ORIGINAL ARTICLE

MATERNAL FACTORS ASSOCIATED WITH INTRAUTERINE GROWTH RESTRICTION

Taj Muhammad, Asmat Ara Khattak, Shafiq-ur-Rehman, Muhammad Amjad Khan, Afzal Khan, Muhammad Aqeel Khan

Department of Paediatrics, Leady Reading Hospital, Peshawar, Pakistan

Background: Intrauterine growth restriction is a major neonatal health issue. Maternal factors have been found to have greater impact on IUGR. Studying these factors can help in reducing the mortality and morbidity associated with IUGR. **Methods:** This Case-control study was conducted at the department of Paediatrics Post-graduate medical institute Lady Reading Hospital Peshawar from March 2008-April 2009. Small-for-gestational age (SGA, i.e., IUGR cases and n=200) live born babies were compared with appropriate-for-gestational age (AGA, i.e., controls and n=200) babies. Information regarding socio-demographics of mothers, gestational age and birth weight of baby, maternal clinical characteristics, and medical and obstetric complications during pregnancy was recorded on a pre-designed proforma. Data analysis was done through SPSS-16. To find the maternal factors associated with the intrauterine growth restriction, multivariable logistic regression was used. We also did two different sets of logistic regression analysis for Symmetric and Asymmetric SGA babies as Cases. **Results:** After adjusting for other variables in the multivariable model we found that the mothers of IUGR babies were of younger age (OR=0.8, CI=0.7–0.9), were poor (OR=2.5, CI=1.4–4.4) and underweight (OR=3.5, CI=1.1–5.7) and had anaemia (OR=2.7, CI=1.3–5.4) in the index pregnancy, and had history of Previous IUGR birth (OR=9.7, CI=3.3–18.3) and placenta previa (OR=3.2, CI=1.1–6.6). There was an interaction between pregnancy induced hypertension and parity of mother with a primary-para mother with pregnancy induced hypertension (PIH) having an increased risk for IUGR babies (OR=10.1, CI=1.0–23.2). **Conclusion:**. The studied factors need special attention in hospital based settings in order to improve the perinatal outcome in IUGR babies.

Keywords: intrauterine growth restriction, pregnancy induced hypertension, maternal malnutrition, anaemia

INTRODUCTION

Intrauterine Growth Restriction (IUGR) is defined as birth weight less than 10th centile for gestational age[1]. Infants with Intrauterine Growth Restriction (IUGR) or Small for gestational age (SGA) are at increased risk of perinatal morbidity and mortality. They also have higher rates of physical, neurological and mental impairment than babies with appropriate intrauterine growth.[1–3] IUGR is observed in 23.8% of the newborn and approximately thirty million babies world wide suffer from IUGR every year. Nearly 75% of all affected babies are born in Asia.[4] In Pakistan too the IUGR babies are an important problem with the reported incidence of SGA infants is 10–25%.[5]

The high incidence of IUGR in developing countries is multi-factorial and involves a complex interaction between foetal, placental and maternal factors, but maternal factors are probably more important causes of IUGR.[4,5]

Various maternal factors leading to IUGR among newborns in developing countries include low socioeconomic status, under nutrition, anaemia, chronic illness and inadequate prenatal care.[2] Other factors such as teenage pregnancies[6], short inter-pregnancy interval[7], previous IUGR births[8,9] and multiparity[8] are also encountered more frequently. Similarly hypoxemic conditions due to respiratory and cardiac diseases are also associated with IUGR.[10–13]

So far limited data is available from Pakistan to focus on this important problem. The aim of this study is to determine the maternal risk factors which lead to IUGR and its different subtypes, i.e., symmetrical and asymmetrical SGA. Identifying the factors responsible for the intrauterine growth restriction is very important, so that early interventions could be suggested to improve the perinatal outcome. This is particularly important in Pakistan's context as IUGR babies are very important age group in terms of morbidity and mortality associated with them.

MATERIAL AND METHODS

The study was conducted at the Department of Paediatrics, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar from March 2008 to April 2009. Singleton babies between 28–42 weeks gestation, without lethal congenital anomalies and birth weight >500 gram were included. Weight of baby was measured within 24 hours of birth and recorded in decimal of kilograms. Detailed examination of each baby was carried out by physicians conducting the study. Babies were

categorised as small for gestational age, i.e., SGA (birth weight less than 10^{th} centile) and appropriate for gestational age, i.e., AGA (birth weight between 10^{th}–90^{th} centile) based on foetal growth charts developed by Lubchenco *et al.*[14] SGA babies were further categorized into asymmetric IUGR and symmetric IUGR based on updated Ponderal Index (calculated as weight in gram ×100/length in cm^3) percentiles developed by Landmann *et al.*[15]

Two hundred consecutive SGA babies (cases) fulfilling the inclusion criteria were recruited for the study over the study period. For each SGA baby, the subsequent AGA admission was identified as a control baby. Gestational age (recorded as completed weeks) was assessed from maternal last menstrual period (LMP), ultrasound scan in the first trimester and Dubowitz examination results.[16] If there was discrepancy for more than two weeks between these three methods then Dubowitz examination results alone were used to determine gestational age.

Informed consent was taken from parents who participated in the study. A pre-designed proforma was filled in for each mother after delivery to collect information about her age, parity, education, socioeconomic status, antenatal check-up, inter-pregnancy interval and previous IUGR births. Postnatal weight and height of mother was used to calculate Body mass index (BMI) for mother. Information regarding pregnancy induced medical disorders and obstetrical complications like placenta previa and placental abruption and anaemia was also obtained. Pregnancy induced hypertension and gestational diabetes were identified either because of entry on the hospital record or use of medications. Economic status was defined on the basis of family income in rupees/month and was categorised as low (<8000/month), middle class (8,000–16,000/month) and upper middle class (>16,000/month). Previous IUGR was suspected on the basis of prior history of low birth weight baby of full term gestation. Inter-pregnancy interval was based on the number of months between conception for index pregnancy and the preceding delivery, abortion or stillbirth.

Sample size was calculated using EPI Info software. Taking level of significance of 5%, power of 80%, with an anticipated probability of exposure in controls of 17 % (pregnancy induced hypertension**)**, anticipated odds ratio of 2, and ratio of controls to cases of 1, the required sample size was 400 babies, with 200 each in both the IUGR (cases) and age appropriate (control) groups. Data was entered in computer by using SPSS version 16.

Descriptive analysis including Mean±SD for continuous variables and frequencies as percentages for qualitative variables were done. Cross tabulations were done to see the independent variables across the categories of outcome (SGA and AGA). For these, results were compared by using Chi-square test for qualitative variables and t-test for quantitative variables, and $p < 0.05$ was considered significant.

To see the association of the maternal factors with the intrauterine growth restriction we used multivariable logistic regression. Multivariable analysis was done for the variables that were found to be significant on univariate analysis ($p \leq 0.25$). Adjusted Odds ratio and 95% CIs for these were calculated. A cut off of $p=0.05$ was taken as significant for the multivariable analysis. We assessed the potential interactions between the independent variables and possible confounding by the variables, before dropping the insignificant variables from the model to get the final parsimonious model.

As a further analysis we sub grouped the SGA (IUGR) babies into Symmetric SGA and Asymmetric SGA babies. We used 200 AGA babies as controls and run two sets of multivariable logistic regression to identify the maternal factors that contribute to these subtypes specifically. Adjusted Odds ratio and 95% CIs for the independent variables were calculated after adjusting for the effect of the other variables in the model.

RESULTS

Majority of the study births were male (66.3%), and majority of the mothers were illiterate (88.8%), were poor (69.8%), and of primary parity (42.3%). Table-1 shows the descriptive characteristics and univariate analysis for the study variables.

No significant difference was seen in the gender distribution of the infants ($p=0.7$) and gestational age of the babies ($p=0.6$) between the cases (n=200) and control (n=200) groups.

The mean birth weight in SGA group was 1.8±0.33 Kg and was significantly lower than that for AGA group, i.e., 2.8±0.5 Kg ($p=0.001$). Mothers in the SGA group as compared to mothers of AGA babies were of significantly lower age (22.9±4.5 years vs 26.8±4.8 years, $p=0.001$), shorter length (1.51±0.04 m vs 1.56±0.06 m, $p=0.05$) and lower weight (54.2±9.7 Kg vs 60.0±7.8 Kg, $p=0.001$).

At univariate level low SES of mothers (OR=2.5, $p=0.001$), anaemia in pregnancy (OR=1.6, $p=0.013$), low BMI (underweight) (OR=2.7, $p=0.001$), having previous IUGR births (OR=8.4, $p=0.013$), having a primary parity (OR=2.7, $p=0.002$), placenta previa (OR=3.1, $p=0.048$) and pregnancy induced hypertension (OR=2.7, $p=0.001$) were found to be significantly associated with IUGR.

On multivariable analysis (after adjusting for other variables) with IUGR babies as outcome, the maternal factors such as age of mother, pregnancy

induced hypertension, previous IUGR birth, maternal BMI, anaemia in pregnancy, placenta previa, socioeconomic status, and parity of the mother had significant effects on the intrauterine growth retardation.

Compared to the normal BMI mothers, mother who were underweight were 3.4 times more likely to give birth to an IUGR (SGA) baby. The mothers who were overweight had a significant protective effect. Overweight mothers were 50% less likely to give birth to IUGR babies as compared to mothers with normal BMI. The odds of giving birth to an IUGR baby by mothers belonging to poor socio-economic strata was 2.5 times that of mothers belonging to middle or upper middle social stratum.

Table-1: Descriptive characteristics of the IUGR (SGA babies) and AGA babies

Risk factors	Over All (Mean±SD)	Small for gestational Age (Mean±SD)	Appropriate for Gestational Age (Mean±SD)	OR (95% CI)	*p*-Value
Weight (Kg)	2.3±0.6	1.8±0.3	2.8±0.5		0.001
Gestational age (weeks)	37.5±1.0	37.5±1.8	37.5±2.0		0.65
Age of the mother (years)	24.8±4.1	22.9±4.5	26.8±4.8	0.88 (0.85–0.92)	0.001
Height of mother (meters)	1.5±0.05	1.51±0.04	1.56±0.06		0.05
Weight of mother (Kg)	57.1±6.0	54.2±9.7	60.0±7.8		0.001
Inter pregnancy Interval (month)	26.0±9.5	26.8±9.1	25.6±7.1		0.5
Gender of Baby	**n (%)**	**n (%)**	**n (%)**		0.7
Males	265 (66.3)	131 (65.5)	69 (67.0)		
Females	135 (33.7)	134 (34.5)	66 (33.0)		
BMI of Mother					0.001
Normal BMI	221 (55.3)	126 (63.0)	95 (47.5)	1.0	
Underweight	28 (7.0)	22 (11.00)	6 (3.0)	2.7 (1.1–4.3)	
Overweight	135 (33.8)	46 (23.0)	89 (44.5)	0.4 (0.25–0.6)	0.001
Obese	16 (4.0)	6 (3.0)	10 (10.0)	0.5 (0.2–1.0)	0.04
Socioeconomic status (SES) of the mothers					0.001
Lower SES	279 (69.8)	158 (79.0)	121 (60.5)	2.5 (1.6–3.8)	
Middle SES*	112 (28.0)	39 (19.5)	73 (36.5)	1.0	
Upper Middle SES*	9 (2.3)	3 (1.5)	6 (3.0)		
Maternal Education					0.46
Illiterate	355 (88.8)	173 (86.5)	182 (91)	1.8 (0.1–5.0)	
Primary	28 (7.0)	18 (9.0)	10 (5.0)	1.2 (0.06–3.9)	
Secondary and higher	17 (4.2)	9 (4.5)	8 (4.0)	1.0	
Parity of the mother					0.003
Primary Para	169 (42.3)	101 (50.5)	68 (34.0)	2.7 (1.5–4.1)	
Multi Para	168 (42.0)	75 (37.5)	93 (46.5)	1.3 (0.6–2.3),	
Grand multi-Para	63 (15.8)	24 (12.0)	39 (19.5)	1.0	
Placenta Previa					0.04
Yes	16 (4.0)	12 (6.0)	4 (2.0)	3.1 (1.0–5.3)	
No	384 (96.0)	188 (94.0)	196 (98.0)	1.0	
Placental Abruption					0.26
Yes	12 (3.0)	8 (4.0)	4 (2.0)		
No	388 (97.0)	192 (96.0)	196 (98.0)		
Anaemia in pregnancy					0.13
Yes	50 (12.5)	30 (15.0)	20 (10.0)	1.6 (10.9–2.9)	
No	350 (87.5)	170 (85.0)	180 (90.0)	1.0	
Previous IUGR					0.001
Yes	50 (12.5)	42 (21.0)	9 (4.5)	8.3(3.4–16.5)	
No	350 (87.5)	158 (79.0)	191 (95.5)	1.0	
Pregnancy Induced Hypertension					0.001
Yes	62 (15.5)	50 (25.0)	12 (6.0)	3.8 (1.2–6.9)	
No	338 (84.5)	150 (75.0)	188 (94.0)	1.0	
Gestational diabetes					0.46
Yes	9 (2.3)	3 (1.5)	6 (3.0)	0.5 (0.1–3.0)	
No	391 (97.8)	197 (98.5)	194 (97.0)	1.0	
Cardiac disease in mother					0.9
Yes	5 (1)	3 (1.5)	2 (1.0)	0.1 (.01–1.7)	0.28
No	395 (99)	197 (98.5)	199 (99.0)	1.0	
Antenatal Check-up					0.9
0–1	91 (45.5)	46 (47.9)	45 (43.3)	1.3 (0.1–1.8)	
2–4	105 (52.5)	48 (50.0)	57 (54.8)	1.1 (0.5–1.6)	
>4	4 (2.0)	2 (2.1)	2 (1.9)	1.0	

*taken into one category

Table-2: Multivariate analysis for maternal factors associated with IUGR

Risk factors	Adjusted OR	95% CI	*p*-value
Age of the mother	0.8	(0.7–0.9)	0.001
PIH*Parity of mother			0.01
Grand multipara and no PIH	1.0	(Reference)	
Grand multipara and mother with PIH	1.2	0.3–8.6	
Primary para and no PIH	0.4	0.1–1.1	
Primary Para and mother with PIH	10.1	1.0–23.2	
Multipara and no PIH	0.5	0.2–1.1	
Multipara*mother with PIH	7.4	3.0–14.9	
Previous IUGR	9.7	3.3–18.3	0.001
Socioeconomic status			0.002
Middle or Upper middle	1.0		
Low	2.5	(1.4–4.4)	
BMI of Mother			0.001
Normal BMI	1.0		
Underweight	3.4	(1.1–5.7)	
Overweight	0.5	(0.3–0.9)	
Placenta previa			0.04
No	1.0		
Yes	3.2	(1.1–6.6)	
Anaemia in pregnancy			0.01
No	1.0		
Yes	2.7	(1.3–5.4)	

*Interaction between variables indicated

Table-3: Multiple logistic regression for maternal factors associated with symmetric IUGR babies

Risk factors	OR	95% CI	*p*-value
Age of the mother	0.8	(0.7–0.9)	0.001
Pregnancy Induced Hypertension	7.1	(3.1–11.6)	0.001
Previous IUGR	10.1	(4.5–20.1)	0.001
Socioeconomic status			
Middle or Upper middle	1.0		
Low	2.5	(1.2–4.7)	0.01
Placenta previa			
No	1.0		
Yes	3.3	(1.0–6.9)	0.004

Table-4: Multiple logistic regression for maternal factors associated with asymmetric IUGR babies

Risk factors	OR	95% CI	*p*-value
Age of the mother	0.8	(0.7–0.9)	0.001
Pregnancy Induced Hypertension	6.4	(3.1–9.7)	0.001
Previous IUGR	9.3	3.3–16.9	0.001
Socioeconomic status			
Middle or Upper middle	1.0		
Low	2.3	(1.2–4.6)	0.02
BMI of Mother			
Normal BMI	1.0	(Reference)	
Underweight	4.8	(3.1–6.7)	0.001
Overweight	0.6	0.3–0.9	0.04
Anaemia in pregnancy			
No	1.0		
Yes	3.8	(2.0–5.2)	0.001

The adjusted OR for anaemia in pregnancy was 2.7 as compared to mothers with no anaemia. The adjusted OR for mothers who had a placenta previa was 3.2, and the adjusted OR for mothers who had previous IUGR births, was 9.7.

PIH and parity of the mothers had an interactive effect on the outcome (IUGR birth). Compared to a mother who was grand multipara and had no PIH (reference category), the odds of having an IUGR baby was 10.1 times higher for mothers who were Primary Para and had PIH.

For the subtypes of SGA babies (Symmetric SGA and Asymmetric SGA babies), the maternal factors as PIH, previous IUGR, placenta previa and age of the mother was significantly associated with the symmetric SGA babies (Table-3).

For Asymmetric SGA babies the maternal factors such as PIH, previous IUGR, age of the mother, BMI of mother, socioeconomic status, and anaemia during pregnancy were significantly associated with outcome (Table-4).

DISCUSSION

In the present study after controlling for potential confounding, we observed significant differences for maternal factors as age, parity, SES, BMI, anaemia, pregnancy induced hypertension and previous IUGR between the IUGR and age appropriate babies.

In this study, besides an assessment of maternal factors for IUGR, SGA subgroups were also analysed for possible risk factors. Maternal malnutrition and uteroplacental insufficiency are usual causes for asymmetric IUGR while congenital infections acquired early in pregnancy have association with symmetric IUGR.[1] Maternal age, pregnancy induced hypertension; previous IUGR and placenta previa are found in our study to contribute to both subtypes (Symmetric and Asymmetric) of IUGR babies. Moreover the maternal malnutrition, poverty and anaemia contributed to the asymmetric IUGR babies.

Young maternal age as a risk factor in our study is consistent with studies conducted by Jamal *et al* in Pakistan and Ferraz *et al* in Brazil.[8,17]

At univariate level there was a dose response relationship for the parity of mother and the IUGR. Primiparity was also a significant factor for IUGR at multivariable level. Similar findings are also reported by Fikree *et al*[5] and Thompson *et al*[18]. Hypertension during pregnancy is a proven factor causing growth restriction.[8–11] Pregnancy induced Hypertension was found to significantly and strongly contribute to IUGR babies in our study. Mothers with a PIH had 7.1 times higher risk of having Symmetric IUGR and 6.4 times higher risk for the Asymmetric IUGR, after adjusting for the confounding. Similar findings are reported by Thompson *et al*[18] who have reported an adjusted OR of 2.4 (1.1–5.4) for pre-eclampsia and OR of 5.4 (CI=1.8–16.7) for pre-existing hypertension toxaemia during pregnancy. We also found an interaction between the parity and PIH in mothers with primary

parity, and PIH having a multiplicative effect in causing the IUGR.

Growth restriction in previous pregnancies was also identified as a risk factor in our study. This may be due to the persistence of unknown factors causing IUGR as reported by the literature.[18–20] Placenta previa was an important factor in our study for the symmetric IUGR. Placenta previa as a risk factor is reported in literature although Mavalankar *et al* did not report its significance.[21] Placental abruption was not significant in our study. Babies with this complication usually need early delivery. As the number of preterm babies with history of placental abruption in our study was small, so this may be the reason for insignificant association.

Maternal malnutrition is a well known factor to influence the birth weight as described in Kramer's meta-analysis and studies conducted in various developing countries.[19–24] For our study we found a dose response relationship between maternal nutritional status (BMI) and the IUGR births, with overweight mothers having a protective effect (OR=0.5, CI=0.3–0.9) underweight mothers at higher risk (OR=3.4, CI=1.1–5.7), as compared to normal weight mothers (OR=1). BMI also contributed strongly to asymmetric IUGR births (OR=4.8 for underweight mothers).

Similarly studies have reported that average birth weight is lower among the poorer section of any society.[5,10] Belongings to a poor social strata was associated with higher risk of IUGR (OR=2.5, CI=1.4–4.4) in our study. A study by Patricia HC *et al* in Brazil has also reported 1.7 times higher risk for families with low incomes.[23] Poor SES in our study was also important factor for Symmetric IUGR babies (OR=2.3, CI=1.2–4.6). Anaemia in pregnancy was a significant factor in our study which is consistent with findings of Radhakrishnan *et al*[20] but in contrast to the Kramer's meta-analysis[19].

Illiteracy and less antenatal visits described as important risk factors for IUGR were also not significant in our study. The importance of antenatal care must not be ignored, because it results into better outcome of pregnancy. In addition regular antenatal visits are necessary for timely diagnosis of IUGR and early intervention of modifiable risk factors.[8]

Our study has its limitations. Firstly design of our study has its limitations, as the problems of recall and reporting bias are commonly associated with studies relying on the information of the respondents. We however tried to overcome this by checking the hospital records of the patients for whom it was available, and recorded the information from these records. However still for a number of patients we had to rely on their history and previous investigations/medications brought by them in hospital. We used well defined criteria for inclusion of the cases (IUGR) and tried to overcome the selection bias by these stringent criteria.

In spite of limitations, our study provides interesting information which can be helpful in planning maternal and child health services, particularly in hospital based settings. More importantly some of the factors as maternal malnutrition, poverty, maternal anaemia etc are amenable to modification. Proper control of hypertension during pregnancy would be expected to reduce SGA births. Similarly improved nutrition in pregnancy might also have a beneficial effect. Our study provides important information for the subtypes of IUGR babies as well. These findings need to be supported by further studies to identify and quantify the risk factors based on local evidence for an important paediatric group (IUGR babies).

CONCLUSION & RECOMMENDATIONS

We recommend both short-term and long-term interventions. Interventions for short term impact include food supplementation and proper antenatal assessment of complications like placenta previa and hypertension. Long term interventions include improvement of economic conditions of society. All these measures will have a major impact in decreasing the incidence of SGA babies in our country.

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Address for Correspondence:

Dr. Taj Muhammad, Department of Paediatrics, Unit-B Lady Reading Hospital Peshawar, Peshawar, Pakistan.
Cell: +92-334-7216063
Email: dr.tajmahsud2000@gmail.com