ASSESSMENT OF RISK FACTORS AND EVALUATION OF MATERNOFOETAL OUTCOMES IN FOETAL GROWTH RESTRICTION- A CONTROLLED STUDY AT A TEACHING HOSPITAL IN SOUTH INDIA

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ABSTRACT

BACKGROUND

Foetal Growth Restriction (FGR) is a relatively common, but dreaded obstetric and paediatric complication with adverse foetal and perinatal outcomes whose sequelae continue to haunt for a lifetime. Knowledge of predisposing factors and outcomes can help us manage these pregnancies and neonates in better ways.

MATERIALS AND METHODS

The study was conducted at ESIC Medical College Teaching Hospital over a period of two years; 116 cases were registered as FGR and suitable controls without FGR were selected. Risk factor occurrence, maternal outcomes, mode of delivery, neonatal characteristics, postnatal outcomes and perinatal mortality were recorded in both groups and compared by suitable statistical tests to assess the significance of observations noted.

RESULTS

Statistically significant relationship was observed between smoking, maternal malnutrition, pregnancy-induced hypertension, maternal anaemia and chronic infection (all significant with $p < 0.05$). A higher rate of caesarean section was observed in study group compared to control group (62% vs. 18.1%), which was significant ($p < 0.0001$). Meconium stained liquor and reduced liquor was seen more in study group, 42 and 29 patients compared to 15 and 21 patients in control group, respectively. Still births occurred to the tune of 8.6% in study group. Mean birth weight was 2105 ± 50 gms at mean gestational age 36.6 ± 1.2 weeks in FGR foetuses compared to 2850 ± 107 gm at 38.9 ± 0.6 weeks in foetuses without FGR. Respiratory distress syndrome (P - 0.007), Necrotising enterocolitis (P - 0.03), Sepsis (P - 0.01) and Retinopathy of prematurity (P - 0.04) were more common in study group versus control group. Perinatal mortality was 20.75% (22 babies) in FGR group compared to 0.9% (3 babies) in control group ($P < 0.0001$).

CONCLUSION

FGR adversely affects the foetus and neonate. In light of recent evidence, there has been an emphasis on life-term risks in babies born with FGR. The psychological trauma on the mother to have a child with FGR and to raise it is enormous, herculean and heart breaking. An understanding of predisposing factors and outcomes can help us better predict pregnancy outcomes in these cases in clinical settings.

KEYWORDS

Foetal Growth Restriction, Small for Gestational Age, Foetal Surveillance, Still Births, Perinatal Mortality.

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BACKGROUND

The Royal College of Obstetricians and Gynaecologists (RCOG) defines Small for Gestational Age (SGA) foetus as foetal Abdominal Circumference (AC) or Estimated Foetal Weight (EFW) less than 10th centile [a]. The RCOG further classifies SGA foetuses into constitutionally small and Foetal Growth Restriction (FGR).

FGR represents a severe pathological affliction of foetal growth, whereas SGA also constitutes constitutionally small babies apart from FGR. Hence, FGR can be differentiated from SGA by oligohydramnios and/or foetal Doppler changes.

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The RCOG describes Umbilical Artery (UA) Doppler as the primary surveillance tool in SGA foetuses.[1] FGR is hence being described as AC or EFW less than 3rd centile or less than 10th centile with Doppler changes and/or oligohydramnios, whereas SGA being described as EFW or AC more than 3rd centile and less than 10th centile with normal Doppler studies.[2,3] Abnormal Doppler changes are defined as pulsatility or resistance index more than 2SD above the mean for Gestational Age (GA) in UA.[1]

The development of FGR is determined by maternal, foetal and placental factors. Many of these factors are preventable like smoking, alcohol abuse, infections, pregnancy-induced hypertension (PIH), maternal malnutrition, assisted reproductive techniques and multifoetal gestation.[4]

FGR predisposes a foetus to adverse outcomes in foetal, neonatal and infantile periods, whose sequelae continue well into childhood and adulthood. Perinatal mortality has increased in FGR foetuses and new-borns.[5] A modern classification system of stillbirth, ReCoDe has shown that FGR

is the most common factor identified in stillborn babies. In addition, it has serious consequences for babies who survive.

FGR is associated with increased risk of premature birth, increased morbidity among premature neonates including necrotising enterocolitis, low APGAR score, hypoxic brain injury and its long-term sequelae, the need for respiratory support and chronic lung disease, retinopathy of prematurity, prolonged Neonatal Intensive Care Unit (NICU) care and mortality.[6] Furthermore, a number of causes of FGR are associated with an increased risk of FGR and intrauterine death in mother's subsequent pregnancy.[7] Such infants are also at a higher risk of sepsis because of a compromised immune system. In long-term, babies born with FGR are shorter and lighter and more likely to be diagnosed with cerebral palsy and have a lower Intelligence Quotient.[8]

The high incidence of FGR in general obstetric population (~10%) and its low recognition (<40%) together lead to increasing perinatal morbidity and mortality.[9] More so in a developing country like India where predisposing risk factors occur at high levels in mothers.

Objectives

FGR poses a life-threatening challenge to the foetus in-utero, which could lead to bad obstetric consequences and undesirable perinatal outcomes. The study aims at evaluating the risk factors and materno-foetal outcomes in mothers with FGR in comparison to matched controls. Knowledge of modifiable risk factors could reduce the incidence of FGR and a study of outcomes could help in better management.

MATERIALS AND METHODS

The study was conducted as a prospective comparative study at ESIC Medical College Hospital over a period of two years from 2015 - 2017. ESIC Medical College Hospital is a tertiary care teaching hospital catering to obstetric referrals from 35 ESIC Hospitals and Dispensaries, in addition to its own patients.

Antenatal mothers who presented for regular antenatal check-up were considered for the study. Approval was obtained from the Institutional Ethics Committee and subjects and controls were recruited only after informed consent.

A 30 weeks, third trimester scan was considered for assessment of foetal growth. The study group consisted of 116 mothers diagnosed with EFW less than 3rd centile or less than 10th centile with foetal UA Doppler changes or oligohydramnios. Suitably 116 women were taken as controls after matching age, parity and GA whose EFW was more than 10th centile and less than 90th centile. Socioeconomic status was not matched as ours being a Government hospitals, all patients come from similar background. Foetal growth chart proposed by Kramer and coherent with WHO Growth standards version were used in the study.[10]

Questionnaire method was followed for literate patients and interview was done for uneducated patients, for risk factor assessment apart from a thorough clinical history and review of antenatal records. Risk factors like cord and placental pathology were assessed after the delivery. Patients were followed up closely with repeat Ultrasonographic (USG) examination for foetal morphometric analysis. Foetal surveillance was performed by UA Doppler in accordance with RCOG Guidelines.[1] Middle Cerebral Artery (MCA) Doppler, Cardiotocography (CTG) and Biophysical profile were not considered for foetal assessment in accordance with RCOG guidelines.[1] Ductus venosus and Umbilical Vein Doppler could not be performed due to technical shortcomings.

Abnormal UA Doppler with Absent or Reduced End Diastolic Velocities (AREDV) detected before 32 weeks were delivered before 32 weeks; those with UA Doppler with AREDV detected after 32 weeks were delivered before 37 weeks. Any foetus with abnormal MCA Doppler was delivered before 37 weeks. Mode of delivery was determined by EDV in UA. Foetuses who presented with presence of UA-EDV were allowed to set spontaneously or given induction with Electronic Foetal Monitoring (EFM) and those with UA-AREDV were taken for emergency caesarean section.

Data regarding intrapartum foetal surveillance and obstetric outcomes was recorded. After birth the neonate was carefully assessed and anthropometric findings and APGAR scores were recorded. Those with a compromised state were admitted to NICU and were thereafter followed by a paediatrician. These babies were also followed up to 1 week and findings were noted. The data was tabulated and statistically evaluated by Social Science and GraphPad online Software.

Selection Criteria for Study Group

1. Patients between 18 - 40 years of age.
2. Spontaneous conception.
3. EFW and/or AC less than 10th centile with signs of foetal compromise.
4. EFW and/or AC less than 3rd centile.
5. Foetal viability at the time of diagnosis.
6. Known and unknown GA at the time of presentation.

Selection Criteria for Comparison Group

1. Age, parity and GA matched to the case.
2. EFW and/or AC greater than 10th centile, but less than 90th centile.
3. Absence of pre-existing medical disorders.
4. Absence of obstetric disorders or factors complicating pregnancy.
5. Occurrence of FGR or any other obstetric disorder during pregnancy.

Research involving Human Participants

- All procedures performed on the patient were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.
- All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms of the RCOG.
- Foetal sex was neither detected nor informed in accordance with the PNDT Act 1994.

RESULTS

There were 7,256 admissions to the labour room in the past 2 years, which brings the incidence of SGA to 17.9% and true FGR to 1.25%. As shown in Table 1, differences in demographic details of the study and control group are statistically insignificant, as they were appropriately matched for age, parity, gestational week and socioeconomic status and hence comparable. The highest incidence of FGR occurs in 21 - 25 years (45.6%), Primis (44.8%) at 36 - 37 weeks gestation (31.89%). This is statistically significant in the sample studied by goodness of fit.

Distribution of Age							
Age	**< 20 yrs.**	**21 - 25 yrs.**	**26 - 30 yrs.**	**31 - 35 yrs.**	**> 35 yrs.**	**P value†**	**P value‡**
Frequency in Study group (N = 116)	11	53	34	13	5	< 0.001*	0.99‡‡
Frequency in Control group (N = 116)	10	56	36	11	3	< 0.001*	
Distribution of Order of Birth							
Parity	Primi	Gravida 2	Gravida 3	Gravida 4	Grand Multi	P value†	
Frequency in Study group (N = 116)	52	34	16	10	4	< 0.001*	0.63‡‡
Frequency in Control group (N = 116)	56	36	17	5	2	< 0.001*	
Distribution of Age at Presentation							
Gestational Age	30^{+0} wks to 31^{+6} wks	32^{+0} wks to 33^{+6} wks	34^{+0} wks to 35^{+6} wks	36^{+0} wks to 37^{+6} wks	38^{+0} wks to 39^{+6} wks	P value†	
Frequency in Study Group (N = 116)	16	20	24	37	19	< 0.001*	1‡‡
Frequency in Control Group (N = 116)	16	20	24	37	19	<0.001*	

Table 1. Demographic Distribution of Study and Control Subjects

P†- value calculated by Chi Square Test for goodness of fit | P‡- value calculated by Chi Square Test. * - Statistically Significant | ‡‡ - Statistically insignificant.

Table - 2, illustrates the aetiologic relationship between various predisposing risk factors and FGR. Maternal malnutrition appears to be significantly related with FGR (P - < 0.0001); 8.6% of study group had exposure to tobacco smoke compared to 2.5% in control group, which appears statistically significant (P - 0.04). Acute febrile infections in the mother had no effect on foetal growth, whereas chronic infections in the mother significantly restricted foetal growth (P - 0.46 and P - 0.01 respectively). Placental and cord pathology were seen in 9 and 13 patients respectively in FGR group compared to 2 and 5 patients respectively in control group (statistically significant in both cases with p 0.03 and 0.04 respectively). Alcoholism does not appear to be a risk factor statistically, which could be due to very low incidence of alcoholism in women in our community. PIH (25% - P 0.003) and Anaemia (26.7% - P 0.05) in the FGR group appears to significantly increase the risk of foetal growth aberrations.

Sl. No.	Risk Factor	Risk Factor Characterisation	Study Group FGR (N = 116) n (%)	Control Group No FGR (N = 116) n (%)	P† - value	Relative Risk
1.	Smoking (Active and/or Passive)	No Smoking	106 (91.3%)	113 (97.4%)	0.04*	1.58
		Smoking	10 (8.6%)	3 (2.5%)		
2.	Alcoholism	No Alcoholism	111 (95.6%)	113 (97.4%)	0.47‡‡	1.25
		Alcoholism	5 (4.3%)	3 (2.5%)		
3.	Antenatal Care	Booked	69 (59.4)	61 (52.5%)	0.28‡‡	0.86
		Unbooked	47 (40.5%)	55 (47.4%)		
4.	Maternal Malnutrition	BMI > 18.5 kg/m²	73 (62.9%)	99 (85.3%)	< 0.0001*	1.68
		BMI < 18.5 kg/m²	43 (37%)	17 (14.6%)		
5.	Pregnancy Induced Hypertension (PIH)	No PIH	87 (75%)	104 (89.6%)	0.003*	1.55
		PIH	29 (25%)	12 (10.3%)		
6.	Maternal Anaemia	No Anaemia	85 (73.2%)	97 (78.4%)	0.05*	1.32
		Anaemia	31 (26.7%)	19 (16.3%)		
7.	Placental Pathology (PcP)	No PcP	107 (92.2%)	114 (98.27%)	0.03*	1.68
		PcP Present	9 (7.7%)	2 (1.7%)		
8.	Cord Pathology (CoP)	No CoP	103 (88.7%)	111 (95.6%)	0.04*	1.50
		CoP Present	13 (11.2%)	5 (4.3%)		
9.	Chronic Infection (CoI)	No CoI	100 (86.2%)	111 (95.6%)	0.01*	1.60
		CoI Present	16 (13.8%)	5 (4.3%)		
10.	Acute Infection (AcI)	No AcI	81 (69.8%)	86 (74.1%)	0.46‡‡	1.11
		AcI	35 (30.1%)	30 (25.8%)		

Table 2. Evaluation of Risk Factors in Causation of FGR

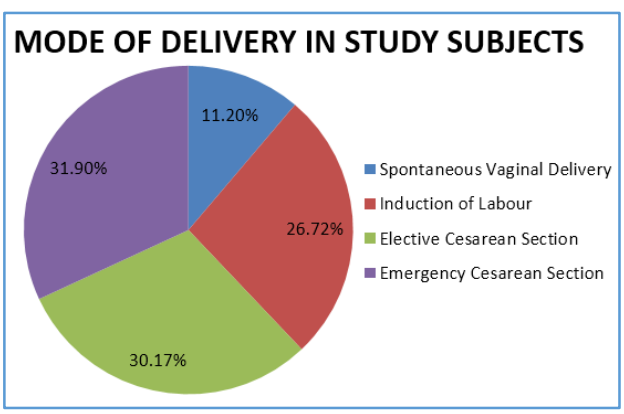
P† – value calculated by Chi Square Test. * - Statistically Significant | ‡‡ - Statistically Insignificant.

Obstetric Outcomes are tabulated in Table 3, intrapartum foetal monitoring in labour with cardiotocography shows a higher percentage of foetuses (60 vs. 21) in FGR group had non-reassuring pattern (P < 0.0001). Colour of liquor shows statistically significant differences between FGR and non-FGR groups, thereby signifying that liquor characteristics can be used for intrapartum monitoring. Morbidity was more in mothers of study group due to operative interference, as caesarean section rate was at 62% in them compared to 18.1% in control group (P < 0.0001); 10 still births were recorded in FGR babies (8.6%) compared to 2 still births in non-FGR babies (1.7%) and this association was significant with P value of 0.03; 12 babies in excess had neonatal asphyxia in study group with P - 0.15. Figure 1 represents the mode of delivery in study group.

Sl. No.	Outcome	Outcome Characterisation	Study Group FGR (N = 116)	Control Group No FGR (N = 116)	P† – value
1.	Cardiotocography (CTG)	Reassuring	56 (48.2%)	95 (81.8%)	< 0.0001*
		Non-Reassuring	60 (51.7%)	21 (18.1%)	
2.	Colour of Liquor	Clear and Adequate	26 (22.4%)	78 (67.2%)	< 0.0001*
		Clear and Less	29 (25%)	21 (18.1%)	
		Meconium Stain	42 (36.2%)	15 (12.9%)	
		Nil liquor	19 (16.3%)	2 (1.7%)	
3.	Mode of Delivery	Vaginal	44 (37.9%)	95 (81.8%)	< 0.0001*
		Caesarean	72 (62%)	21 (18.1%)	
4.	Neonatal Asphyxia	No Asphyxia	96 (82.75%)	108 (93.1%)	0.15*
		Asphyxia	20 (17.24%)	8 (6.89%)	
5.	Still Births	Live Born	106 (91.3%)	114 (98.2%)	0.03*
		Still Born	10 (8.6%)	2 (1.7%)	

Table 3. Obstetric Outcomes in Study and Control Groups

P† – value calculated by Chi Square Test | * - Statistically Significant.



Average age of delivery in study group was much earlier at 36.6 ± 1.2 weeks compared to 38.9 ± 0.6 weeks in non-FGR group, which could potentially cause prematurity and related complications (P < 0.0001). Statistically significant differences were observed in the birth weight of FGR group (2105 ± 50 gms) compared to 2850 ± 107 gms in non-FGR group with P < 0.0001. The same when charted on foetal growth chart showed significant difference of 4.2nd vs. 20.6th centile respectively. APGAR scores also showed statistically significant difference at birth and 5 minutes of life. The same is demonstrated in Table 4.

Sl. No.	Outcome at Birth	Mean of Study Group FGR (106)	SD in Study Group	Mean in Control Group No FGR (114)	SD in Control Group	P‡ - value
1.	Age at Delivery	36.6 wks	± 1.2	38.9 wks	± 0.6	< 0.0001*
2.	Birth Weight	2105 gm	± 50	2850 gm	± 107	< 0.0001*
3.	Centile of weight	4.2nd centile	± 0.4	20.6th centile	± 2.8	< 0.0001*
4.	APGAR at birth	6.43 score	± 0.21	7.96 score	± 0.91	< 0.0001*
5.	APGAR at 5 minutes	7.27 score	± 0.36	8.64 score	± 0.63	< 0.0001*

Table 4. Neonatal Outcomes in Study and Control Group

P‡ – value calculated by Unpaired 't' Test | * - Statistically Significant

Table 5 represents 33% of FGR foetuses (35) had prematurity compared to 5.2% of non-FGR foetuses (6), and this brings us to a conclusion that statistically significant prematurity is seen in FGR babies (P < 0.0001). Complications associated with prematurity like RDS (P - 0.007), NEC (P - 0.03) and ROP (P - 0.04) were found more in FGR babies compared to control group; 12 patients in study group had sepsis (11.3%) compared to 3 patients (2.6%) in control group, which was significant by Chi Square Fisher exact calculation).

Sl. No.	Outcome	Outcome Characterisation	Study Group FGR (N = 106)	Control Group No FGR (N = 114)	P† – value
1.	Prematurity	No Prematurity	71 (67%)	108 (94.7%)	< 0.0001*
		Prematurity	35 (33%)	6 (5.2%)	
2.	Respiratory Distress Syndrome (RDS)	No RDS	91 (85.8%)	110 (96.4%)	0.007*
		RDS	15 (14.1%)	4 (3.5%)	
3.	Sepsis	No Sepsis	94 (88.6%)	111 (97.3%)	0.01*
		Sepsis	12 (11.3%)	3 (2.6%)	
4.	Pathological Brain Scans (PBS)	No PBS	95 (89.6%)	109 (95.6%)	0.11‡‡
		PBS	11 (10.3%)	5 (4.3%)	
5.	Retinopathy of Prematurity (ROP)§	No ROP	96 (90.5%)	111 (97.3%)	0.04*
		ROP	10 (9.5%)	3 (2.6%)	
6.	Necrotising Enterocolitis (NEC)	No NEC	99 (93.4%)	113 (99.1%)	0.03*
		NEC	7 (6.6%)	1 (0.9%)	
7.	Early Neonatal Deaths (END) (mortality in first 7 days)	Late Neonates	94 (88.6%)	113 (99.1%)	0.001*
		Early Neonatal Death	12 (11.3%)	1 (0.9%)	
8.	Perinatal Mortality (Still Births + END) (N = 116)	Late Neonates	94 (88.6%)	113 (99.1%)	< 0.0001*
		Perinatal Deaths	22 (20.75%)	3 (0.9%)	

Table 5. Outcomes in NICU in Study and Control Group

P† – value calculated by Chi Square Test (Fisher Exact Test – Two tailed) * - Statistically Significant | ‡‡ - Statistically Insignificant | § Follow-up at 4 weeks by Ophthalmologist.

DISCUSSION

Barker and his colleagues reported in several epidemiological and anthropological studies that in foetal life, tissues and organs go through the so-called 'critical' periods of development. These may coincide with periods of rapid cell division. Although, the foetal growth is influenced by its genes, several studies suggest that it is usually limited by intrauterine environment, in particular the nutrients and oxygen received from the mother.[11,12]

Our statistics are in conformation with the results of Andzane D et al,[4] Stanisic Chou T et al[13] and Romo A et al.[14] Few differences have been noted as factors predisposing to FGR are present in higher concentrations in Indian society. More so our hospital deals with patients from low socioeconomic strata, which could cause certain statistical differences when compared with other studies.

Some studies mention that 75% of all FGR cases are not diagnosed till birth and are only diagnosed retrospectively by neonatal anthropometry.[15] Such cases have not been included in the study, as our main focus was correlation between antenatally diagnosed true FGR and its outcomes. Also to be considered is the fact that Indian babies are constitutionally smaller than babies in the US, keeping this in mind Indian studies have recommended using growth charts prepared for Indian babies,[16] but these have not yet been popularised for use and hence standard charts currently in use have been used in the study.

Sharifzadeh et al in his study found a positive correlation between SGA and low maternal BMI before pregnancy.[17] Albu et al[18] and Andzane D et al[4] have reported similar aetiologic relationships with risk factors as mentioned in our study. Natalija Vedmedovska et al in 2010 described the average GA around 36.3 weeks, which closely resembles the GA in our study group.[19] The rate of elective caesarean section was 30% in our study, which corresponds to 26.3% in a study by Andzane et al,[4] but the average GA in the same study was around 39.3% which is much higher than our study.

Neonatal and post-natal outcomes measured in our study are in close agreement to the findings of Visentin et al[2] and Gomez et al.[3] They too reported a higher incidence of complications and the need for caesarean section in the FGR group with statistically comparable differences in the non-FGR group. Visentin et al also reported statistically significant non-reassuring foetal pattern on CTG in foetuses affected with FGR.[2]

CONCLUSION

Foetal Growth Restriction is a major obstetric problem. It is a major cause of perinatal mortality and morbidity, and it is associated with several health problems throughout life. There is recent emerging evidence in the form of 'developmental origins of adult disease,' the Barker hypothesis which proposes that certain diseases originate through adaptations of the foetus when it is undernourished. These adaptations may be cardiovascular, metabolic or endocrine, and they may permanently change the structure and function of the body, increasing coronary heart disease risk factors such as hypertension, type 2 diabetes mellitus, insulin resistance and hyperlipidaemia. It is not just the foetus, but also the mother which is adversely affected by FGR in terms of operative interference and psychological upset. An assessment of risk factors and knowledge of probable outcomes can help us in understanding FGR better and to offer better counselling to mothers whose foetuses are affected with FGR. Further research is essential to evaluate the long-term effects of FGR and to explore therapeutic options to reduce the end effects of FGR on the foetus.

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