



Perinatal Outcomes of Fetal Growth Restriction, Classified According to the Delphi Consensus Definition: A Prospective Observational Study

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Abstract Fetal Growth Restriction has been redefined on the basis of biometry (Abdominal Circumference/Estimated Fetal Weight) beyond the original definition of failure of a fetus to reach its full growth potential irrespective of its size. The Delphi consensus has standardised the definition of early and late onset FGR using size (biometry) as well as functional parameters (doppler blood flow). The clinical validity of this consensus in terms of perinatal outcomes has yet to be tested. The aim of the study was to assess and compare the incidence and perinatal outcomes of fetal growth restriction classified by the Delphi consensus as against conventional definitions. This was a prospective cohort study of 500 consecutive patients from February 2018 onwards, in a tertiary hospital (Sir Ganga Ram Hospital, New Delhi) with a fully equipped neonatal intensive care unit. 70 patients were excluded by predefined exclusion criteria. 430 subjects were enrolled as the study population. Enrolled subjects, apart from a dating scan at first visit and an anomaly scan in the 2nd trimester had a transabdominal scan using a 5 MHz curvilinear probe for fetal assessment between 26 and 32 weeks with at least one scan at 31–32 weeks to identify early onset FGR. A repeat USG between 35 and 36 weeks was conducted to identify late onset FGR. All recruited subjects were categorised as Conventional FGR i.e. AC/EFW < 10th% ile (C), early onset (C1) and late onset (C2), Delphi defined FGR (D) based on

Delphi Consensus criteria, early onset (D1) and late onset (D2), Non Delphi Conventional FGR as (C-D), early onset (C1-D1) and late onset (C2-D2). Rest of the fetuses were designated as Non FGR (> 10th% ile). The association of incidence along with perinatal outcomes in each group were compared. The incidence of FGR was as follows: conventional criteria: 35.8%, Delphi criteria: 22.7% and Non Delphi Conventional FGR: 13.1%. Delphi defined FGR had statistically significant increased incidence of PPHTN, hypoglycemia and NICU admission in comparison to Conventional FGR. Delphi defined FGR also had statistically significant increased frequency of Apgar < 7, PPHTN, hypoglycemia, seizures, NICU admissions and prolonged stay as compared to Non Delphi Conventional FGR group. Comparing Non FGR fetuses with Non Delphi Conventional FGR fetuses, neonatal outcomes were similar in both groups. Delphi defined FGR is associated with increased frequency of adverse perinatal outcomes as compared to conventionally defined FGR. Delphi defined criteria, should be routinely applied to a fetus who is small (AC/EFW < 10th% ile). This will timely identify a truly growth restricted fetus, who is at risk for adverse perinatal outcome and save the rest from unnecessary monitoring and intervention. The findings of our study call for larger studies validating the use of Delphi consensus in clinical practise.

Keywords Fetal growth restriction · Delphi defined FGR · Perinatal outcomes of FGR

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Introduction

Fetal Growth Restriction (FGR) is defined as a failure to achieve the expected growth potential. It complicates 5–10% of pregnancies [1]. A large body of evidence has linked FGR

with high perinatal mortality, morbidity, poor postnatal growth, long term neurological handicaps and metabolic diseases in adult life [2, 3, 4, 5, 6, 7]. There is a wide variation in criteria used to classify FGR by different professional bodies because of lack of consensus. The American College of Obstetricians and Gynaecologists (ACOG) defines FGR as Estimated Fetal Weight (EFW) below the 10th centile, whereas the Royal College of Obstetricians and Gynaecologists (RCOG) considers either Abdominal Circumference (AC) or EFW less than 10th centile as criteria for FGR [8, 9]. Of late, classifying a fetus as FGR based only on body size alone, is being questioned, as 1/3rd of these fetuses might be constitutionally small and perinatal outcomes may be comparable to those of a normally grown fetus [10]. True FGR means failure of a fetus to reach its full growth potential irrespective of the fact that EFW is less than or more than the 10th centile [11]. Two recent studies have highlighted that abnormal functional parameters of the fetus i.e. altered blood flow in vessels are determinant of adverse outcomes along with smallness [10, 12].

To rest this dilemma a consensus was sought in 2016 for defining FGR using the Delphi procedure by involving a panel of international experts on FGR [13]. Delphi consensus has standardised the definition of early and late onset FGR using both biometry and functional parameters as against conventional definition based only on biometry. The Delphi consensus has yet to be validated in terms of predicting perinatal outcomes, besides standardising the definition of FGR. With this background, we undertook this study to determine the incidence and perinatal outcomes of fetal growth restriction based on Delphi consensus definition as compared to FGR defined using conventional criteria.

Methodology

This prospective observational study was conducted at the Institute of Obstetrics and Gynaecology, Fetal Medicine and Department of Neonatology, Sir Ganga Ram Hospital, New Delhi. The study was approved by the institutional ethics committee. All pregnant women attending the antenatal clinic at Institute of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, New Delhi, between February 2018 and May 2019 were eligible for enrolment in the study if their first visit was during the first trimester. Multiple pregnancies, spontaneous/missed abortion, uncertain dates, known fetal chromosomal or structural anomalies were a priori exclusion criteria (Fig. 1).

All enrolled subjects were assessed for their demographic and clinical characteristics. The enrolled subjects underwent Ultrasonography (US) evaluation during the first trimester for dating the pregnancy using crown rump length. Subsequently, US assessment was repeated during second

trimester for identification of fetal anomalies. Further scans were done between 26 and 32 weeks with at least one scan at 31–32 weeks to identify early onset FGR and at 35–36 weeks to identify late onset FGR. Additional US and doppler assessments and pregnancy management was at the discretion of treating obstetrician. Estimation of fetal weight was determined by using the Hadlock formula [14]. Doppler of uterine artery, umbilical artery and middle cerebral artery was done and, resistive index, pulsatility index and cerebroplacental ratio were computed using Sonocare software. For classification of fetal growth and doppler blood flows, National Institute of Child Health and Human Development (NICHD) charts on Asian population were followed.

Early onset FGR (EOFGR) was defined as onset before 32 weeks and late onset FGR (LOFGR) was defined as onset at 32 weeks or later. Conventional FGR was defined as AC/EFW < 10th centile for gestation and was labelled as Group C (C1- EOFGR, C2- LOFGR). Criteria for EOFGR as per Delphi consensus was- solitary AC/EFW < 3rd centile OR umbilical artery (UA) absent end diastolic velocity (AEDV) OR contributory AC/EFW < 10th centile combined with Pulsatility index in uterine/umbilical artery > 95th centile. Criteria for LOFGR were – solitary AC/EFW < 3rd centile, contributory as at least two out of following: AC/EFW < 10th centile, AC/EFW crossing centiles > 2 quartiles on growth centiles, CPR < 5th centile/ Pulsatility index in Umbilical Artery (UA) PI > 95th centile. Delphi defined FGR was labelled as Group D (D1-EOFGR, D3-LOFGR). Cases defined as FGR by conventional definition but not by Delphi consensus were classified as non-Delphi FGR (C-D, C1-D1 EOFGR, C2-D2 LOFGR).

The following neonatal outcomes were assessed in enrolled patients: meconium stained amniotic fluid, Apgar score at 5 min, birth asphyxia, hypoxic ischemic encephalopathy, respiratory distress syndrome, meconium aspiration syndrome, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, polycythemia, feed intolerance, seizures, need for NICU admission. Birth asphyxia was defined as per ACOG criteria (presence of all of following: Arterial cord pH < 7.0, Apgar score of 3 or less for greater than 5 min, evidence of altered neurological status (seizures, obtundation, etc.) and multi-system organ failure. Hypoxic ischemic encephalopathy was defined as altered neurological status in presence of features of perinatal asphyxia. Diagnosis of respiratory distress syndrome (RDS) was considered in a neonate in presence of tachypnea, chest retractions, grunting or need for supplemental oxygen shortly after birth. Meconium aspiration syndrome (MAS) was defined as respiratory distress in newborn infants born through meconium-stained amniotic fluid (MSAF) whose symptoms cannot be otherwise explained. Persistent pulmonary hypertension (PPHTN) was defined as presence of hypoxemia or need for respiratory support with echocardiographic evidence of right to left shunt in absence of congenital heart disease.

Fig. 1 Flow diagram for methodology of study

Consecutive 500 patients delivering from February 2018 till May 2019 were recruited.

70 patients excluded, as per the predefined exclusion criteria. Final 430 subjects enrolled as study population.

Detailed history with clinical examination and routine investigations

1st trimester scan and mid trimester anomaly scan

Transabdominal ultrasound for fetal assessment between 26-32 weeks with at least one at 31-32 week using Delphi and Conventional Criteria.

Repeat transabdominal ultrasound between 35-36 weeks using Delphi and Conventional Criteria for FGR.

Excluded- 70 patients

- Multiple pregnancies:5
- Spontaneous/ missed abortions:15
- Uncertain dates:10
- Fetal chromosomal anomalies:4
- Fetal structural anomalies:8
- Lost to follow up:28

Conventional FGR (C) Delphi defined FGR (D) Non Delphi Conventional FGR(C-D)

Early onset (C1) Early onset (D1) Early onset (C1-D1)

Late onset (C2) Late onset (D2) Late onset (C2-D2)

Perinatal outcomes:

- Apgar <7
- Meconium stained amniotic fluid
- Hypoxic ischemic encephalopathy
- Respiratory distress syndrome
- Meconium aspiration syndrome
- Persistent pulmonary hypertension
- Hypoglycemia
- Hypocalcemia
- Polycythemia
- Feed intolerance
- Seizures
- NICU admissions
- NICU stay

Analysis, Results, Interpretation and Presentation.

Hypoglycemia was defined as blood glucose value <40 mg/dl. Hypocalcaemia was defined as total serum calcium concentration <8 mg/dl (<2 mmol/L) in term infants or <7 mg/dl (1.75 mmol/L) in preterm infants. Polycythemia was defined as venous hematocrit >65%. Feed intolerance was defined as abdominal distension and /or abnormal gastric residue/ vomiting necessitating interruption of enteral feeding [15].

Sample Size Estimation:

With an estimated prevalence of FGR of 10% in our population, for a precision of 2% and a significance level of 95%, sample size was found to be 385. To overcome 20% dropouts, a target sample size of 482 was planned.

Statistical Method

Statistical analysis was done using SPSS version 21. The numeric data was expressed as mean (SD) or median (interquartile interval), as applicable, categorical data are presented as number (proportions). Comparison in outcomes between groups was done using Chi Square or Fisher Exact test, as applicable.

Results

During the study period, 500 women visited antenatal clinics at our institute, of which 458 were enrolled in the study, 42 were excluded due to various reasons, as depicted in

Table 1 Association of medical disorders in enrolled population

	Non FGR (n=276)	FGR (conventional) (n=154)	p value
Hematological disorders	31(11.2)	31(20)	0.011
Hypertensive disorders	0(0)	13(8.4)	0.000
Pre gestational diabetes	0(0)	4(2%)	0.007
Gestational diabetes	28(10)	11(7.1)	0.298
Liver diseases	21 (0.76%)	10(6.4)	0.667
Thyroid disorders	58 (21)	7(4.5)	0.000

the study flow chart (Fig. 1). Of 458 women enrolled, 28 were lost to follow up and the remaining 430 were assessed and analyzed. As per conventional definition, FGR was diagnosed in 154 (35.8%) pregnancies, of which 114 (74%) were early onset and 40 (26%) were late onset. As per the Delphi consensus, 98 (22.7%) pregnancies were classified as FGR, of which 67 (68%) were early onset and 31 (32%) were late onset. Fifty-six pregnancies in conventional FGR group were not fulfilling criteria for FGR as per Delphi consensus and hence were categorized as non-Delphi FGR. Mean age of the study cohort was 29.28 (R 20–39), mean BMI was 24.6 (R 18.4–36). Sixty four percent of women, who had FGR pregnancies, were nullipara as against 47% with non-FGR pregnancies. Association of medical disorders amongst study cohort is depicted in Table 1. Mean gestational age and mean birth weight at delivery for non-FGR pregnancies was 38.35 (r 35–40) weeks, 2.83 (r2.065–3.785) kg respectively. There was no significant difference in mean gestational age and birth weight for non-FGR pregnancies: Conventional FGR 35.57 (r 32–40) weeks and birth weight-2.432 (r

1.42–3.03) kg. Corresponding figures for Delphi FGR were 35.5 (r 32–38) weeks, birth weight 2.34 (r 1.42–2.87) kg and for Non-Delphi Conventional FGR 36 (r 31–40) weeks, birth weight 2.58 (1.69–3.03) kg. Perinatal outcomes of FGR and Non-FGR pregnancies are presented in Table 2. The FGR group had higher risk of low apgar, RDS, MAS, PPHTN, hypoglycemia, hypocalcemia, seizures, feed intolerance, need for NICU admission, and perinatal mortality, as compared to non-FGR. Perinatal outcomes of conventional, Delphi, and non-Delphi FGR are presented in Table 3. Delphi defined FGR group had higher incidence of low apgar, MSAF, MAS, PPHTN, hypoglycemia, seizures and need for admission to NICU as compared to non-Delphi FGR. Perinatal outcomes of early and late FGR in above groups are depicted in Tables 4 and 5, respectively. Incidence of most of morbidities was higher in Delphi defined early FGR as compared to non-Delphi early FGR. In late onset FGR, difference in perinatal outcomes other than NICU admissions was statistically insignificant in Delphi defined FGR and non-Delphi FGR. In comparison to non-FGR, Non-Delphi FGR group had higher incidence of low apgar and RDS; rest of perinatal outcomes were comparable Table 6.

There was no perinatal/neonatal death amongst the entire study cohort.

Discussion

FGR has been associated with increased risk of perinatal and neonatal morbidities [16–30]. The conventional definition of FGR is based on estimated fetal weight < 10th centile for gestation. However, using fetal weight < 10th centile as criteria may overclassify FGR, as many of these fetuses might be constitutionally small and otherwise healthy and would not be at increased risk of adverse perinatal outcomes

Table 2 Perinatal outcomes of FGR vs non-FGR

	Non FGR (n=276)	FGR (n=154)	p value	OR (95%CI)
Apgar < 7 at 5 min	3 (1)	48 (31.1)	0.000	41.2 (12.5–135.15)
MSAF	46 (16.6)	35 (22.7)	0.123	1.47 (0.89–2.4)
HIE	0 (0)	0 (0)	–	–
RDS	8 (2.8)	30 (19.4)	0.000	8.1 (3.6–18.19)
MAS	12 (4.3)	23 (14.9)	0.000	3.8 (1.85–7.94)
PPHTN	12 (4.3)	43 (34.4)	0.000	8.5 (4.3–16.7)
Hypoglycemia	16 (5.79)	42 (27.9)	0.000	6.09 (3.2–11.29)
Hypocalcemia	7 (2.5)	12 (7.79)	0.011	3.2 (1.25–8.4)
Polycythemia	6 (2.17)	5 (3.24)	0.499	1.51 (0.45–5.03)
Feed intolerance	4 (1.44)	14 (9.09)	0.000	6.3 (2.05–19.6)
Seizures	0 (0)	9 (5.8)	0.000	–
NICU admissions	48(17.4)	104(67.5)	0.000	9.88 (6.2–15.6)
Perinatal death	0 (0)	0 (0)	–	–
Neonatal deaths	0 (0)	0 (0)	–	–

Table 3 Perinatal outcomes of conventional, Delphi, and non-Delphi FGR

	Conventional FGR (C) (n = 154)	Delphi FGR (D) (n = 98)	Non-Delphi FGR (C-D) (N = 56)	p value conventional vs Delphi	P value Delphi vs Non-Delphi
Apgar < 7	48 (31.1)	41 (41.8)	7 (12.5)	0.11	<0.01
MSAF	35 (22.7)	30 (30.6)	5 (8.9)	0.21	<0.01
HIE	0 (0)	0 (0)	0 (0)	–	–
RDS	30 (19.4)	21 (21.4)	9 (16.07)	0.83	0.41
MAS	23 (14.9)	22 (22.44)	1(1.7)	0.13	<0.01
PPHTN	43 (34.4)	43 (43.8)	0 (0)	0.01	<0.01
Hypoglycemia	42 (27.9)	39 (39.79)	3 (5.3)	0.04	<0.01
Hypocalcemia	12 (7.79)	9 (9.1)	3 (5.3)	0.69	0.39
Polycythemia	5 (3.24)	3 (3.06)	2 (3.5)	1.00	0.86
Feed intolerance	14 (9)	11 (11.22)	3 (5.3)	0.73	0.22
Seizures	9 (5.8)	9 (9.1)	0 (0)	0.45	0.019
NICU admissions	104 (67.5)	93 (94.8)	9 (16.07)	<0.01	<0.01

Table 4 Perinatal outcomes of Early onset conventional, Delphi, and non-Delphi FGR

	Conventional FGR (C1) (n = 114)	Delphi FGR (D1) (n = 67)	Non-Delphi FGR(C1-D1) (N = 47)	p value conventional vs Delphi	p value Delphi vs Non-Delphi
Apgar < 7	35 (30.7)	29 (43.2)	6 (12.7)	0.12	<0.01
MSAF	23 (20.1)	20 (29.8)	3 (6.3)	0.19	<0.01
HIE	0 (0)	0 (0)	0 (0)	–	–
RDS	19 (16.6)	13 (41)	6 (12.7)	0.79	0.49
MAS	14 (12.2)	14 (20.8)	0 (0)	0.18	<0.01
PPHTN	30 (26.3)	30 (44.7)	0 (0)	0.01	<0.01
Hypoglycemia	28 (24.5)	27 (40.2)	1 (2.1)	0.02	<0.01
Hypocalcemia	7 (6.1)	6 (8.9)	1 (2.1)	0.68	0.13
Polycythemia	2 (1.7)	1 (1.4)	1 (2.1)	0.87	0.79
Feed intolerance	9 (7.8)	7 (10.4)	2 (4.2)	0.75	0.30
Seizures	6 (5.2)	6 (8.9)	0 (0)	0.51	0.04
NICU admissions	72 (63.1)	64 (95.5)	6 (12.7)	<0.01	<0.01

Table 5 Perinatal outcomes of Late onset conventional, Delphi, and non-Delphi FGR

	Conventional FGR (C2) (n = 40)	Delphi FGR (D2) (n = 31)	Non-Delphi FGR (C2-D2) (N = 9)	p value conventional vs Delphi	P value Delphi vs Non-Delphi
Apgar < 7	13 (32.5)	12 (38.7)	1 (11.1)	0.94	0.22
MSAF	12 (30)	10 (32.2)	2 (22.2)	0.83	0.69
HIE	0 (0)	0 (0)	0 (0)	–	–
RDS	11 (27.5)	8 (25.8)	3 (33.3)	0.87	0.67
MAS	9 (22.5)	8 (25.8)	1 (11.1)	0.96	0.65
PPHTN	13 (32.5)	13 (41.9)	0 (0)	0.56	0.01
Hypoglycemia	14 (35)	12 (38.7)	2 (22.2)	0.94	0.45
Hypocalcaemia	5 (12.5)	3 (9.6)	2 (22.2)	1.00	0.31
Polycythemia	3 (7.5)	2 (6.4)	1 (11.1)	1.00	0.54
Feed intolerance	5 (12.5)	4 (12.9)	1 (11.1)	1.00	1.00
Seizures	3 (7.5)	3 (9.6)	0 (0)	1.00	1.00
NICU admissions	32 (80)	29 (93.5)	3 (33.3)	0.01	<0.001

Table 6 Perinatal outcomes of Non FGR vs Non Delphi FGR (C-D)

	Non FGR (n=276)	Non-Delphi FGR (n=56)	P value
Apgar < 7	3 (1)	7 (12.5)	<0.01
MSAF	46 (16.6)	5 (8.9)	0.14
HIE	0 (0)	0 (0)	–
RDS	8 (2.8)	9 (16.07)	<0.01
MAS	12 (4.3)	1(1.7)	0.70
PPHTN	12 (4.3)	0 (0)	–
Hypoglycemia	16 (5.79)	3 (5.3)	1
Hypocalcaemia	7 (2.5)	3 (5.3)	0.38
Polycythemia	6 (2.17)	2 (3.5)	0.26
Feed intolerance	4 (1.4)	3 (5.3)	0.09
Seizures	0 (0)	0 (0)	–
NICU admissions	48 (17.39)	9 (16.07)	0.80

[10, 11]. Recently, the Delphi consensus has standardised the classification of FGR, which defines FGR as EFW < 3rd centile for gestation or presence of doppler abnormalities in combination of EFW < 10th centile. In the present study, we assessed perinatal outcomes of FGR, using conventional as well as Delphi consensus definition.

As per the conventional definition, the incidence of FGR in our study was 35.8%, which is substantially higher than the reported global incidence of 10% [1, 8, 9]. As per Delphi consensus definition, incidence of FGR in our population was 22.7%. A higher FGR rate in our study could be due to variation in population characteristics or to a referral bias, as ours is a high risk perinatal center.

We found a higher incidence of Apgar < 7, RDS, MAS, PPHTN, hypoglycemia, feed intolerance, seizures, and NICU admissions in FGR group as compared to non-FGR. Incidence of perinatal morbidities was higher in Delphi defined FGR groups as compared to conventional FGR group. The comparison of conventionally defined FGR with Delphi defined FGR, perhaps, would be less meaningful because these two groups are not exclusive and Delphi FGR is a part of conventional FGR. A more logical approach would be to compare outcome of Delphi defined FGR with that of FGR by conventional definition but not by Delphi consensus i.e. non-Delphi FGR. The difference in perinatal morbidities was even more striking when comparison was made between Delphi FGR and non-Delphi FGR. Similar trends were observed when outcomes of early FGR were explored. Among late FGR, difference in most perinatal outcomes between Delphi FGR and non-Delphi FGR was statistically insignificant, possibly due to small number of participants. In our study, Non-Delphi FGR group had perinatal outcomes closer to non-FGR group with most morbidities being comparable in two groups. Non-Delphi FGR had higher incidence of low apgar and RDS as compared to non

FGR, which could be contributed by lower mean gestation in earlier group (36 wk vs 38.3 weeks), rather than being an effect of FGR. Our findings are in corroboration with a previous report, where authors observed that conventional FGR criteria didn't have statistically significant association with adverse neonatal outcomes, while Delphi FGR criteria were associated with increased risk of adverse outcomes [31]. The authors concluded that although the newly postulated Delphi defined criteria detects less neonatal SGA, there is a slight improvement in predicting adverse neonatal outcomes. These observations suggest that Delphi consensus definition reduces the probability of overdiagnosis of FGR and is more strongly associated with adverse perinatal outcomes. This might have significant implication for practice in settings with limited resource, where using Delphi consensus definition would reduce caseload on health facilities, possibly without an untoward effect on clinical outcomes. There is a need for further testing this hypothesis in large scale studies in different settings.

To summarize our findings, use of Delphi consensus definition reduced the diagnosis of FGR as compared to the conventional definition. Perinatal morbidities were higher in Delphi defined FGR in comparison to non-Delphi FGR. Outcomes of non-Delphi FGR were comparable to non-FGR.

Declarations

Conflict of Interest None.

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