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Original Research Article

Risk factors for fetal growth restriction in preterm births: a retrospective case control study

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ABSTRACT

Background: Fetal growth restriction (FGR) and preterm birth (PTB) are two adverse pregnancy outcomes. There are many maternal risk factors that predispose to preterm and FGR independently. Very few studies have identified risk factors for combinations of preterm and FGR. The aim of the study was to find out whether risk factors for preterm FGR are different from the preterm non FGR.

Methods: It was a retrospective case control study in which a total of 204 subjects (102 cases and 102 controls) were analyzed. Singleton, live as well as still births that occurred between 28+0 and 36+6 weeks of gestation were included in this study. FGR was defined as birth weight less than the 10th percentile as per intergrowth 21 charts. Odds ratios for the occurrence of preterm FGR and preterm non-FGR newborns, and respective 95% confidence intervals were estimated for each exposure variable.

Results: Logistic regression analysis identified four significant risk factors for preterm FGR; low socioeconomic status (OR=1.9), manual labour (OR=12.9), BMI<18.5 kg/m^2 (OR=9.2), passive smoking (OR=2.48). After adjusting these factors in multivariate analysis, underweight (OR=8.37) and manual work (OR=9.99) were found to be independent risk factors for FGR among preterm births.

Conclusions: 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

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%.[1] 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.

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.[2] Approximately 2.8 million of those infants were born with both the conditions. This preterm SGA new borns experience the highest neonatal mortality risk of 10-40 times more than a preterm AGA infant.[3]

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.[4,5] 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.[9,10] In this study we will identify sociodemographic, anthropometric, lifestyle-related, and obstetric risk factors for FGR among preterm births. With this information suitable interventions can be developed to prevent preterm FGR newborns.

METHODS

A retrospective case control study was performed over one-year period between December 2020 to Oct 2021 at the Maulana Azad Medical College, Lok Nayak Hospital. 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/m^2 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.[11]

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 newbornswith 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.

The normality of each variable were 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.

Institutional ethics committee approval was taken.

RESULTS

A total of 612 mothers who gave birth to singleton preterm infants were recruited in our study. Of these, mothers of 102 infants who had FGR were assigned to the study group and the consecutive 102 mothers, whose infants had no FGR were assigned to the control group.

Most of the subjects in the study group and control group were in the age group 26-30 years. The mean age of subjects were 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 as shown in Table 1.

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/m^2) whereas in the control group only 9.8% were underweight and most of them (71.6%) had normal BMI (18.5-24.9 kg/m^2). 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 as shown in Table 1.

In terms of daily work during pregnancy, there was a statistically significant difference between the two groups (p<0.001). Over 20.6% of subjects in the study group whereas only 2% in the control group were doing manual work during pregnancy. The odds of women doing manual work during pregnancy was 12 times greater in the study group [OR=12.77 (95%CI=2.88-56.68)] than in the control group as shown in Table 2.

In our study, 27.5% of subjects in the study group and 24.5% 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 as shown in Table 2.

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 as shown in Table 2.

There was no statistically significant difference in the obstetric risk factors such as parity, inter-pregnancy interval, antenatal care, supplements, gestational hypertension, GDM, previous history of intrauterine death (IUD) or PTB or FGR between the two groups as shown in Table 3.

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 102 births in the study group, 8 were stillbirths (6 antepartum IUD and 2 intrapartum IUD) whereas, in the control group out of 102 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)] as shown in Table 4.

All those risk factors which are found to be significant were included in the multivariate logistic analysis. After adjusting these factors, the independent risk factors for preterm FGR births were low BMI [adjusted Odds ratio (AOR)=8.37; 95% CI=3.83-18.30], and manual work during pregnancy [AOR=9.99 (95% CI=2.12-46.99)] as shown in Table 5.

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

Exposure variables	Preterm FGR (study group) (n=102) (%)	Preterm non-FGR (control group) (n=102) (%)	Odds ratio (95%CI)	P value
Maternal age (years)				
<18	0	0	-	0.17
18-35	100 (98.0%)	95 (93.1%)	Ref	
>35	2 (2.0%)	7 (6.9%)	0.27 (0.05-1.34)	
Mean age±standard deviation	26.84±4.63	26.41±5.03		
Socioeconomic status				
Upper class	2 (1.9%)	1 (0.9%)	3.02 (0.26-34.68)	0.37
Upper middle	2 (1.9%)	7 (6.8%)	0.39 (0.07-2.04)	
Lower middle	33 (32.3%)	46 (45.1%)	Ref	
Upper lower	61 (59.8%)	47 (46%)	1.80 (1.00-3.25)	
Lower	4 (4.08%)	1 (0.9%)	2.05 (1.16-3.61)	
Height (cms)				
<145	13 (12.7)	10 (9.8)	1.30 (0.47-3.55)	0.79
145 TO 155	66 (64.7)	69 (67.6)	0.95 (0.48-1.86)	
>155	23 (22.5)	23 (22.5)	Ref	
BMI (kg/m^2)				
<18.5 (underweight)	51 (50.0)	10 (9.8)	8.86 (4.07-19.27)	
18.5 to 24.9	42 (41.2)	73 (71.6)	Ref	

Continued.

Exposure variables	Preterm FGR (study group) (n=102) (%)	Preterm non-FGR (control group) (n=102) (%)	Odds ratio (95%CI)	P value
(Normal BMI)				<0.001
>25(overweight)	9 (8.8)	19 (18.6)	1.21 (0.50-2.92)	

Table 2: Comparison of maternal lifestyle-related risk factors

Exposure variables	Preterm FGR (study group) (n=102) (%)	Preterm non-FGR (control group) (n=102) (%)	Odds ratio (95%CI)	P value
Work				
Housewife	60 (58.8)	73 (71.6)	Ref	<0.001
Sedentary work	21 (20.6)	27 (26.5)	0.94 (0.48-1.83)	
Manual work	21 (20.6)	2 (2.0)	12.77 (2.88-56.68)	
Stress				
No	74 (72.5)	77 (74.5)	Ref	0.75
Yes	28 (27.5)	25 (24.5)	1.16 (0.63-2.18)	
Smoking				
Never	65 (63.7)	83 (81.4)	Ref	<0.001
Passive smoking	37 (36.3)	19 (18.6)	2.48 (1.31-4.72)	
1 to 10	-	-		
>10	-	-		
Alcohol				
No	102	102	-	-
Yes	0	0		
Domestic violence				
No	102	102		-
Yes	0	0	-	

Table 3: Comparison of obstetrics risk factors by groups

Exposure variables	Preterm FGR (study group) (n=102) (%)	Preterm non-FGR (control group) (n=102) (%)	Odds ratio (95%CI)	P value
Parity				
Nulliparous	49 (48.0)	44 (43.1)	1.51 (0.81-2.79)	0.23
Primiparous	31 (30.4)	42 (41.2)	Ref	
Multiparous	22 (21.6)	16 (15.7)	1.86 (0.84-4.12)	
Interpregnancy interval (months)				
<18	15 (27.8)	13 (20.0)	1.64 (0.60-4.52)	0.59
18 to 60	25 (46.3)	32 (49.2)	1.60 (0.70-3.67)	
>60	14 (25.9)	20 (30.8)	Ref	
ANC visits				
<4	30 (29.4)	30 (29.4)	1.0 (0.54-1.82)	1.00
>4	72	72	Ref	
Supplements taken				
No	30 (29.4)	27 (26.5)	1.15 (0.62-2.13)	0.64
Yes	72 (70.6)	75 (73.5)	Ref	
Gestational hypertension				
No	78	85	Ref	0.22
Yes	24 (23.5)	17 (16.7)	1.48 (0.74-2.97)	
Gestational diabetes mellitus (GDM)				
No	89	87	Ref	0.68
Yes	13 (12.7)	15 (14.7)	1.18 (0.53-2.62)	
Previous h/o intrauterine death (IUD)				
No	96	98	Ref	0.74
Yes	6 (5.9)	4 (3.9)	1.53 (0.42-5.59)	

Continued.

Exposure variables	Preterm FGR (study group) (n=102) (%)	Preterm non-FGR (control group) (n=102) (%)	Odds ratio (95%CI)	P value
Previous h/o preterm				
No	89	93	Ref	0.49
Yes	13 (12.7)	9 (8.8)	1.51 (0.61-3.70)	
Previous h/o IUGR				
No	93	98	Ref	0.25
Yes	9 (8.8)	4 (3.)	2.37 (0.71-7.96)	

Table 4: Pregnancy outcomes associated with preterm FGR births.

Outcome variables	Preterm-FGR (study group) (n=102) (%)	Preterm-non-FGR (control group) (n=102) (%)	Relative risk (95% CI)	P value
Type of delivery				
Induced	24 (23.5)	13 (12.7)	1.09 (0.82-1.46)	0.04
Spontaneous	78 (76.5)	89 (87.3)	Ref	
Mode of delivery				
Vaginal delivery	74 (72.6)	70 (68.7)	Ref	0.53
Cesarean section	28 (27.4)	32 (31.2)	0.87 (0.57-1.34)	
Live birth				
No	8 (7.8)	3 (2.9)	Ref	0.21
Yes	94 (92.2)	99 (97.1)	0.53 (0.20-1.40)	
Birth weight (g)				
≥2000 g	35 (34.4)	90 (88.3)	Ref	<0.001
<2000 g	67 (65.6)	12 (11.7)	3.02 (1.45-2.12)	
Mean±standard deviation (g)	1740±345.76	2363±349.13		
NICU admission				
No	36 (38.2)	80 (81.6)	Ref	<0.001
Yes	58 (61.7)	18 (18.4)	2.91 (1.91-4.44)	
Neonatal mortality				
No	77 (82)	97 (98)	Ref	<0.001
Yes	17 (18)	2 (2)	5.29 (1.42-19.77)	

Table 5: Multivariate logistic regression analysis of independent risk factors for FGR among preterm births.

Exposure variables	Categories	Adjusted Odds ratio (95% CI)	P-value
BMI (kg/m^2)	<18.5	8.37 (3.83-18.30)	<0.001
	18.5 or above		
Work	Housewife/ Sedentary work		<0.01
	Manual work	9.99 (2.12-46.99)	
Passive smoking	No	1.57 (0.74-3.34)	0.23
	Yes		

DISCUSSION

Univariate analysis has identified three risk factors (underweight, manual work, and passive smoking) which were significantly FGR among preterm births. After adjusting these factors in multivariate analysis, underweight and manual work were found to be independent risk factors for FGR among preterm births. These findings are not directly comparable to much of the existing literature, as many of them have compared preterm small for gestational age (SGA) with the term appropriate for gestational age (AGA) as a control group. Some have evaluated the risk factors for preterm and SGA separately. Only a few studies had compared preterm FGR with preterm non FGR like our study. However, all these studies have defined that SGA as birth weights <10th percentile by age-sex specific standard growth charts and preterm as GA <37 weeks similar to our study.

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.[7] A study by Chen et al compared the association of pre-pregnancy BMI between preterm SGA births and preterm non-SGA births.[9] The inclusion criteria was similar to our study. Although this study was conducted on the population of rural China which was also a low-middle-income country as India, unlike our observations they found no associated risk for preterm FGR births in those women who were in the underweight category. The likely explanation for this was, in our study we have taken BMI as a categorical variable and analyzed the association of underweight category in both the groups whereas in the study by Chen et al they had analyzed BMI as a continuous variable and the median BMI were in normal BMI category and was comparable between preterm SGA verses preterm non-SGA groups (20.3 verses 20.7 kg/m^2).[9]

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.[7] 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.[12] But they had classified work during pregnancy differently as primary sectors and unemployed and did not classify considering the physical exertion associated with the employment.

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.[13,14] Sharma et al have found 3 times increased risk for neonatal mortality for preterm SGA infants which was lower compared to our study.[13] This can be explained as this study was conducted in the U.S population and availability of the high quality of intrapartum care including access to care, human resources, and drugs or medical equipment may be responsible for lowered mortality risk. However, a study by Gidi et al has found no significant difference in neonatal mortality rates among preterm SGA and preterm AGA pregnancies.[14] 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.[13,14]

There are few limitations. Our study being a retrospective study, we could not consider an important risk factor i.e., weight gain during pregnancy which could have been important covariates for this analysis. In addition, documenting self-reported information such as alcohol intake, domestic violence, maternal smoking, and iron and folic acid compliance, responses may be misclassified because of social desirability bias. We also assessed gestational age by LMP, which is prone to error and likely leads to misclassification.

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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