group as compared to the study group receiving dydrogesterone (39% vs 23.3%, p=S).
Conclusion: Dydrogesterone for the treatment of IUGR looks promising as it favourably affects the fetal birth weight and nursery stay.

Keywords: Fetal growth restriction, Progesterone, Doppler, Pregnancy, Birth weight

INTRODUCTION

Intrauterine growth restriction (IUGR) is one of the most common complications of pregnancy and represents a major cause of perinatal morbidity and mortality. It is defined as less than 10 percent of predicted fetal weight for gestational age. The occurrence of any deprivation or insult during pregnancy may interfere with intrauterine growth, thus preventing the fetus from attaining its original growth potential. The management of growth restricted fetus continues to present with a daunting challenge. The most common cause of fetal growth restriction is impaired nutrition supply to the fetus. This may result from impaired maternal nutrition, decreased blood flow to the uterus or placenta. This may require maternal nutritional supplementation, maternal hyperoxygenation, or pharmacological manipulations aimed at increasing blood flow.

Various treatment modalities are being practiced for treating idiopathic IUGR. Many studies have established the association of IUGR with low progesterone levels.[1,2] Progesterone supplementation in IUGR may be

associated with improved uteroplacental circulation. It acts on the myometrium and suppresses the action of estrogen by inhibiting the replacement of cytosolic estrogen receptors and it exerts a direct effect on the biosynthetic processes of the uterus through its own cellular receptor.[3] The immunomodulatory effect of progesterone via progesterone induced blocking factor (PIBF) may play a role in improving the outcome in pregnancy with fetal growth restriction.[4,5]

In the current study, the treatment potential of dydrogesterone, an oral analogue of progesterone in IUGR was evaluated. Micronised progesterone has a poor oral bioavailability and there is no literature on its effect on the cytokine profile. Dydrogesterone, however has very good oral bioavailability and a longer half life (8-24 hours) with immunomodulatory effect and hence was chosen for the study. It is structurally and pharmacologically very similar to natural progesterone and has selective progestational activity in humans.

Aims and Objectives

The objective of this study was

a) To evaluate the therapeutic efficacy of dydrogesterone in the treatment of Idiopathic IUGR

b) To compare the outcome with the group receiving conventional treatment in the form of rest and high protein diet.

METHODS

This prospective trial was conducted between July 2004 and November 2006 in the department of Obstetrics and Gynecology, Lok Nayak hospital, New-Delhi. Ninety five pregnant women with idiopathic IUGR between 28-34 weeks gestation were included in our study after taking informed consent. Women with fetal congenital or chromosomal anomaly and the presence of complications like hypertension, diabetes, renal disease, cardiovascular disease, connective tissue disease were excluded from the study.

The period of gestation was ascertained using definite menstrual history and or ultrasound scan done in the first trimester of pregnancy. The patients were randomly allocated to study and control group by computer generated random number sequence. Hospital ethical committee clearance was procured before initiation of the trial.

The study group received dydrogesterone (Duphaston) 10 mg BD besides the conventional treatment in the form of iron, folic acid, rest and high protein diet and the control group received conventional treatment in the form of rest and high protein diet. The patients were treated till delivery or a minimum period of four weeks. Monitoring was done by serial clinical and ultrasound examination. Clinical examination included general examination particularly noting blood pressure, edema, weight gain and abdominal examination. Monitoring by ultrasound included calculation of fetal weight by Hadlock formula; biophysical scoring and Doppler velocimetry. Pregnancy was terminated if fetal compromise occurred as raised S/D ratio on doppler after 34 weeks, reversed or absent diastolic flow at any gestational age or at 37 completed weeks whichever was earlier.

Primary outcome were compared in terms of fetal birth weight, apgar at birth, perinatal morbidity and mortality. Secondary outcomes in terms of changes in Doppler indices, gestational age at delivery, requirement for inductions, need for caesarean sections for IUGR, fetal distress in labour were compared.

Statistical analysis: All data obtained were analysed using the Chi square test. The population was normally distributed. The test was considered significant if the p value was <0.05.

RESULTS

The prevalence of IUGR in our hospital was 4.8% and idiopathic IUGR was 1.5%.During the study period, 95 cases of idiopathic IUGR were detected out of which 84 patients completed the study. The study and control groups were comparable in terms of maternal age, parity, socioeconomic status, education and religion (Table 1).

Table 1: Demographic profile.

Baseline characteristics	Study group (n=43)	Control group (n=41)	*p* value
Age	23.44 ± 2.59	24.4 ± 2.72	0.08 (NS)
Parity (para 1)	29	31	0.2 (NS)
Socio economic status	35	26	0.9 (NS)
Education	33	28	0.3 (NS)
Religion	67	75	0.4 (NS)

Table 2: Maternal and fetal outcome.

	Study Group (n=43)	Control Group (n=41)	*p* value
Gestational age at delivery	36.9 ± 1.93	36.4 ± 2.34	0.3 (NS)
Inductions for IUGR	21 (48%)	23 (56%)	0.5 (NS)
NVD C - sections	33(76.7%) 10(23.3%)	25(61%) 16 (39%)	0.05 (S)
Oligoamnios	10 (23.3%)	9 (22%)	

Table 2 shows the maternal and fetal outcomes in patients with IUGR. The average birth weight in the study group was 2.03 ± 0.04 kg where as it was 1.71±0.37 kg in the control group which was statistically significant. There was significant reduction in the caesarean section rates in the study group (23.3% vs 39%). Although the gestational age at delivery was slightly prolonged in the study group but the results were not statistically significant (p=0.3). No significant difference was observed in the number of inductions of labour for IUGR. Oligoamnios was almost equally associated in the babies of both the study and control groups (23.3% vs 22%) and showed no improvement in either groups.

The requirement of neonatal admission to nursery was higher in the control group as compared to the study group (46% vs 18.6%, p=0.002). However poor apgar scores, seizures and sepsis showed no difference in both the groups (table 3). There were two neonatal deaths in the study group due to septicaemia (after 24 days in the nursery) and the other due to respiratory distress after 10 days of birth. Three neonatal deaths were recorded in the control group out of which one was antepartum intrauterine death at 30 weeks gestation, one still birth during delivery and another occurred 5 days after birth due to lung hypoplasia. Significant improvement in the umbilical artery Doppler indices was also noted in the study group. Four out of eleven patients with abnormal Doppler indices showed improvement while such a change was not evident in the control group. However, Doppler changes in the middle cerebral artery showed no improvement in either of the groups (Table 4).

Table 3: Neonatal morbidity and mortality.

	Study Group (n=43)	Control Group (n =41)	*p* value
Average birth weight	2.03± 0.4	1.71± 0.37	<0.001(S)
Poor apgar	9(20.9%)	12(29.3%)	0.3(NS)
Nursery admission	8(18.6%)	19(46%)	0.002(S)
Seizures	1	1	0.9(NS)
Sepsis	3	6	0.06(NS)
Mortality	2(4.7%)	3(7.3%)	0.6(NS)

Table 4: Doppler changes.

	Study Group (n=43)	Control Group (n =41)	*p* value
Umbilical artery S/D ratio improvement	4/11	0/15	0.01(s)

DISCUSSION

IUGR results where any abnormality prevents tissue from growing or causes cell to decrease in size. Various treatment modalities have been tried for treating IUGR which includes abdominal decompression, rest, high protein diet, allyestrenol, intravenous hyperalimentation, beta adrenergic agents, fish oils, ritodrine, theophylline, HBO, arginine, ANP, IGF-1, aspirin, zinc, epidural ropivacaine, Viagra etc.[6-15] In our study, dydrogesterone was administered to evaluate whether it improves the outcome in pregnant women with fetal growth restriction. The basis for using dydrogesterone relates to the 1) decreased levels of progesterone in IUGR pregnancies.[1,2] 2) Dydrogesterone may improve the myometrial perfusion in IUGR gestation by promoting myometrial small arterial vasodilatation, decreasing peripheral resistance and increasing the flow within the uteroplacental bed. 3) T cell during normal pregnancy predominantly secrete anti-inflammatory cytokines (TH2 response i.e; IL-3, IL-4, IL-10, PGF) compared to pro inflammatory cytokines (TH1 response i.e; IL-2, IL-12, TNF-α).[4] The inability of mother to switch from TH1 to TH2 cytokine profiles at the fetal neonatal interface has been proposed as one of the primary causes of miscarriage, IUGR, pre eclampsia.[16]

Dydrogesterone manifests an immunomodulatory effect by inducing Progesterone induced blocking factor (PIBF) production. PIBF inhibits natural killer cell activity, causes TH2 bias and increases asymmetric antibody which acts as a blocking antibody and protects the antigen from potentially harmful cell mediated response. All this eventually leads to an improvement in IUGR fetus.

Dydrogesterone, an oral analogue of progesterone appears to be efficacious in improving the pregnancy outcome. Its role in decreasing the ill effects of IUGR looks promising. However the study is not very powerful as the sample size is not sufficiently large. Further, large randomized trials are needed to establish the role of dydrogesterone in treating IUGR.

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