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Original Research Article

A Hospital Based Analytical Assessment of the Maternal Risk Factors for Fetal Growth Restriction in Pre-Term Births

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Abstract

Aim: The aim of the study was to find out whether risk factors for preterm FGR are different from the preterm non FGR.

Methods: The present study was conducted in the Department of Obstetrics and Gynaecology, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India for 12 months. A total of 500 mothers who gave birth to singleton preterm infants were recruited in our study. Of these, mothers of 100 infants who had FGR were assigned to the study group and the consecutive 100 mothers, whose infants had no FGR were assigned to the control group.

Results: Most of the subjects in the study group and control group were in the age group 26-30 years. The mean age of subjects was identical in both the groups. Most of the subjects in both the groups belonged to upper lower socioeconomic status by modified Kuppuswamy scale. In both the groups most of the subjects had a height of 145-155 cm. In terms of BMI, the two groups were statistically significantly different ($p<0.001$). In our study, 28% of subjects in the study group and 25% of subjects in the control group had a stressful event during pregnancy which was statistically not significant.

Conclusion: Interventions to promote early attendance to ANC services, reducing poverty, educating to avoid smoking and manual labour may significantly decrease the burden of FGR and preterm birth.

Keywords: Risk factors, Fetal growth restriction, Preterm births

Introduction

In the attempt to achieve the United Nations' Millennium Development Goals, a global effort has been made to address the preventable causes of maternal and child mortality and to improve maternal and child health. [1-4] As notable gains are being made, poorly understood causes, such as preterm birth (PTB), are contributing to an increasingly large proportion of maternal and child morbidity and mortality. [5] The World Health Organization estimates that approximately 15 million babies are born preterm each year, among whom 1 million die, making prematurity the leading cause of neonatal death worldwide and the second-leading

cause of under-age-5 mortality. [5,6] Importantly, this figure is on the rise, with increases noted in the numbers of both iatrogenic PTBs (iPTB) and spontaneous PTBs (sPTB). [5-8] The pathophysiology of sPTB is poorly understood. [5,7,9,10] Better understanding of the mechanisms involved might allow screening and intervention.

The recurrence of adverse birth outcomes (stillbirth, PTB, and SGA, as a proxy for FGR) from one pregnancy to the next has been widely acknowledged. [11-14] A recent meta-analysis of 16 studies investigating the recurrence of stillbirth reported a four-fold increase in the relative risk. [11] Women with PTB in the first birth have a 2.5- to 10.6-fold increased risk of recurrence [15,16] and the risk of recurrence is nearly 14 times greater for PTB <34 weeks of gestation. [17] Women who experienced SGA (and its proxy FGR) in the previous pregnancy have at least an eight-fold increased risk of recurrence. [12]

Fetal growth restriction (FGR) refers to a condition where fetus has failed to achieve its genetically determined growth potential and this remains as one of the prime challenges in maternity care. PTB and FGR are distinct but they are related pregnancy outcomes like low birth weight, increased risk for perinatal mortality and morbidity. Numerous factors (maternal, placental, fetal or environmental causes) contribute to the high burden of FGR and PTB, with less understood about these risk factors. These broad array of risk factors had been studied among these two outcomes PTB and FGR separately by some studies. [18] while few studies had explored these risk factors among Preterm SGA while comparing with term AGA.6-8 There are only a few studies that explored maternal risk factors for preterm FGR as compared to preterm non-FGR pregnancies. [19,20]

The aim of the study was to find out whether risk factors for preterm FGR are different from the preterm non FGR.

Materials and Methods

The present study was conducted in the Department of Obstetrics and Gynaecology, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India for 12 months.

Methodology

A total of 500 mothers who gave birth to singleton preterm infants were recruited in our study. Of these, mothers of 100 infants who had FGR were assigned to the study group and the consecutive 100 mothers, whose infants had no FGR were assigned to the control group. Institutional ethics committee approval was taken.

Birth registers were searched to identify all the singleton deliveries occurring between 28+0 to 36+6 weeks of gestation for a period of one to 1.5 years to meet the sample size. The case files of eligible candidates were retrieved from the record room. Based on the information available, they are divided as cases and controls. Women with preterm birth and FGR were assigned as cases and the woman with preterm birth and without FGR were assigned as controls. These women were contacted telephonically and those who were willing to participate were recruited. Gestational age at delivery was calculated as according to the last menstrual period using Naegele's rule. FGR was defined as: (a) abdominal circumference (AC) less than 10th percentile for gestation as per intergrowth-21 charts in any fetal ultrasound at or beyond 28 weeks; and (b) If (a) is not available: neonatal birth weight for gestation is less than 10th percentile as per intergrowth-21 charts.

Variables of interest were selected based on known and available potential maternal and pregnancy characteristics associated with FGR (i.e.; socio-demographic, anthropometric, lifestyle related, and

obstetric factors). For socio-demographic factors, we assessed maternal age (<18, 18 to 35 as reference, >35 years), socio-economic status calculated by modified Kuppuswamy scale. For anthropometric factors, we included maternal height (<145 cm, 145 to 155 cm, >155 cm as reference), pre-pregnancy body mass index (BMI <18.5 i.e. underweight, 18.5 to 24.9 as reference, >24.9 kg/m2 i. e.; overweight). BMI was calculated only for women who had a weight taken before 20 weeks gestation.

For lifestyle related factors, we included (a) work during pregnancy: (housewife as reference; sedentary work; manual work). Manual work was defined as those employed in agricultural works, household workers, those work associated with lifting weights, prolonged standing hours, factory workers, sanitation workers, sellers, police. Sedentary work was defined as those who do mental work as teachers, researchers, financial workers, lawyers, editors, managers; (b) any stressful events like hospitalization, surgery, or death of a family member, family conflicts; (c) smoking (passive, active, no smoking)- 'active smoker' means if she smoked at least four cigarettes per day during pregnancy; a 'passive' smoker if she was closely exposed to tobacco smoke by people such as her husband, family members, and co-workers. A non-smoker is a woman who stated that she did not smoke during pregnancy or was not exposed to passive smoking; (d) domestic violence-India passed the Protection of Women from Domestic Violence Act 2005 which defined 'domestic violence' as one which includes any act, omission or commission, or conduct of actual abuse or the threat of abuse that is physical, sexual, verbal, emotional, and economic. [21]

The obstetric and pregnancy outcome variables included in the analysis were parity, inter-pregnancy interval, antenatal visits, supplements intake, gestational hypertension, gestational diabetes, previous obstetrical outcomes, type of delivery, mode of delivery, birth weight, need for NICU admission, neonatal mortality as shown in the table. A structured questionnaire was designed, which contains the information regarding the above variables. This information was carefully recorded in predesigned proforma through telephonic interview and maternal case records. Those newborns with major congenital malformations and those with missing information on key variables were excluded from the study. For analysis, we compared mothers of preterm-FGR and preterm non-FGR newborns.

Statistical anslysis

The normality of each variable was assessed by using the Kolmogorov-Simirnov test. Quantitative data was expressed by mean, standard deviation or median with interquartile range and depends on normal distribution, the difference between two means was tested by Mann Whitney U test. Qualitative data was expressed in percentage and difference between the proportions was tested by chi square test. Odds ratios for the occurrence of preterm FGR and preterm non-FGR newborns, and respective 95% confidence intervals were estimated for each exposure variable, using logistic regression analysis. All those variables which are found to be significant were included in the multivariate logistic analysis. After adjusting the other factors, the independent risk factors for preterm FGR births were found. P value was considered statistically significant, if it is less than 0.05. Statistical analysis was performed in SPSS-25 version.

Results

Table 1: Comparison of socio-demographic and anthropometric risk factors

Exposure variables	Preterm FGR (study group) (n=100) (%)	Preterm non-FGR (control group) (n=100) (%)	Odds ratio (95%CI)	P value
Maternal age				
<18	0	0	0	0.16
18-35	98 (98)	95 (95)	Ref	
>35	2 (2)	5 (5)	0.27 (0.05-1.34)	
Mean age±standard deviation	26.84±4.63	26.41±5.03		
Socioeconomic status				
Upper class	2 (2)	1 (1)	3.02 (0.26-34.68)	0.36
Upper middle	2 (2)	7 (7)	0.39 (0.07-2.04)	
Lower middle	32 (32)	45 (45)	Ref	
Upper lower	60 (60)	46 (46)	1.80 (1.00-3.25)	
Lower	4 (4.08)	1 (1)	2.05 (1.16-3.61)	
Height (cms)				
<145	12 (12)	10 (10)	1.30 (0.47-3.55)	0.80
145 TO 155	65 (65)	68 (68)	0.95 (0.48-1.86)	
>155	23 (23)	22 (22)	Ref	
BMI				
<18.5 (underweight)	50 (50.0)	10 (10)	8.86 (4.07-19.27)	
18.5 to 24.9	42 (42)	72 (72)	Ref	
(Normal BMI) >25(overweight)	8 (8)	18 (18)	1.21 (0.50-2.92)	<0.001

Most of the subjects in the study group and control group were in the age group 26-30 years. The mean age of subjects was identical in both the groups. Most of the subjects in both the groups belonged to upper lower socioeconomic status by modified Kuppuswamy scale. In both the groups most of the subjects had a height of 145-155 cm. In terms of BMI, the two groups were statistically significantly different ($p<0.001$). Over 50% of subjects in the study group were underweight (BMI<18.5 kg/m2) whereas in the control group only 10% were underweight and most of them (72%) had normal BMI (18.5-24.9 kg/m2). The odds of being underweight was 8.86 times higher in the study group [(OR= 8.86 (95%CI=4.07-19.27)] as compared to the control group.

Table 2: Comparison of maternal lifestyle-related risk factors

Exposure variables	Preterm FGR (study group) (n=100) (%)	Preterm non-FGR (control group) (n=100) (%)	Odds ratio (95%CI)	P value
Work				
Housewife	60 (60)	72 (72)	Ref	<0.001
Sedentary work	20 (20)	26 (26)	0.94 (0.48-1.83)	
Manual work	20 (20)	2 (2)	12.77 (2.88-56.68)	

Stress				
No	72 (72)	75 (75)	Ref	0.75
Yes	28 (28)	25 (25)	1.16 (0.63-2.18)	
Smoking				
Never	65 (65)	80 (80)	Ref	<0.001
Passive Smoking	35 (35)	20 (20)	2.48 (1.31-4.72)	

In our study, 28% of subjects in the study group and 25% of subjects in the control group had a stressful event during pregnancy which was statistically not significant. None of the mothers in our study had reported a history of domestic violence or a history of alcohol intake during pregnancy. Although, none of the subjects in both groups had reported any history of active smoking. There was a statistically significant difference between the two groups with regard to passive smoking with odds of 2.48 times greater in the study group [OR=2.48 (95%CI=1.31-4.72)] than in the control group.

Table 3: Comparison of obstetrics risk factors by groups

Exposure variables	Preterm FGR (study group) (n=100) (%)	Preterm non-FGR (control group) (n=100) (%)	Odds ratio (95%CI)	P value
Parity				
Nulliparous	48 (48)	44 (44)	1.51 (0.81-2.79)	0.25
Primiparous	30 (30)	42 (42)	Ref	
Multiparous	22 (22)	14 (14)	1.86 (0.84-4.12)	
ANC visits				
<4	30 (30)	30 (30)	1.0 (0.54-1.82)	1.00
>4	70 (70)	70 (70)	Ref	
Gestational hypertension				
No	78 (78)	85 (85)	Ref	0.23
Yes	22 (22)	15 (15)	1.48 (0.74-2.97)	
Gestational DM				
No	90 (90)	88 (88)	Ref	0.68
Yes	10 (10)	12 (12)	1.18 (0.53-2.62)	
Previous h/o preterm				
No	89 (89)	92 (92)	Ref	0.50
Yes	11 (11)	8 (8)	1.51 (0.61-3.70)	
Previous h/o IUGR				
No	93 (93)	98 (98)	Ref	0.24
Yes	7 (7)	2 (2)	2.37 (0.71-7.96)	

There was no statistically significant difference in the obstetric risk factors such as parity, antenatal care, gestational hypertension, GDM, previous history of PTB or FGR between the two groups.

Table 4: Pregnancy outcomes associated with preterm FGR births

Exposure variables	Preterm FGR (study group) (n=100) (%)	Preterm non-FGR (control group) (n=100) (%)	Odds ratio (95%CI)	P value
Type of delivery				
Induced	24 (24)	12 (12)	1.09 (0.82-1.46)	0.04
Spontaneous	76 (76)	88 (88)	Ref	
Mode of delivery				
Vaginal delivery	72 (72)	70 (70)	Ref	0.55
Cesarean section	28 (28)	30 (30)	0.87 (0.57-1.34)	
Live birth				
No	8 (8)	3 (3)	Ref	0.21
Yes	92 (92)	97 (97)	0.53 (0.20-1.40)	
Birth weight (g)				
>2000 g	35 (35)	88 (88)	Ref	<0.001
<2000 g	65 (65)	12 (12)	3.02 (1.45-2.12)	
NICU admission				
No	36 (36)	80 (80)	Ref	<0.001
Yes	64 (64)	20 (20)	2.91 (1.91-4.44)	
Neonatal mortality				
No	80 (80)	98 (98)	Ref	<0.001
Yes	20 (20)	2 (2)	5.29 (1.42-19.77)	

There is a significant difference between the two groups in terms of birth weight. The mean birth weight of infants in the study group was 1740±345.76 g whereas in the control group was 2363±349.13 g. The risk of NICU admission for infants born to mothers in the study group was 2.9 times higher when compared to the control group which was statistically significant [RR=2.91 (95%CI=1.91-4.44)]. Out of 100 births in the study group, 8 were stillbirths (6 antepartum IUD and 2 intrapartum IUD) whereas, in the control group out of 100 births, 3 were stillbirths (2 antepartum IUD and 1 intrapartum IUD). The rate of neonatal mortality in the study group was 18% whereas in the control group it was 2%. A statistically significant difference was found between the two groups and the risk of neonatal mortality was 5.29 times higher in the study group than that of the control group [RR=5.29 (95%CI=1.42-19.77)].

Discussion

Preterm birth (PTB) is defined as a birth occurring before 37 weeks of gestation and after the period of viability. The incidence of PTB in India is between 10-15%. [22] It was estimated that 32.4 million neonates are born with low birth weight each year in low and middle income countries (LMIC), with national prevalence of FGR reaching as high as 60% in parts of South Asia.1 In addition, 13.7 million neonates are also estimated to be preterm. [23] Approximately 2.8 million of those infants were born with both the conditions. This preterm SGA newborns experience the highest neonatal mortality risk of 10-40 times more than a preterm AGA infant. [24]

Our study shows that the underweight mothers were at 8 times increased risk for FGR babies when compared with mothers who had a normal BMI. Similarly, a study by Kozuki et al which was conducted in rural Nepal, also showed that women in the underweight category had an increased risk of 2 times for SGA babies than AGA

babies among the preterm births as compared to women with normal BMI. [19] A study by Chen et al compared the association of pre-pregnancy BMI between preterm SGA births and preterm non-SGA births. [25]

In our study, maternal passive smoking was significantly associated with FGR among preterm births in uni variate analysis. However, after adjusting the confounders in multivariate analysis, this association was not found to be significant. No subjects in our study had reported a history of active smoking during pregnancy. As this was a retrospective study and the reported data may not be true because of the cultural biases. The study by Kozuki et al have also shown maternal smoking to be a risk factor for preterm FGR births.19 They evaluated the risk of maternal smoking in preterm SGA births as compared to term AGA and results showed that smoking at any time during pregnancy had 2 times increased risk for preterm SGA births. None of the reviewed studies had analyzed passive smoking as the exposure variable to find the association of passive smoking with FGR among preterm births.

The uniqueness of our study is that we have looked at an association between the daily work during the pregnancy and FGR among preterm deliveries and found manual work as a significant independent risk factor. Those women who did manual work during pregnancy had 10 times increased risk for developing FGR among preterm births. We defined manual work as those employed in agricultural works, household workers, those work associated with lifting weights, prolonged standing hours, factory workers, sanitation workers, sellers, and police. However, the Indian study by Rai et al found that PTB and SGA have no association with employment. [26] In the current study, we found that among the preterm births, the infants who were FGR had 5 times higher risk for neonatal mortality as compared to non-FGR babies. Two studies by Sharma et al and Gidi et al have compared the neonatal mortality rates between preterm SGA and preterm AGA. [27,28]

However, a study by Gidi et al has found no significant difference in neonatal mortality rates among preterm SGA and preterm AGA pregnancies. [28] This can likely be explained by the fact that in this study the mortality rate could have been partly modified because the antenatal dexamethasone was received more by the SGA group than the AGA group which may lead to similar mortality rates in both groups. Our study also found that preterm FGR infants had a statistically significantly increased risk for NICU admission [OR=2.91 (95%CI=1.91-4.44)] when compared to preterm non-FGR, which is likely due to related risk of comorbidities that FGR infants have. These findings are consistent with those observed in some of the previous studies. [27,28,29]

Conclusion

The risk of preterm FGR is significantly increased by nine-fold when the mother has a low BMI. This may be a useful clinical tool to identify women at higher risk for having a preterm FGR baby at birth. Passive smoking and manual work are the modifiable risk factors. Interventions to promote early attendance to ANC services, reducing poverty, educating to avoid smoking and manual work may significantly decrease the burden of FGR and preterm birth.

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