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# Etiology and perinatal outcome in periviable fetal growth restriction associated with structural or genetic anomalies

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**Running head:** Aetiology and outcome in periviable FGR.

**Keywords:** Preterm delivery, amniocentesis, fetal anatomy, abnormal fetal growth, aneuploidy

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## Contribution

What does this work add to what is already known?

The association of structural abnormality with a genetic defect and FGR at periviable gestation is invariably lethal.

What are the clinical implications of this work?

The combination of periviable FGR and structural defect in the absence of a confirmed genetic abnormality is associated with an overall chance of perinatal survival of one in three.

## Abstract

### Objective

To investigate the aetiology and the perinatal outcome of fetuses diagnosed with periviable fetal growth restriction (FGR) associated with structural defects or genetic anomalies.

### Methods

Retrospective study conducted at a referral Fetal Medicine unit. Singleton pregnancies seen between 2005 and 2018 in which FGR, defined by fetal abdominal circumference  $\leq 3$ rd percentile for the gestational age, was diagnosed between 22<sup>+0</sup>-25<sup>+6</sup> weeks of gestation were enrolled. The study group included periviable FGR associated with genetic or structural anomalies ("anomalous FGR"), while the control group consisted in structurally and genetically normal FGR ("non-anomalous FGR"). The results of the genetic tests, of the TORCH screening and of the post-mortem examination as well as the perinatal outcomes were investigated.

### Results

Of 255 cases, 188 fetuses were eligible, of whom 52 (28%) were anomalous FGR and 136 (72%) non-anomalous FGR. Confirmed genetic abnormalities accounted for 17/52 cases (33%) of anomalous FGR, with trisomy 18 constituting over 50% (9/17, 53%). The most common structural defects associated with FGR were CNS abnormalities (13/35, 37%). Overall, 12 cases survived the neonatal period. No differences were found in terms of perinatal survival between anomalous and non-anomalous FGR.

## Conclusions

Of anomalous FGR, most are associated with structural defects. The association of structural abnormality with a genetic defect and FGR at perivable gestation was invariably lethal, while the combination of perivable FGR and structural defect in the absence of a confirmed genetic abnormality was associated with survival into infancy in four out of five cases, with an overall chance of perinatal survival of one in three. These data can be used for the counselling of the prospective parents.

## Introduction

Fetal growth restriction (FGR) is strongly associated with poor neonatal condition at birth, impaired neurodevelopment and perinatal death. It is most commonly caused by placental insufficiency but may be secondary to other conditions such as intrauterine infections, congenital anomalies or genetic syndromes<sup>1,2</sup>.

According to the most widely accepted definition, early FGR is diagnosed when the criteria for impaired fetal growth are met before a gestational age cut-off threshold of 32 weeks<sup>3</sup>. Recent evidence has shown that the short term and the 2-year outcome of growth restricted fetuses from singleton gestations diagnosed between 26 and 32 weeks is unexpectedly good, the overall mortality being 8% and survival without impairment 82%<sup>4-8</sup>. More recently, two retrospective studies have also reported high survival rates for non-anomalous growth restricted fetuses diagnosed at periviable gestation between 22 and 26 weeks<sup>1</sup> and at previable gestational age between 17 and 22 weeks<sup>9</sup> albeit the different criteria used for the definition of fetal smallness<sup>10</sup>.

Though survival data for otherwise normal growth restricted babies is well reported, there is little or no data in relation to early FGR associated with structural or genetic abnormalities but it is our experience that these outcomes are thought to be universally poor. Such information would potentially be important in informing obstetric and neonatal planning decisions, however. Hence the aim of this study was to describe the aetiology of FGR diagnosed at periviable gestation associated with genetic or structural abnormalities ("anomalous FGR") and to compare its perinatal outcome with that of a cohort of FGR where there was no structural or genetic cause found ("non-anomalous FGR") of

comparable gestation.



## Methods

This was a retrospective cohort study conducted at a tertiary maternity unit between 2005 and 2018. We included all singleton pregnancies in which FGR was defined by fetal abdominal circumference (AC)  $\leq$ 3rd percentile for the gestational age<sup>11</sup>, diagnosed on ultrasound examination at a periviable gestation defined as being between 22<sup>+0</sup> and 25<sup>+6</sup> weeks. Once cases were identified from the ultrasound database (Astraia Software GmbH, Munich, Germany), review of electronic ultrasound records and, where appropriate, case notes was undertaken.

The study group included periviable FGR associated with antenatally diagnosed genetic or structural abnormality, while the control group consisted of structurally and/or genetically non-anomalous FGR. The aetiology and the short-term outcome of fetuses from our unit belonging to this latter group have been reported previously within a multicentre dataset<sup>1</sup>. Cases for which the postnatal outcome up to 28 days was incomplete or missing were excluded.

We considered the data retrieved from the first qualifying ultrasound examination in which the diagnosis of FGR was performed. A diagnosis of intrauterine death (IUD) at this “diagnostic scan” represented an exclusion criterion for the study.

Gestational age was based on dating at the routine first-trimester ultrasound, performed between 11<sup>+0</sup> and 13<sup>+6</sup> weeks of gestation. Fetal biometry and Doppler studies were performed by accredited fetal medicine specialists.

The maternal demographics included maternal age, parity and mode of conception, while the recorded ultrasound parameters consisted of the gestational age at inclusion, fetal anatomy assessment and biometry (biparietal diameter (BPD), head circumference (HC), AC, femur length (FL), estimated fetal weight (EFW) using the Hadlock four-parameter model<sup>12</sup>, and HC/AC ratio) as well as the subjective assessment of AFI (amniotic fluid volume), Doppler findings and the placental appearance. Doppler indices included umbilical artery (UA) pulsatility index (PI) and UA end-diastolic flow (EDF) and, where available, middle cerebral artery (MCA) PI, cerebroplacental ratio (CPR), ductus venosus (DV) PI and DV a-wave in the fetus as well as mean uterine artery (UtA) PI in the mother. The placenta was defined as abnormal if jelly-like as defined by a subjectively thickened placenta with patchy echogenicity<sup>13</sup> or calcified. Information regarding invasive testing and congenital infection screening tests was collected when available. Genetic testing was performed by QF-PCR and karyotype until 2014 and with CGH-array onwards. All data were anonymized and recorded on a preformatted Microsoft Excel 2007 spreadsheet. We did not collect information regarding previous medical and obstetric history as these data were not reported routinely in the ultrasound scan reports.

Fetal and maternal outcomes were retrieved from the hospital clinical database, while neonatal outcomes were obtained from the regional neonatal database (BadgerNet, NHS Patient Data Management System, Clevermed, Edinburgh, UK; CERNER, US Cerner Health Facts®, Cerner Corp., Kansas City, MO). For all cases we aimed to retrieve details on the results of the genetic investigations, of the TORCH screening as well as the post-mortem examination. Outcomes for pregnancies that were referred back to local hospitals for delivery were collected by direct telephone enquiries to the respective units. Gestational

age at delivery, diagnosis-to-delivery interval, birth weight and pregnancy outcome in terms of postnatal survival (i.e. live birth, neonatal death (NND), IUD and feticide/termination of pregnancy (TOP)) were among the evaluated postnatal data. NND was defined as a death within 28 days after birth.

Each case of periviable FGR with structural abnormality was assigned to a category based on the type of structural defect diagnosed. The following categories of structural abnormalities were identified: (1) central nervous system (CNS), (2) gastrointestinal (GI), (3) cardiac, (4) genitourinary, (5) skeletal, (6) thoracic, (7) multiple malformations and (8) minor abnormalities. For data analysis, all cases with either a structural or a genetic defect were pooled in the “anomalous FGR” group, whose features and outcomes were eventually compared to that of the “non-anomalous FGR” group, which represented the control. In order to allow for true comparisons in relation to the primary outcome – i.e. the perinatal outcome of “anomalous FGR” compared to that of “non-anomalous FGR” – cases that underwent TOP were excluded in both groups.

For this study, research ethics approval was not required as all cases were routinely and retrospectively collected and datasets were fully anonymized prior to analysis, and was registered with the audit department.

Statistical data analysis was performed with IBM SPSS Statistics v. 20.0 (IBM, Armonk, NY, USA). Outcome frequencies were calculated and compared across the groups with the Kruskal–Wallis test. We considered  $p < 0.05$  as statistically significant. This study was reported according to the STROBE guidelines<sup>14</sup>.

## Results

Overall, 188 fetuses were eligible, of whom 52 (27.7%) were anomalous FGR and the remaining 136 (72.3%) were non-anomalous FGR (Figure 1).

The demographic features and the sonographic findings at diagnosis in anomalous and in non-anomalous FGR are summarized in Table 1. In the “anomalous” FGR group a significantly higher number of invasive testing was performed (71.2% vs 39.0%,  $p < 0.001$ ), while the occurrence of hypertensive disorders of the pregnancy was almost eight times higher in the “non-anomalous” group (30.1% vs 3.8%,  $p < 0.001$ ). As regards the sonographic findings, a significantly higher frequency of normal amniotic fluid was noted and the subjective appearance of the placenta appeared more frequently normal in the “anomalous” compared to the “non-anomalous” FGR group (63.5% vs 47.8% and 94.2% vs 69.9%,  $p < 0.01$  for both). As regards the Doppler parameters at diagnosis, a significantly lower UA PI and a significantly lower frequency of absent/reversed EDF were noted in the “anomalous FGR” group ( $p = 0.04$  and  $p < 0.01$ ), while the CPR was significantly lower ( $p = 0.02$ ) in the “non-anomalous” FGR group.

Table 2 shows the perinatal outcome according to the categorization of the underlying cause of FGR in the “anomalous” group. Genetic testing was performed in 90/188 cases (47.8%), most commonly in the “anomalous” group (37/52, 71.2% vs 53/136, 39.0%,  $p < 0.001$ ), and declined in the remaining. Antenatally or postnatally confirmed genetic abnormalities accounted for 17/52 (32.7%) cases of anomalous FGR, among whom trisomy 18 occurred in over 50% of cases (9/17, 52.9%). The most common structural defects associated with FGR were represented by CNS abnormalities (13/35, 37.1%), with those

involving the posterior fossa were diagnosed in over two third of cases (9/13, 69.2%), while gastrointestinal abnormalities represented the second most common abnormality associated with FGR in the “anomalous FGR” group (8/35, 22.9%). Overall, 12 “anomalous” cases survived the neonatal period, while NND, IUD and TOP were recorded in 8, 12 and 18 cases, respectively.

The association of perivable FGR and structural abnormality within the context of a genetic defect proved to be invariably lethal as all but one case did not survive beyond the neonatal period and the remaining case, that of Russell-Silver syndrome, died at 10 months of age. The combination of perivable FGR and structural defect in the absence of a confirmed genetic abnormality was associated with long-term survival into infancy in 10 out of 12 cases (83.3%) that survived the neonatal period.

The survival rate according to the gestational age at delivery in anomalous and non-anomalous FGR is shown in Figure 2 and summarized in Table S1. Below 28 weeks none of the anomalous and only 7% of the non-anomalous FGR were alive after 28 days of life, however the perinatal survival showed a progressive increase throughout gestation in both groups up to 73% and 89% in the “anomalous” and in the “non-anomalous” group, respectively. Statistical comparison did not yield significant difference between the two groups with the only exception of the gestational age window comprised between 32<sup>+1</sup> and 36<sup>+0</sup> weeks (22% survival for “anomalous” FGR vs 82% survival for “non-anomalous” FGR,  $p < 0.01$ ). The TOP rate was not significantly different between the two groups (18/52, 34.6%, in the “anomalous” groups vs 29/107, 27.1%, in the “non-anomalous” group,  $p 0.06$ ).

The relationship between delivery characteristics and perinatal outcome in non-anomalous and anomalous FGR is shown in Table 3. The “anomalous FGR” group showed mean gestational age at delivery and birthweight significantly higher compared to the “non-anomalous FGR” group ( $34^{+0}$  weeks ( $25^{+0} - 42^{+1}$ ) vs  $28^{+3}$  ( $23^{+0} - 41^{+2}$ ),  $p < 0.01$  and 1280 grams ( $262 - 3420$ ) vs 610 ( $200 - 3420$ ),  $p 0.04$ , respectively), however no differences were found in terms of perinatal outcome and overall short-term survival.

## Discussion

In anomalous FGR diagnosed between 22<sup>+0</sup> and 25<sup>+6</sup> weeks of gestation the combination of periviable FGR and structural abnormality within the context of a genetic defect was invariably lethal, while in the absence of a confirmed genetic abnormality the survival into infancy occurred in four out of five cases. The overall survival at one month of age was approximately one quarter, this being strongly related to gestation of delivery, and was not different to non-anomalous FGR. Given that APGAR scores, cord pH values and the caesarean section rate was no different in the two groups, it is unlikely that obstetric management played a part in the birth and neonatal outcomes.

No data exists on the aetiology and the perinatal outcomes of early FGR associated with genetic abnormalities or structural defects. Indeed, in the studies on FGR including two large Randomized Controlled Trials<sup>4,5,15-17</sup>, early FGR was considered as one diagnostic group and assumed to be of uteroplacental origin, while cases affected by structural and/or genetic abnormalities represented exclusion criteria for these studies. This means that FGR with other abnormalities remains systematically unreported. Our data show that umbilical and cerebral Doppler abnormalities, and oligo/anhydramnios associated with uteroplacental insufficiency were more common in the “non-anomalous FGR” group, as might be expected based on the biology of the different aetiologies of FGR. Indeed, oligohydramnios and abnormal appearance of the placenta are common features of uteroplacental insufficiency but not of FGR secondary to different aetiologies, therefore it is not surprising that the placental appearance was almost invariably normal and the amniotic fluid within or above the normal range in seven out of ten cases of “anomalous FGR”.

These findings demonstrate the importance of a thorough anatomical assessment in fetuses diagnosed with periviable FGR. Furthermore, the short-term survival of anomalous FGR was not different from FGR of presumed uteroplacental origin except for a gestational age at delivery between 32 and 36 weeks of gestation. However, where a diagnosis of “anomalous” FGR was made, they proceeded to a later gestation and higher birthweight compared to periviable FGR of presumed uteroplacental origin. This is explained in part by the different biology of the two conditions, being the uteroplacental aetiology commonly associated with fetal Doppler abnormalities which may indicate early delivery<sup>4,5</sup>, in part by the higher incidence of hypertensive conditions in FGR of presumed uteroplacental origin, which we also found in our cohort and is consistent with the aetiology of early FGR of uteroplacental origin<sup>2,4,5,7,8</sup>. More specifically, where a baby with a genetic abnormality was liveborn, this was almost invariably lethal within 28 days from birth. The only exception was a fetus affected by Russel Silver Syndrome who survived to 10 months of age. When considering FGR associated with structural defects in the absence of a confirmed genetic abnormality, survival beyond the neonatal period occurred in one third and fetal losses were observed in combination of FGR where these abnormalities were potentially compatible with survival had FGR not supervened.

Data on periviable FGR from our unit and elsewhere, which include those presented in the current manuscript and those previously published<sup>1</sup>, suggest that FGR diagnosed between 22 and 26 weeks represents a major risk factor for poor pregnancy outcome being associated with a perinatal survival ranging between 30% and 40%. The results previously published on a small case series of structurally and genetically normal fetuses identified as small before 24 weeks gave a survival-until-discharge rate of 60%<sup>18</sup>. More recently, a larger



cohort presented by Temming et al on fetuses diagnosed with FGR between 17 and 22 weeks<sup>9</sup> reported remarkably lower percentages of stillbirth (2.5%) and neonatal death (1.4%) and higher mean birthweight and gestational age at delivery compared to previous studies<sup>1,18</sup>. However, it is important to point out that the criteria adopted for the definition of FGR were different across the studies<sup>10</sup>. In the paper by Temming, FGR was defined based on an estimated fetal weight less than the 10<sup>th</sup> percentile according to the definition adopted by the American College of Obstetricians and Gynecologists<sup>19</sup>, whereas in the current study FGR was defined according to the consensus definition by Gordijn et al<sup>3</sup> as we do believe that a cut-off threshold of the 3<sup>rd</sup> percentile is more reliable in defining pathological smallness only based on biometry criteria, in the absence of information on maternal or fetal Doppler.

The main strength of this study is that there is no previously published data on early FGR associated with structural abnormalities. We are aware that due to our decision to define periviable FGR only based on biometry criteria and not on the basis of the combination of biometry and Doppler criteria<sup>3</sup> an undefined number of cases of fetuses fulfilling the criteria for periviable FGR may have been not included in the study cohort, however we believe that the definition of FGR used for the inclusion of cases has led to the identification of a more homogeneous population for paired comparison between anomalous and non-anomalous cases. Additionally, this group consisted of a heterogeneous cohort of periviable FGR from the point of view of aetiology and malformations, however to allow for true comparisons cases that underwent TOP were excluded in both groups as the TOP rate was not significantly different between the “anomalous” and the “non-anomalous” group. Of note, the perinatal outcome according to gestational age at delivery was not dissimilar prior to

and after exclusion of cases of TOP. Therefore, it is unlikely that the exclusion of such cases of TOP has impacted on the results. A limitation is that half of the cases from our cohort overall did not undergo genetic testing antenatally or postnatally. Finally, over a quarter of the potentially eligible cases were excluded due to missing neonatal outcome, we cannot say whether this data was truly missing at random or not.

In conclusion, this study adds knowledge on the aetiology and the perinatal outcome of anomalous FGR diagnosed at periviable gestation. Our findings suggest that the outlook of structurally abnormal FGR is not dissimilar to that of FGR of uteroplacental origin in terms of perinatal survival, while genetic abnormalities almost invariably carry a poor prognosis. These data can be used for counselling of the prospective parents.

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## Figure legends

Figure 1 - Flow chart according to STROBE guidelines (14) for inclusion of cases.

Figure 2 – A) Perinatal outcome of 182 cases of periviable fetal growth restriction (FGR) (50 anomalous and 132 non-anomalous) according to gestational age at delivery. (Two anomalous cases had unknown gestational age at delivery: one IUD and one TOP. Four non-anomalous cases had unknown gestational age at delivery: one NND and three IUD). B) Perinatal outcome of 135 cases of periviable FGR (32 anomalous and 103 non-anomalous) according to gestational age at delivery after exclusion of TOP. (One anomalous case had unknown gestational age at delivery: IUD. Four non-anomalous cases had unknown gestational age at delivery: one NND and three IUD). IUD: intrauterine death. TOP: termination of the pregnancy. NND: neonatal death. Survived: survived neonatal period.

Figure 1 - Flow chart according to STROBE guidelines (13) for inclusion of cases.

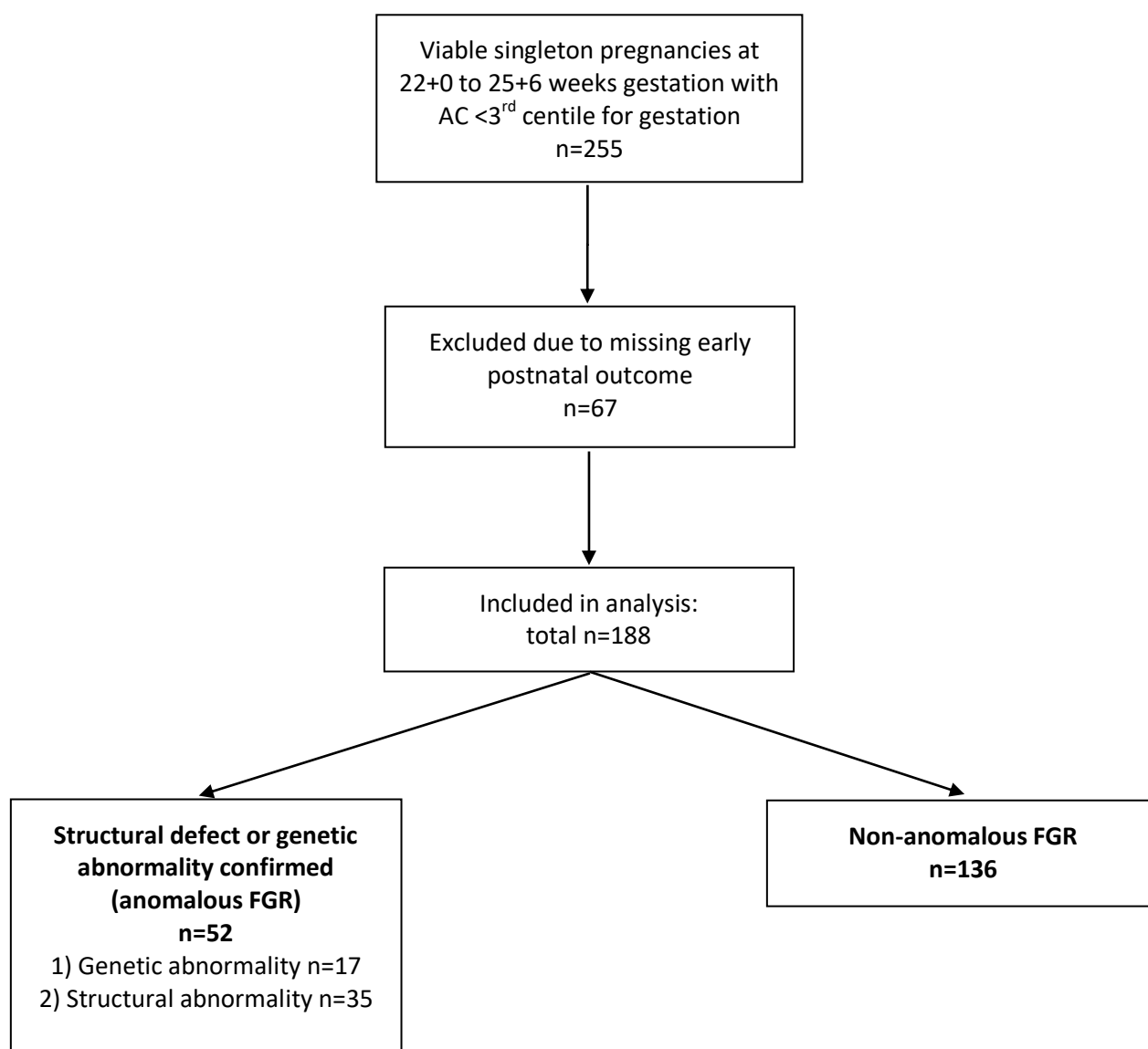
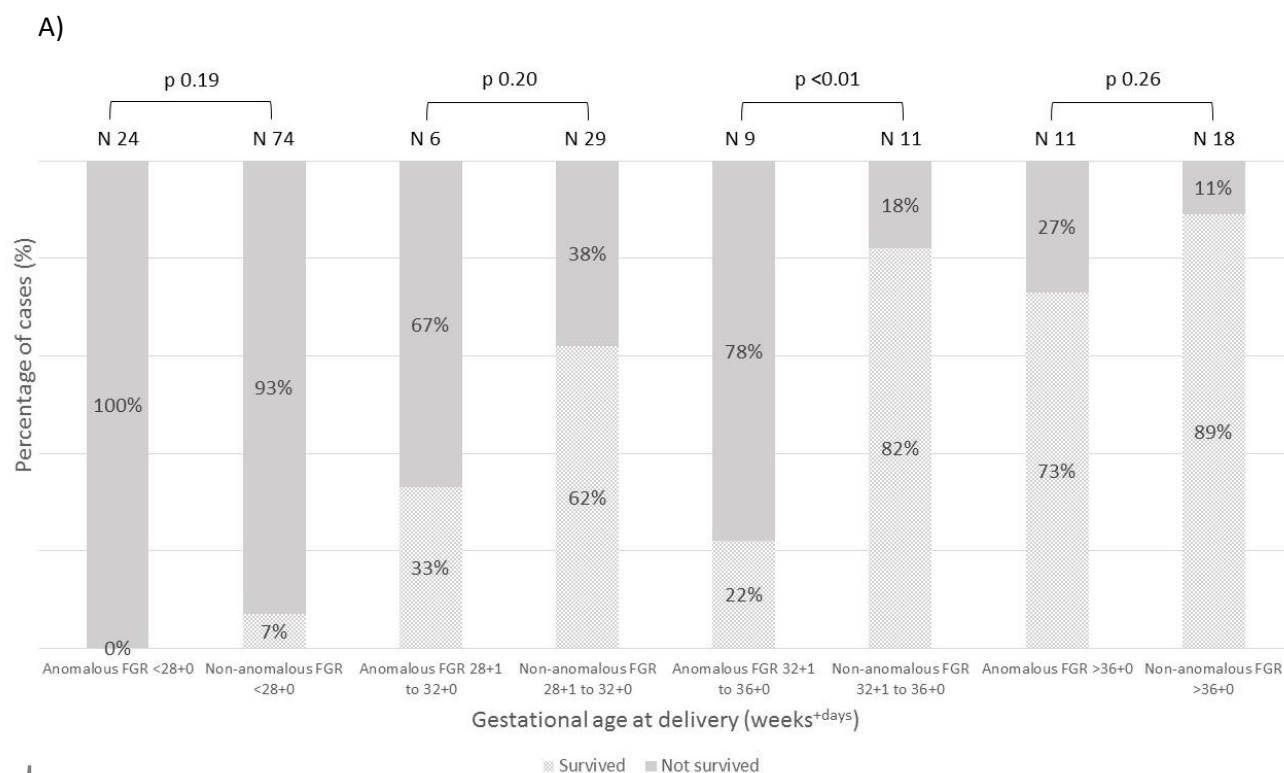




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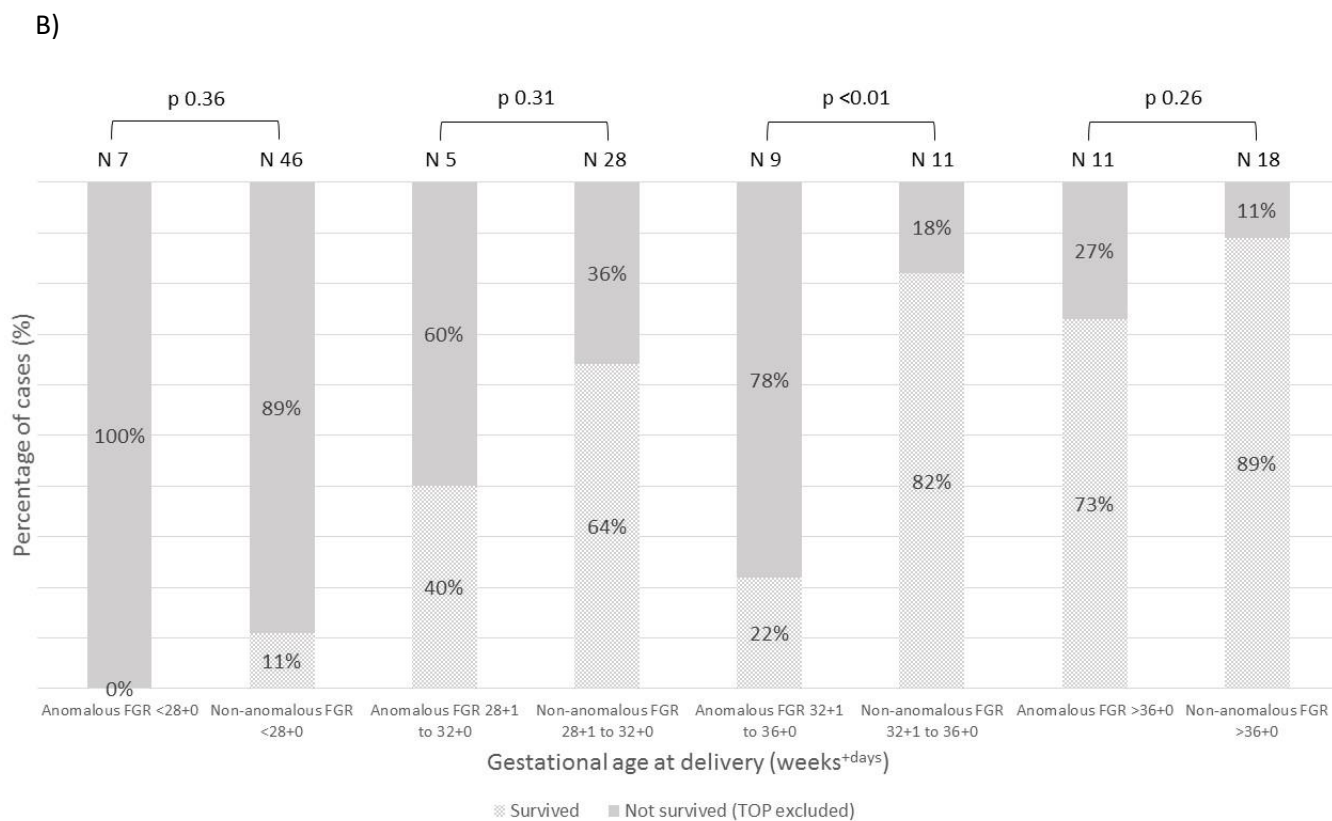


Table 1 – Demographic features and sonographic findings at diagnosis in the included cases.

	Anomalous FGR N 52	Non-anomalous FGR N 136	p*
<b>Baseline demographics</b>			
Maternal age (years) Median (range)	29 (17 – 43)	32 (17 – 46)	0.01
Parity n (%) n=124	Nulliparae 14 (43.8%)	Nulliparae 44 (47.8%)	0.69
IVF conception n (%)	0 (0%)	6 (4.4%)	0.12
Genetic testing n (%)	37 (71.2%)	53 (39.0%)	<0.001
Hypertensive disorder of the pregnancy n (%)	2 (3.8%)	41 (30.1%)	<0.001
<b>Characteristics at diagnosis</b>			
Gestational age (weeks <sup>+days</sup> ) Median (range)	23 <sup>+4</sup> (22 <sup>+0</sup> – 25 <sup>+6</sup> )	23 <sup>+4</sup> (22 <sup>+0</sup> – 25 <sup>+5</sup> )	0.77
Amniotic fluid volume n (%)	Normal 33 (63.5%) Oligo/anhydramnios 16 (30.8%) Polyhydramnios 3 (5.8%)	Normal 65 (47.8%) Oligo/anhydramnios 71 (52.2%) Polyhydramnios 0 (0%)	<0.01
Placental appearance n (%)	Normal 49 (94.2%)	Normal 95 (69.9%)	<0.01
EFW (grams) Median (range)	378 (194 – 518)	345.5 (168 – 586)	0.75
AC (mm) Median (range)	147 (120 – 180)	149 (107 – 180)	0.40
AC/HC ratio Median (range)	1.31 (1.00 – 1.63)	1.25 (1.11 – 1.55)	0.07
Uterine PI Median (range) n=107	1.33 (0.51 – 2.28)	1.68 (0.72 – 3.35)	0.10
Umbilical artery PI Median (range) n=133	1.42 (0.90 – 3.74)	1.66 (0.63 – 4.16)	0.04
Umbilical artery EDF n (%) n=168	Positive 30 (76.9%) Absent 6 (15.4%) Reverse 3 (7.7%)	Positive 55 (42.6%) Absent 53 (41.1%) Reverse 21 (16.3%)	<0.01
MCA PI Median (range) n=130	1.45 (0.93 – 2.87)	1.37 (0.80 – 4.49)	0.08
CPR Median (range) n=99	1.05 (0.56 – 3.09)	0.78 (0.30 – 4.05)	0.02
DV PI Median (range) n=36	0.70 (0.22 – 0.81)	0.82 (0.35 – 1.40)	0.13
DV A wave	Positive 26 (96.3%)	Positive 99 (85.3%)	0.28

<b>n (%)</b> <b>n=143</b>	Absent 1 (3.7%) Reverse 0 (0%)	Absent 11 (9.5%) Reverse 6 (5.2%)	
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Data presented as number (%) or as median (range)

\*p values for Chi-square test and Mann-Whitney U-test

n 188 unless otherwise stated

EFW: estimated fetal weight

AC: abdominal circumference

HC: head circumference

PI: pulsatility index

EDF: umbilical artery end diastolic flow

MCA: middle cerebral artery

CPR: cerebroplacental ratio

DV: ductus venosus

Table 2 – Genetic abnormalities and structural defects in the “anomalous FGR” group.

	Type of abnormality (n)	Perinatal outcome (n)
<b>Genetic abnormality</b> n=17	Trisomy 18 (9)	TOP (4) IUD (4) NND (1)
	Trisomy 21 (1)	IUD
	Trisomy 13 1	TOP
	Trisomy 22 mosaic (1)	TOP
	Triploidy (1)	IUD
	Russell Silver syndrome (1)	Survived neonatal period but died at 10 months of age
	Wolf Hirschhorn syndrome (1)	NND
	Osteogenesis imperfecta (1)	TOP
	“Abnormal” amniocentesis but unknown result (1)	TOP
<b>Structural defect</b> n=35	CNS abnormality (13) - Posterior fossa abnormality (9) - ACC (1) - Complex abnormality of the brain development (1) - Spina bifida (1) - Ventriculomegaly (1)	TOP (6) IUD (2) NND (3) Survived neonatal period (2)
	Gastrointestinal abnormality (8) - Exomphalos (5) - Gastroschisis (2) - Bowel obstruction (1)	NND (1) Survived neonatal period (6) Survived neonatal period but died at 3 months of age (1)
	Multiple major abnormalities (4)	TOP (1) IUD (2) NND (1)
	Cardiac abnormalities (3) - CoA (2) - Tetralogy of Fallot (1)	IUD (1) NND (1) Survived neonatal period (1)
	Renal abnormalities (2) - Bilateral renal agenesis (2)	TOP (2)
	Skeletal abnormalities with normal genetic testing (2)	TOP (2)
	Thoracic abnormalities (1) - CDH (1)	Survived neonatal period (1)
	Other structural abnormalities (2) - Bilateral talipes (2)	IUD (2)

FGR: fetal growth restriction

CNS: central nervous system

ACC: agenesis of the corpus callosum

CoA: coarctation of the aorta

CDH: congenital diaphragmatic hernia

TOP: termination of the pregnancy

IUD: intrauterine death

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Table 3 – Delivery and perinatal outcome of the included cases.

	<b>Anomalous FGR N 52</b>	<b>Non-anomalous FGR N 136</b>	<b>p*</b>
<b>Gestational age at delivery (weeks<sup>+days</sup>)</b> <b>Median (range)</b> <b>(TOP excluded)</b> <b>n=135</b>	34 <sup>+0</sup> (25 <sup>+0</sup> – 42 <sup>+1</sup> )	28 <sup>+3</sup> (23 <sup>+0</sup> – 41 <sup>+2</sup> )	<0.01
<b>Birthweight (grams)</b> <b>Median (range)</b> <b>(TOP excluded)</b> <b>n=126</b>	1280 (262 – 3420)	610 (200 – 3420)	0.04
<b>Diagnosis-to-delivery interval (weeks<sup>+days</sup>)</b> <b>Median (range)</b> <b>(TOP excluded)</b> <b>n=135</b>	9 <sup>+4</sup> (0 <sup>+0</sup> – 17 <sup>+3</sup> )	5 <sup>+1</sup> (0 <sup>+3</sup> – 18 <sup>+1</sup> )	0.07
<b>Mode of delivery</b> <b>n (%)</b> <b>(TOP excluded)</b>	Vaginal 19 (57.6%) Caesarean section 14 (42.4%)	Vaginal 49 (45.8%) Caesarean section 58 (54.2%)	0.24
<b>APGAR 1</b> <b>Median (range)</b> <b>(TOP &amp; IUD excluded)</b> <b>n=75</b>	9 (1 – 10)	7 (1 – 10)	0.07
<b>APGAR 5</b> <b>Median (range)</b> <b>(TOP &amp; IUD excluded)</b> <b>n=75</b>	9 (0 – 10)	9 (3 – 10)	0.07
<b>Arterial pH</b> <b>Median (range)</b> <b>(TOP &amp; IUD excluded)</b> <b>n=40</b>	7.26 (6.96 – 7.40)	7.26 (6.90 – 7.38)	0.94
<b>Perinatal outcome</b> <b>n (%)</b>	Survived 12 (23.1%) NND 8 (15.4%) IUD 13 (25.0%) TOP 19 (36.5%)	Survived 48 (35.3%) NND 15 (11.0%) IUD 44 (32.4%) TOP 29 (21.3%)	0.09
<b>Perinatal outcome</b> <b>n (%)</b>	Survived 12 (23.1%) Not survived 40 (76.9%)	Survived 48 (35.3%) Not survived 88 (64.7%)	0.11

\*p values for Chi-square test and Mann-Whitney U-test

n=188 unless otherwise stated

FGR: fetal growth restriction

TOP: termination of the pregnancy

IUD: intrauterine death