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ORIGINAL ARTICLE

Maternal and Placental Risk Factors associated with Intrauterine Growth Restriction and the Perinatal Outcomes

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ABSTRACT

Objectives: Identifying the factors responsible for the intrauterine growth restriction (IUGR) is very important, so that early interventions could be suggested to improve the perinatal outcome. The major objectives of this study are to analyze the impact of risk factors, specifically the maternal and placental risk factors, on IUGR and the perinatal outcomes.

Materials and methods: A prospective study was done on 60 women with IUGR pregnancies from January 2013 to January 2014, at Pushpagiri Medical College Hospital, Thiruvalla. Inclusion criteria were: singleton pregnancies, above the gestational age of 28 weeks, clinically diagnosed IUGR and confirmed subsequently on ultrasound. The statistical analysis was performed utilizing Statistical Package of the Social Sciences (SPSS) software and the significance level of p-value <0.05 was accepted as statistically significant.

Results: Statistical analysis shows that maternal risk factors like chronic hypertension, pre-eclampsia, low socioeconomic status of mother, overt diabetes, anemia, gestational diabetes mellitus, low prepregnancy body mass index and hypothyroidism were significantly associated with IUGR. In this study, placental factors like chorangiomatosis, increased syncytial knotting, villous infarction, increased perivillous fibrinoid deposition, accelerated villous maturation, retroplacental hemorrhage and acute chorioamnionitis were significantly associated with IUGR.

Conclusion: Alertness toward antenatal risk factors for poor pregnancy outcome is important for the optimal management of IUGR pregnancies. Despite antenatal recognition of IUGR and associated risk factors, not all perinatal deaths can be prevented.

Keywords: Asymmetric IUGR, Intrauterine growth restriction, Small for gestational age, Symmetric IUGR.

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INTRODUCTION

Intrauterine growth restriction (IUGR) refers to a condition in which a fetus has failed to achieve its genetically determined growth potential. This definition intentionally excludes of fetuses that are small for gestational age (SGA) but are not pathologically small. According to American College of Obstetricians and Gynecologists and Royal College of Obstetricians and Gynecologists, fetal growth restriction implies a pathological restriction of the genetic growth potential.[1,2] Analysis of fetal growth trajectories has been identified as an important factor in the differentiation between physiological small for gestational age and pathological intrauterine growth restriction.[3] Intrauterine growth restriction fetuses are at greater risk of perinatal mortality,[4] birth hypoxia, neonatal complications, impaired neurodevelopment[5] and manifestations of the metabolic syndrome in adult life.[6] Intrauterine growth restriction is categorized as symmetric or asymmetric. Symmetric intrauterine growth restriction refers to fetuses with equally poor growth velocity of the head, the abdomen and the long bones. Asymmetric intrauterine growth restriction refers to infants whose head and long bones are spared compared with their abdomen and viscera.[7]

The common risk factors for IUGR include maternal, placental, environmental and fetal causes. The major objectives of this study are to analyze the impact of maternal and placental risk factors associated with fetal growth restriction and the perinatal outcomes.

MATERIALS AND METHODS

The present study was carried out in Pushpagiri Medical College Hospital, Thiruvalla. The period of study was from January 2013 to January 2014. The study population consisted of 60 pregnant women with IUGR and these women either attended the antenatal clinics at Pushpagiri Medical College Hospital or were referred from the peripheral hospitals in view of IUGR. For each IUGR cases, the subsequent normal admission was identified as a control group.

Inclusion criteria were: singleton pregnancies, above the gestational age of 28 weeks, clinically diagnosed IUGR, confirmed subsequently on ultrasound when the fetal abdominal circumference was less than 2SD (standard deviation) from mean value and placental dysfunction was considered in pregnancies with umbilical artery Doppler S/D ratio ≥3 or those with absent end diastolic or reversed end diastolic flow. Exclusion criteria were: multiple pregnancies and congenital anomalies in the fetus.

A standard proforma was compiled for each patient documenting all the details of clinical history, examinations and investigations. The laboratory data, ultrasonographic data, placental histopathology data, and the neonatal data were the major sources of data for this study. The outcome data were collected including gestational age at birth, sex of the baby, birth weight and Apgar scores. The statistical analysis was performed utilizing Statistical Package for the Social Sciences (SPSS) software and the significance level of p-value <0.05 was accepted as statistically significant.

RESULTS

In this study, out of 60 IUGR cases 37 (61.7%) had hypertension complicating pregnancy, of these five (8.3%) had chronic hypertension and 32 (53.3%) had pre-eclampsia. Among the fetal growth restricted mothers there were 19 (31.7%) gestational diabetes, 14 (23.3%) overt diabetes, 13 (21.7%) anemia, 16 (26.7%) hypothyroidism, 3 (5%) previous pregnancy with IUGR, two (3.3%) on anticonvulsants, one (1.7%) renal disease and two (3.3%) antiphospholipid syndrome cases. There were 12 (20%) low socioeconomic status cases, 36 (60%) nullipara cases, four (6.7%) cases of extreme maternal age and 37 (61.7%) female babies.

Histopathological examination reports of the placenta showed abnormality or pathological changes in 40 (66.7%) cases. The placental changes seen in the study group were 24 (40%) chorangiomatosis, 19 (31.7%) increased syncitial knotting,[29] (48.3%) villous infarction, 18 (30%) increased perivillous fibrinoid deposition, 17 (28.3%) accelerated villous maturation, five (8.3%) retroplacental hemorrhage, four (6.7%) acute chorioamnionitis, and one (1.7%) single umbilical artery). On clinical examination, the sympysiofundal height was >3 cm less than the gestational age in 48 (80%) cases. Ultrasound examination showed that the abdominal circumference was less than the tenth percentile in all the 60 IUGR cases. Amniotic fluid index (AFI) showed oligohydramnios (<5 cm) in 15 (25%) cases and in 24 (40%) cases it was between 5 and 8 cm. There were 27 (45%) cases with abnormal biophysical profile scores. Nonstress test was non-reactive in 26 (43.33%) cases. Doppler studies showed fetoplacental insufficiency in 36 (60%) of the cases.

The observed frequency and percentage of observations are presented in Table 1. Chi-square test was used for examining the association between the maternal and placental risk factors and intrauterine growth restriction.

Table 1: Maternal and placental factors associated with IUGR babies

Risk factors	*N*	*Percentage*	*Chi-square*	*p-value*
Chronic hypertension	5	8.3	10.838	0.001
Pre-eclampsia	32	53.3	16.561	0.000
Low socioeconomic status	12	20.0	13.422	0.000
Overt diabetes	14	23.3	16.111	0.000
Anemia	13	21.7	14.746	0.000
Gestational diabetes mellitus	19	31.7	23.654	0.000
Hypothyroidism	16	26.7	18.975	0.000
Extremes of maternal age	4	6.7	0.341	0.559
Previous pregnancy with IUGR	3	5.0	1.037	0.309
Antiphospholipid syndrome	2	3.3	1.976	0.160
Assisted reproductive techniques	2	3.3	0.116	0.733
Anticonvulsants	2	3.3	1.976	0.160
Renal disease	1	1.7	0.977	0.323
Nullipara	36	60.0	65.091	0.000
Low body mass index (BMI)	6	10.0	6.570	0.010
Chorangiomatosis	24	40.0	32.789	0.000
Increased syncytial knotting	19	31.7	23.654	0.000
Villous infarction	29	48.3	44.477	0.000
Increased perivillous fibrinoid deposition	18	30.0	22.038	0.000
Accelerated villous maturation	17	28.3	20.480	0.000
Retroplacental hemorrhage	5	8.3	5.114	0.024
Acute chorioamnionitis	4	6.7	4.044	0.044
Single umbilical artery	1	1.7	0.977	0.323

Chi-square test is conducted at 5% level of significance. There is a positive association between the risk factors and intrauterine growth restriction if the Chi-square test resulted in a 'p-value less than 0.05. If the 'p-value' of the Chi-square test is more than 0.05, then there is no positive association between the risk factors and intrauterine growth restriction.

Statistical analysis shows that maternal risk factors like chronic hypertension (p = 0.000), pre-eclampsia (p = 0.000), low economic status of mother (p = 0.000), overt diabetes (p = 0.000), anemia (p = 0.000), gestational diabetes mellitus (p = 0.000), hypothyroidism (p = 0.000) and low prepregnancy body mass index (BMI) (p = 0.010) were significantly associated with intrauterine growth restriction. In this study, maternal risk factors like extremes of maternal age (p = 0.559), previous pregnancy with IUGR (p = 0.309), antiphospholipid syndrome (p = 0.160), assisted reproductive techniques (p = 0.733), anticonvulsants (p = 0.160), and renal disease (p = 0.323), were found to be not significantly associated with intrauterine growth restriction. Placental factors like chorangiomatosis (p = 0.000), increased syncytial knotting (p = 0.000), villous infarction (p = 0.000), increased perivillous fibrinoid deposition (p = 0.000), accelerated villous maturation (p = 0.000), retroplacental hemorrhage (p = 0.024) and acute chorioamnionitis (p = 0.044) were significantly associated with intrauterine growth restriction. In this study, placental factor of single umbilical artery had no significant effect on the intrauterine growth restriction.

Multinomial logistic regression analysis was used to prove the association of the maternal and placental risk factors with symmetric IUGR babies. A cut off of p = 0.05 was taken as significant for the multinomial logistic regression analysis.

The associations of the maternal and placental risk factors with symmetric IUGR babies are exhibited in Table 2. Maternal risk factors like chronic hypertension (p = 0.038), pre-eclampsia (p = 0.000), low socioeconomic status (p = 0.018), overt diabetes (p = 0.033), anemia (p = 0.029), gestational diabetes mellitus (p = 0.021), hypo-thyroidism (p = 0.013), previous pregnancy with IUGR (p = 0.047), assisted reproductive techniques (p = 0.042), nullipara (p = 0.000) and low prepregnancy BMI (p = 0.010) were significantly associated with the symmetric IUGR babies. Whereas maternal risk factors like extremes of maternal age (p = 0.110), antiphospholipid syndrome (p = 0.696), anticonvulsants and renal disease (p = 0.154) were insignificantly associated with the symmetric IUGR babies. Placental factors like chorangiomatosis (p = 0.000), increased syncytial knotting (p = 0.001), villous infarction (p = 0.000), increased perivillous fibrinoid deposition (p = 0.000), accelerated villous maturation (p = 0.000), and retroplacental hemorrhage (p = 0.003) were significantly associated with the symmetric IUGR babies. The association of factors like acute chorioamnionitis (p = 0.573) and single umbilical artery (p = 0.154) were insignificant in the case of symmetric IUGR babies.

Table 2: Multinomial logistic regression analysis of maternal and placental factors associated with symmetric IUGR babies

Risk factors	*Chi-square*	*p-value*
Chronic hypertension	4.310	0.038
Pre-eclampsia	36.849	0.000
Low socioeconomic status	5.633	0.018
Overt diabetes	3.203	0.033
Anemia	2.049	0.029
Gestational diabetes mellitus	5.308	0.021
Hypothyroidism	6.125	0.013
Extremes of maternal age	2.548	0.110
Previous pregnancy with IUGR	3.953	0.047
Antiphospholipid syndrome	0.153	0.696
Assisted reproductive techniques	4.133	0.042
Anticonvulsants	0.153	0.696
Renal disease	2.036	0.154
Nullipara	30.745	0.000
Low body mass index (BMI)	6.496	0.011
Chorangiomatosis	15.866	0.000
Increased syncytial knotting	12.004	0.001
Villous infarction	12.131	0.000
Increased perivillous fibrinoid deposition	31.851	0.000
Accelerated villous maturation	28.337	0.000
Retroplacental hemorrhage	8.529	0.003
Acute chorioamnionitis	0.317	0.573
Single umbilical artery	2.036	0.154

The impact of the maternal and placental factors associated with asymmetric IUGR babies are presented in Table 3. In this study, the following maternal factors: chronic hypertension (p = 0.028), pre-eclampsia (p = 0.000), low socioeconomic status (p = 0.000), overt diabetes (p = 0.000), anemia (p = 0.000), gestational diabetes mellitus (p = 0.000), hypothyroidism (p = 0.000), extremes of maternal age (p = 0.005), previous pregnancy with IUGR (p = 0.003), nullipara (p = 0.000) and low prepregnancy BMI (p = 0.014) were significantly associated with the asymmetric IUGR babies. Maternal factors like antiphospholipid syndrome (p = 0.172), assisted reproductive techniques (p = 0.172), anticonvulsants (p = 0.172) and renal disease (p = 0.337) were insignificantly associated with the asymmetric IUGR babies. The placental factors like chorangiomatosis (p = 0.000), increased syncytial knotting (p = 0.000), villous infarction (p = 0.000), increased perivillous fibrinoid deposition (p = 0.000), accelerated villous maturation (p = 0.000), and retroplacental hemorrhage (p = 0.015) were significantly associated with the asymmetric IUGR babies. The association of factors like acute chorioamnionitis (p = 0.051) and single umbilical artery (p = 0.337) were insignificant in the case of asymmetric IUGR babies.

Table 3: Multinomial logistic regression analysis of maternal and placental factors associated with asymmetric IUGR babies

Risk factors	*Chi-square*	*p-value*
Chronic hypertension	4.828	0.028
Pre-eclampsia	52.984	0.000
Low socioeconomic status	12.651	0.000
Overt diabetes	15.176	0.000
Anemia	13.895	0.000
Gestational diabetes mellitus	22.241	0.000
Hypothyroidism	17.862	0.000
Extremes of maternal age	8.007	0.005
Previous pregnancy with IUGR	9.122	0.003
Antiphospholipid syndrome	1.867	0.172
Assisted reproductive techniques	1.867	0.172
Anticonvulsants	1.867	0.172
Renal disease	0.923	0.337
Nullipara	65.091	0.000
Low body mass index (BMI)	5.998	0.014
Chorangiomatosis	30.745	0.000
Increased syncytial knotting	22.241	0.000
Villous infarction	41.508	0.000
Increased perivillous fibrinoid deposition	20.730	0.000
Accelerated villous maturation	19.272	0.000
Retroplacental hemorrhage	5.862	0.015
Acute chorioamnionitis	3.818	0.051
Single umbilical artery	0.923	0.337

Birth weight of the IUGR babies ranged from 565 to 2460 gm, of these six (10%) babies were less than 1000 grams, 13 (21.7%) babies between 1000 and <1500 gm, 23 (38.3%) babies between 1500 and <2000 gm and 18 (30%) babies between 2000 and <2500 gm. Gestational age at delivery was more than 28 weeks. The total preterm birth was 45 (75%). Fifty-nine (98.33%) out of 60 babies were admitted to the neonatal intensive care unit. There were 48 (80%) lower segment cesarean sections and 12 (20%) vaginal deliveries. Among the IUGR cases, there were 37 (61.7%) female babies and 23 (38.3%) male babies. One minute Apgar score was less than seven for 32 (53.3%) babies and ≥7 for 28 (46.7%) babies. Perinatal mortality was five (8.33%). Not surprisingly, perinatal deaths occurred more commonly in pregnancies with severe growth restriction (estimated fetal weight <3rd percentile) and associated abnormal Doppler findings resulting in earlier gestational ages at delivery and lower birth weights. All cases of perinatal deaths were delivered by emergency cesarean section between 28 and 34 weeks gestation corresponding to birth weights between 565 and 1479 gm.

The correlation between the pregnancy outcomes in IUGR and non-IUGR babies are detailed in Table 4. On paired samples t-test analysis, the pregnancy outcomes like birth weight (p = 0.000), gestational age at delivery (p = 0.000), total preterm births (<37 weeks) (p = 0.000), admission to neonatal unit and perinatal deaths (p = 0.045) were significantly associated with the IUGR babies.

DISCUSSION

In this study, chronic hypertension and pre-eclampsia were found significantly and strongly contributes to IUGR and this finding is in harmony with the literature on pre-eclampsia and chronic hypertension.[8-12] The low socioeconomic status of the mothers was an important risk factor for IUGR and this finding was consistent with the results of many previous studies.[13,14] Overt diabetes and gestational diabetes mellitus were significant risk factors for IUGR in this study and it was in conformity with the findings of Catalano et al, Tanne and Ornoy.[15-17] In this study, anemia in pregnancy was significantly associated with IUGR which is consistent with findings of Philip, Radhakrishnan, Anand and Garg.[18-20] Numerous research studies have established the association between hypothyroidism and IUGR and the analytical result in this study also prove that hypothyroidism is one of the important risk factors which affect fetal growth in IUGR cases.[21-26]

In contrast to the findings of Fraser et al, Jamal et al and Ferraz et al who reported that extremes of maternal age adversely affect pregnancy outcomes, the researcher in this study did not find a significant effect. This may relate to the lower prevalence of extremes of maternal age in this study compared with theirs and hence a reduced power to detect an effect.[27-29] Women with a history of previous pregnancy with IUGR and adverse pregnancy outcomes are at higher risk of recurrent adverse outcomes such as recurrent pregnancy loss, stillbirth or perinatal deaths.[30] Among the other important maternal risk factors, such as assisted reproductive techniques, antiphospholipid syndrome, anticonvulsants and renal disease had no significant association with IUGR in this study. The reason for insignificant association of these maternal risk factors in statistical analysis is due to their absence in the majority of the IUGR cases.

Table 4: Pregnancy outcomes in relation to IUGR status

Pregnancy outcome	*IUGR (n = 60)*	*Non-IUGR (n-60)*	*Std. deviation*	*Correlation*	*t-value*	*p-value*
Birthweight (gm)	1676	2964	0.523	0.179	–20.271	0.000
Gestational age at delivery (weeks)	34.279	38.5	2.131	0.009	–14.661	0.000
Total preterm births (<37 weeks)	45 (75%)	8 (13.33%)	0.490	0.226	9.742	0.000
Admitted to neonatal unit	59 (98.33%)	11 (18.33%)	0.403	0.062	15.362	0.000
Perinatal deaths	5 (8.33%)	1 (1.67%)	0.251	0.432	2.053	0.045

Placental risk factors like chorangiomatosis, increased syncytial knotting, villous infarction, increased perivillous fibrinoid deposition, accelerated villous maturation, retroplacental hemorrhage were significantly associated with IUGR cases.[31,32] Maternal nutritional status both before and during pregnancy and the BMI were significantly associated with IUGR. It is in compliance with the research findings of Neggers et al, Kramer and Osrin et al that woman with low BMI is at increased risk for a number of adverse pregnancy outcomes, including preterm birth and IUGR.[33-35]

Maternal obesity is associated with an increased risk of perinatal mortality, the occurrence of genetic disorders, macrosomia and intrauterine growth restriction.[36-38] Also in keeping with previous studies, it was found that participants engaged in daily vigorous and high intensity exercise have low maternal BMI, though low to moderate intensity exercise is recommended in pregnancy.[39,40] Less antenatal visits contribute to inadequate care during pregnancy which is a significant independent risk factor for IUGR babies.[41]

Clinical examination, such as abdominal palpation and symphysio fundal height measurement have limited accuracy in identifying IUGR prenatally and serial ultrasound scanning from 26 to 28 weeks of gestation has been proposed in patients with risk factors.[42] Perinatal deaths occurred more commonly among infants with severe growth restriction and associated abnormal umbilical artery Doppler values.[43] A detailed evaluation of the cord and placenta is useful in determining the underlying causes which have led to an IUGR diagnosis. The numerous studies conducted on different populations highlight the association between intrauterine growth restriction and fetal sex as in this study. Although intrauterine programming mechanisms are still unclear and the involvement of other factors and results of the studies are controversial, it seems that the female gender is more likely to develop intrauterine growth restriction.[44]

CONCLUSION

From this study, it is evident that the maternal and placental risk factors are ominously associated with intrauterine growth restriction and the perinatal outcomes. Further study may elucidate preventive or treatment strategies to assist the growth-restricted fetus.

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