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Short term outcome of Periviable SGA: Is our counseling up to date?

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ABSTRACT

Objective

There is limited data for counseling and management of periviable small for gestational age fetuses. We aim to investigate short term outcome in periviable SGA fetuses and relate this to the underlying cause.

Methods

Retrospective database study conduced in three London tertiary fetal medicine centres between 2000 and 2015. We included viable singleton pregnancies with abdominal circumference ≤ 3rd percentile between 22+0 and 25+6 weeks. Data obtained included biometry and placental anomalies, uterine and fetal Doppler and neonatal outcome. We excluded those cases with demonstrated structural abnormalities, proven or suspected abnormal karyotype or genetic syndromes. Cases were categorised as uteroplacental insufficiency, evidence of placental damage with normal uterine artery Doppler, viral infection or unclassifiable.

Results

245 cases were included. At diagnosis 201/245 (82%) were categorised as uteroplacental; 13/245 (5.3%) as suspected placental and 30 could not be assigned to any of these categories. Overall, 101/245 (41%) survived; the rate of in utero fetal demise was 89/245 (36%), 22/245 (9%) were neonatal deaths and 33/245 (14%) of pregnancies were terminated. The diagnosis to delivery interval was 8.1 weeks in those that survived, 2.7 weeks in those that died in utero and 3.9 weeks in those that died neonatally.

Conclusions

Over 90% of periviable SGA cases are associated with uteroplacental insufficiency or intraplacental damage. Survival is related to gestation at delivery, with outcomes better than might be assumed at diagnosis and some pregnancies reaching term.

INTRODUCTION

Despite recent improvements in perinatal survival after birth at preterm gestation as detailed in large prospective studies such as TRUFFLE[1], EPICURE[2], or GRIT[3], management of pregnancies with a very small fetus near the limit of viability remains a challenge[4]. The perinatal and 2-year neurodevelopmental outcomes of growth restricted babies identified after 26 weeks have been evaluated and well characterised in randomised controlled trials, aiding prognostication and counselling[1,3,5]. However, when the diagnosis occurs before 26 weeks of gestation, there are scant data to aid in counseling regarding prognosis; this is particularly important as babies with these conditions combine two major risk factors for morbidity and mortality: pathological smallness and likely extreme prematurity[6,7]. This is usually due to medically indicated preterm delivery because of fetal deterioration or maternal complications.

Careful counseling of the parents is required in such cases in order to have realistic expectations of what the outcome is likely to be, in order to reach a decision on whether (and, if so, when) intervention by delivery is appropriate or desirable[3,6] and what level of neonatal intervention is likely to be required. Given the very limited data on which these decisions are based currently, we aimed to determine the outcome of periviable SGA babies in relation to the likely underlying cause and its natural history in fetuses that were structurally and presumed to be chromosomally/genetically normal at the time of SGA diagnosis.

It is important to note that the terms small for gestational age (SGA) and fetal growth restriction (FGR) are frequently used in different ways and the definitions are not uniform even in international guidelines. We therefore use the term SGA to describe a fetus whose size based on ultrasound scan is very small in relation to gestation without any other qualifying characteristics.

MATERIALS AND METHODS

This was a multicentre retrospective database study conducted in the fetal medicine departments of three tertiary London perinatal units: Queen Charlotte's and Chelsea Hospital (QCCH), Guys and St Thomas's Hospital (GSTH) and St George's Hospital (SGH). All singleton, severely small fetuses, defined as abdominal circumference (AC) ≤3rd percentile for gestation (AC calculated according to UK recommended standard and Chitty chart[8]) diagnosed on ultrasound between 22^{+0} and 25^{+6} weeks from 2000 to 2015 were identified from medical databases used for routine clinical care: Astraia (Astraia software GmbH, Munich) at QCCH and GSTH and Viewpoint (GE healthcare software, Frankfurt) at SGH. For this study research ethics approval was not required as all cases were routinely and retrospectively collected and datasets were fully anonymised prior to analysis. Once the cases were identified, review of electronic ultrasound records and, where appropriate, case notes was undertaken.

The first qualifying ultrasound scan within the set gestation was considered to be the "sentinel scan" and its findings were analysed for the study. Fetuses where intrauterine death (IUD) was diagnosed at the sentinel scan were not included in this study. The gestational age was based on routine first trimester ultrasound dating between 11^{+0} and 13^{+6} weeks' gestation. Fetal biometry and Doppler studies were performed by fetal medicine specialists using a variety of ultrasound machines over the 15 year period. Maternal demographic data were collected including maternal age, parity and diagnosis of pre-eclampsia (PE). Ultrasound parameters were gestational age at inclusion, fetal anatomical assessment, fetal biometry (biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), estimated fetal weight (EFW) using the Hadlock 4 parameter model[9], HC/AC ratio as well as subjective assessment of amniotic fluid volume and placental appearance. Doppler indices included umbilical artery

pulsatility index (UA PI) and umbilical artery end diastolic flow (UA EDF) and, where available, middle cerebral artery pulsatility index (MCA PI), cerebro-placental ratio (CPR), ductus venosus pulsatility index (DV PI) as well as DV a-wave and maternal uterine artery Doppler pulsatility index (Ut Art PI). Information regarding invasive testing and congenital infection screening tests was collected if available. All data was collected anonymised in all centres from a preformatted Excel (Microsoft Corp 2007) spreadsheet. We did not collect information regarding previous medical and obstetric history and mode of conception as this data was not routinely reported in the ultrasound scan reports.

The fetal outcomes were collected from the hospital clinical databases and neonatal outcomes obtained from the regional neonatal database (Badgernet, NHS Patient Data Management System). Outcomes for pregnancies that were discharged from the tertiary centres and referred back to local hospitals for delivery were collected by direct telephone enquiries to the respective units. Postnatal data collected consisted of gestation at delivery, diagnosis-to-delivery interval, birthweight and pregnancy outcome in terms of postnatal survival (i.e.livebirth, neonatal death (NND), IUD and fetocide / termination of pregnancy (TOP). Neonatal death was defined as a death within 28 days after birth. We excluded cases where the postnatal outcome was incomplete or missing. Also excluded were cases with ultrasonographically suspected or confirmed (following an abnormal invasive test result) underlying genetic/chromosomal abnormalities or stigmata of infection.

Each case was selected into a category of suspected underlying cause of small fetal size by the study investigators, two of whom in each centre reached consensus if there was uncertainty about the categorisation. In order to mirror clinical practice this initial categorisation was exclusively

based on the antenatal ultrasound findings documented by the operator at the time of diagnosis at sentinel scan. The operator had no access to the outcome of the case at the time of sentinel scan. Each case was then reviewed a second time postnatally with the knowledge of genetic and infectious screening results - if available - as well as with knowledge of postnatal outcome. In some cases the antenatally suspected cause and categorisation differed from the postnatal cause. The cases were classified into one of four mutually exclusive categories depending on suspected underlying cause:

- Uteroplacental: uterine artery PI above 95th percentile for gestation and/or bilateral notches and/or reduced amniotic fluid.

- Placental: ultrasound evidence of placental abnormality (thickened placenta, extensive lakes or jelly like appearance) with the presence of normal uterine artery Doppler assessment (PI below the 95th centile and absence of bilateral notches).

- Congenital infection.

- Unclassified: in cases that did not fulfill the criteria for the defined categories above, and where no antenatal cause of fetal growth restriction was initially identified.

Statistical data analysis was performed with SPSS Statistical software version 20. Outcome frequencies were calculated and compared across the groups with the Kruskal-Wallis test. We considered $p<0.05$ as significant.

RESULTS

471 pregnancies were identified: 239 from QCCH, 51 from GSTH and 181 from SGH. 245/471 singleton pregnancies fulfilled the inclusion criteria (Figure 1). The median gestational age at sentinel ultrasound was 23^{+4} (22^{+0} – 25^{+6}) weeks gestation. Mothers had a median age of 32 (17–46) years, with 54% nulliparous women and 33% of mothers with PE in the included pregnancy. 75/245 patients underwent viral infection testing. Of the 245 cases 55 underwent invasive testing which confirmed normal results. In 190/245 cases invasive testing was declined by the parents, not offered nor undertaken by the clinicians and of these 3 had low risk results from non-invasive cell free fetal DNA testing.

There were no significant differences between the baseline demographic data (maternal age, gestation at diagnosis, AC, EFW, placental appearance) for the cases analysed (245 cases of structurally normal fetuses with known outcome) and those cases of structurally normal fetuses excluded because of missing outcome data (79 cases). However, PE was more common in those analysed compared to those with no outcome (33% versus 16% p=0.04). Of 245 pregnancies, 33 underwent termination of pregnancy by fetocide or medical TOP; 89 died in utero (IUD) and 123 were liveborn. Of these 101/123 (82%) survived the neonatal period. Figure 2 shows the fetal outcome by categorisation at sentinel scan. Of the 123 babies born alive those born below 28 weeks the survival rate was 13%. Survival increased progressively to 59% between 28 and 32 weeks, to 80% between 32 and 36 weeks and to 94% above 36 weeks (Table 1 and figure 3). Antenatal categorisation at sentinel scan according to the suspected underlying cause identified 201 cases of uteroplacental cause; 13 cases of placental cause and 1 case of suspected viral cause. This case had no ultrasound stigmata typical of in utero infection but there was a clinical history of possible maternal infection which lead to the categorisation at sentinel scan. The remaining 30/245 cases were unclassified. Antenatal ultrasound findings of the included cohort are shown in

table 2. Cases that changed their antenatal category postnatally are shown in table 3. There were 10 cases that were categorised as unclassified antenatally and changed category after postnatal review. Furthermore, there was one case that was antenatally categorised as uteroplacental – and changed to the category unclassified postnatally.

The relationship between antenatal and delivery characteristics in relation to postnatal outcome are shown in table 4: those babies that survived had higher birthweights and a longer diagnosis-delivery interval then those that were IUD, NND and underwent TOP. There were significant differences in the median birthweight, diagnosis-to-delivery interval and Table 5 shows the outcomes by categorisation of SGA: the incidence of PE was highest in SGA associated with uteroplacental insufficiency (34%) and gestation longest in those cases that were unclassified (34.9 weeks). APGAR scores between those fetuses that survived and those that suffered a neonatal death (NND).

There were 143/245 (58.5%) vaginal deliveries and among these two were instrumental deliveries. In 2/245 (1%) no information on mode of delivery was available. Of the 99/245 (40.5%) Caesarean sections, 64/99 (65%) were planned Caesarean sections and 35 (35%) were emergency procedures. Among the 101/245 fetuses (41%) that survived, 82/101 (81%) were delivered by Caesarean section and 18/101 (18%) were delivered vaginally. In one survivor, the mode of delivery was unknown. There were 22/245 neonatal deaths. 5/22 (23%) were delivered vaginally and 16/22 (72.5%) were delivered by Caesarean section. In one neonatal death the mode of delivery was unknown.

DISCUSSION

In this cohort of very small fetuses identified at periviable gestation, survival overall was 41% and, ranging from 13% if delivery was <28 weeks up to >90% if babies were delivered at beyond 36 weeks. The majority of these cases had uteroplacental insufficiency. Noteworthy is that where severely small fetal biometry was identified at periviable gestation, 15% of pregnancies were delivered after 36 weeks with good outcome. Outcome is worse in cases of uteroplacental insufficiency than in those with a primary placental cause; nearly one third of women with uteroplacental SGA develop PET, twice as many as those with placental cause or unclassified SGA. The pregnancies progressing longest from diagnosis and with the best prognosis are those where a cause for SGA cannot be classified at the sentinel scan. These data are of clinical relevance as counseling for parents can be based on the cause identified at sentinel scan.

The small fetus remains a challenge to define and diagnose and there may be overlap between SGA and true FGR, especially if diagnosed at periviable gestation[10]. Doppler and placental assessment carries both diagnostic and prognostic value[11] allowing most fetuses to be classified at presentation. The great majority of structurally normal fetuses found to measure very small at periviable gestation were classified into the utero-placental category, a smaller number of pregnancies being affected by primary placental abnormality and only one by a confirmed viral infection. Twelve percent had no obvious antenatal pathological cause found at sentinel scan and the majority of these fetuses (53%) survived, with the others dying as a result of TOP, IUD or NND. Although it was not possible at time of diagnosis to differentiate between FGR and SGA in all cases, the unclassified cases were likely to represent SGA as they showed no stigmata of uteroplacental or placental problems and some reached a gestation close to term.

In very small fetuses at periviable gestation the differentiation between SGA and FGR is important as it guides prognosis. By measuring and describing the relevant ultrasound findings we are able to classify most fetuses at presentation at periviable gestation, however it remains difficult to predict with any level of precision which fetuses will die in utero or which will progress for many weeks or even to term before requiring delivery. Though termination of pregnancy is often discussed at initial presentation, given the range in gestation at eventual delivery may be far greater than expected, there is in fact little to be lost by conservative management.

When the small fetus has reached a potentially viable weight and gestation the challenge is to optimise timing of delivery: balancing the risk between intrauterine demise or hypoxic damage while gaining maturity versus delivering a live baby at risk of neonatal complications from prematurity and underlying growth restriction[2]. Post delivery neonatal morbidity in fetuses with severe FGR includes respiratory and gastro-intestinal complications and neuro-developmental delay. Not surprisingly, the prognosis of a structurally normal, growth restricted fetus is determined by gestation at delivery, birthweight and cardiovascular status [12,13,14,15].

The strength of this study is that we collected data from three large specialist perinatal centres, making it the largest dataset on periviable fetal growth restriction reported. The three centres had similar reporting and management strategies, though they cannot be considered to be entirely uniform as no guidelines existed (or indeed even exist now) in relation to periviable SGA. This latter point emphasizes the importance of our data and findings. The cases are well characterised and almost all the antenatal and outcome data were held in computerised databases. The data are likely to be valid in other populations due to the diverse mix of ethnicities and socioeconomic backgrounds. We acknowledge the limitations of these data which was retrospectively collected and necessarily only cases where the outcome was known could be included.

Further, it was not possible to investigate the effect of steroid administration, magnesium sulphate use and mode of delivery as this information was not held in the fetal medicine databases and not uniformly documented in delivery databases. This does not affect the validity of the findings, but it does mean that the perinatal/obstetric factors that may contribute to better or worse outcome could not be sub-analyzed. There were a number of cases lost to follow up but this was not a systematic failing as the demographic details did not differ between the cases where outcome was known and not known. No longer term infant or child follow up data are included: this is desirable for a future prospective study.

CONCLUSION

This study contributes to the knowledge on short term outcome of severely small fetuses diagnosed at the limits of viability. The findings suggest that many pregnancies progress weeks beyond what might be envisaged and several unexpectedly reached close to term. We urge caution in offering termination of pregnancy as it is frequently impossible to prognosticate and in particular to predict how long the pregnancy will progress.

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Table 1:

Fetal outcome by gestational age

Delivery at	≤28+0 Weeks	28+1 to 32+0 weeks	32+1 to 36+0 weeks	>36 +0 weeks	Gestation at delivery not known
Survived N 101	17 (13%)	31 (59%)	19 (80%)	34 (94%)	0
Neonatal death N 22	12 (9%)	6 (11%)	1 (4%)	2 (6%)	1
IUD N 89	68 (53%)	14 (26%)	4 (16%)	0	3
Fetocide/TOP N 33	31 (25%)	2 (4%)	0	0	0
Total N 245	128	53	24	36	4

IUD=Intra uterine death

TOP=termination of pregnancy

Table 2:

Antenatal ultrasound features at sentinel scan (n=245)

		N	%
EFW (g) n=245	353 (166 to 677)*	-	-
HC/AC ratio n=245	1.26 (0.98 to 1.55)*	-	-
Amniotic fluid subjective assessment n=234	Anhydramnios	14	6%
	Oligohydramnios / Reduced	91	39%
	Normal	129	55%
Placental appearance n=234	Normal	175	75%
	Abnormal	59	25%
Umbilical PI n=185	1.66 (0.63 to 6.94)*	-	-
Umbilical artery EDF n=134	Positive	57	43%
	Absent	54	40%
	Reversed	23	17%
MCA PI n=159	1.40 (0.80 to 4.49)*	-	-
CPR n=135	0.75 (0.22 to 4.05)*	-	-
DV a-wave n=112	Positive	96	86%
	Absent	11	10%
	Reversed	5	4%

Antenatal ultrasound features at sentinel scan *median (range)

CPR=cerebro-placental ratio
DV a-wave= Ductus venosus a-wave
EFW= Estimated fetal weight
HC/AC ratio= head circumference / abdominal circumference ratio
MCA PI= Middle cerebral artery PI
Umbilical artery EDF= Umbilical artery end diastolic flow
Umbilical PI=Umbilical pulsitility index

Table 3:

Cases that changed category between antenataland postnatal assessment

Antenatal Category at sentinel scan	**Postnatal Category**	**Outcome of case**
Uteroplacental	Unclassified	2920g birth weight, IOL; SVD at 39/40, survived
Unclassified	Uteroplacental	270g birth weight, IUD, at 28/40
Unclassified	Placental	385g birth weight, IUD at 26/40,
Unclassified	Uteroplacental	635g birth weight, 27/40, CS, NND
Unclassified	Uteroplacental	250g birth weight, IUD at 22/40
Unclassified	Placental	2550g birth weight, CS at 38/40, survived
Unclassified	Uteroplacental	900g birth weight , IUD at 32 weeks
Unclassified	Placental	440g birth weight, IUD at 24 weeks
Unclassified	Uteroplacental	330g birth weight, TOP at 25/40
Unclassified	Uteroplacental	2620g birth weight, CS at 39/40, survived
Unclassified	Uteroplacental	512g birth weight, CS at 30/40, NND

CS= caesarean section

IUD= intrauterine death

NND= neonatal death

SVD=spontaneous vaginal delivery

ToP= termination of pregnancy

Table 4:

Antenatal ultrasound variables at sentinel scan and postnatal outcome

	Survived N 101	**NND N 22**	**IUD N 89**	**Fetocide/TOP N 33**	***p****
Gestational age at diagnosis (weeks)[#]	24 (22 to 25.9)	23.63 (22.0 to 25.6)	23.3 (22.0 to 25.7)	23.4 (22.0 to 25.6)	n.s.
EFW at diagnosis (g)[#]	400 (256 to 677)	340 (246 to 586)	333 (166 to 538)	315 (213 to 456)	0.000
HC/AC ratio at diagnosis[#]	1,24 (1.13 to 1.39)	1.29 (1.17 to 1.40)	1.27 (0.98 to 1.55)	1.28 (1.18 to 1.45)	0.013
UtA PI abnormal or bilat notches (uteroplacental cause)	77% (78/101)	86% (19/22)	87% (77/89)	82% (27/33)	n.s.
UA ARED	29% (13/45)	47% (7/15)	72% (34/47)	85% (23/27)	n.s.
DV a-wave absent or reversed	3% (1/33)	0% (0/14)	22.5% (9/40)	24% (6/25)	n.s.
Birthweight (gr)[#]	1020 (435 to 3420)	560 (313 to 2550)	422 (155 to 2570)	345 (220 to 512)	0.000
Diagnosis to delivery interval (weeks)[#]	8.1 (0.3 to 18.1)	4.5 (0.1 to 15.4)	2.8 (0.1 to 10.1)	0.9 (0.1 to 5.4)	0.000

**p* value was calculated comparing the median value by Kruskal-Wallis test [#]Median (range)

DV a-wave= Ductus venosus a-wave
EFW= Estimated fetal weight
g=grams

HC/AC ratio= head circumference / abdominal circumference ratio
IUD= intrauterine death

NND= neonatal death

ToP= termination of pregnancy

UA ARED= Umbilical artery absent or reversed end diastolic flow
UtA PI=Uterine artery pulsatility index

Table 5:

Outcome based on categorisation of small-for-gestational-age

	Survived	NND	IUD	Fetocide or TOP	Total*	Gestation at delivery	Diagnosis to delivery interval	Incidence of PE
Utero-placental	39% 78/201	10% 19/201	38% 77/201	13% 27/201	201 (82%)	27.5 (22.3-40.3) (N 198/201)	3.7 (0-16) (N 198/201)	34% (49/145)
Placental	54% 7/13	0% 0/13	15% 2/13	31% 4/13	13 (5.3%)	27.0 (22.6-38.3) (N 12/13)	3.6 (0-15.9) (N 12/13)	17% (2/12)
Viral	0% 0/1	0% 0/1	100% 1/1	0% 0/1	1 (0.5%)	n.a.	n.a.	0% (0/1)
Unclassified	53% 16/30	10% 3/30	30% 9/30	7% 2/30	30 (12.2%)	34.89 (22.3-41.3) (N 30/30)	11.9 (0-18.1) (N 30/30)	11% 2/18
Total	101	22	89	33	245	27.7 (22.3-41.3) (N 241/245)	3.9 (0-18.1)	30% 53/175

Antenatal outcome by categorisation*

NND= neonatal death

IUD= intrauterine death

ToP= termination of pregnancy

PE= preeclampsia

Figure 1:

Flow chart (according to STROBE guidelines) for inclusion of cases

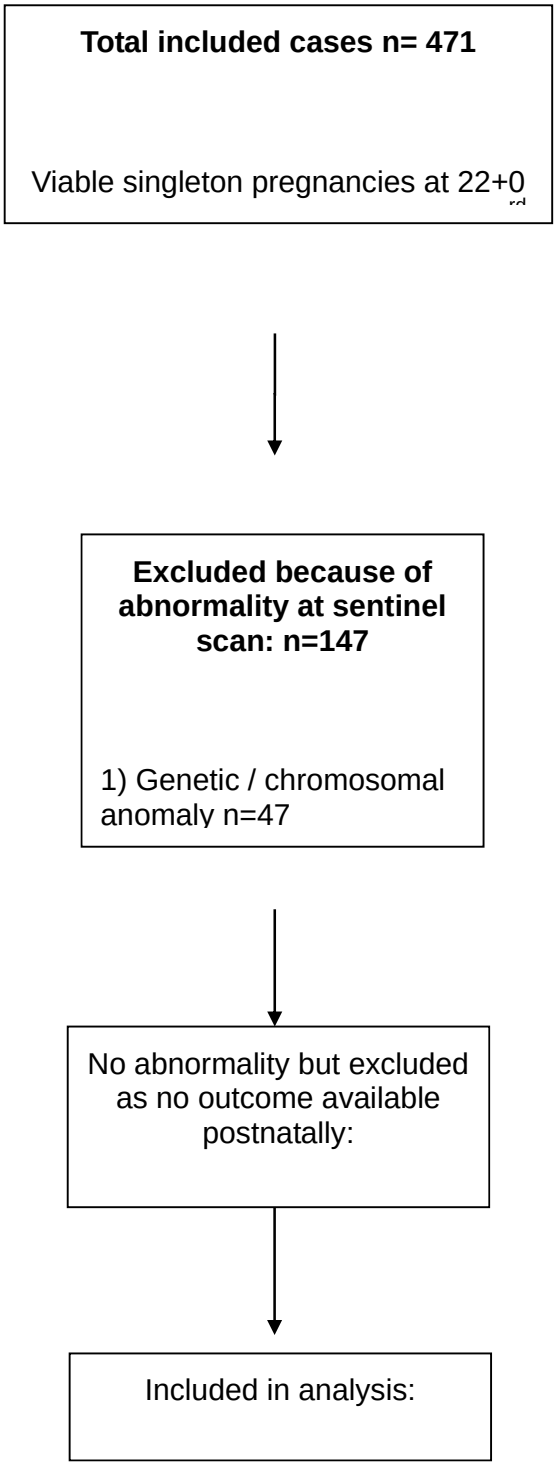
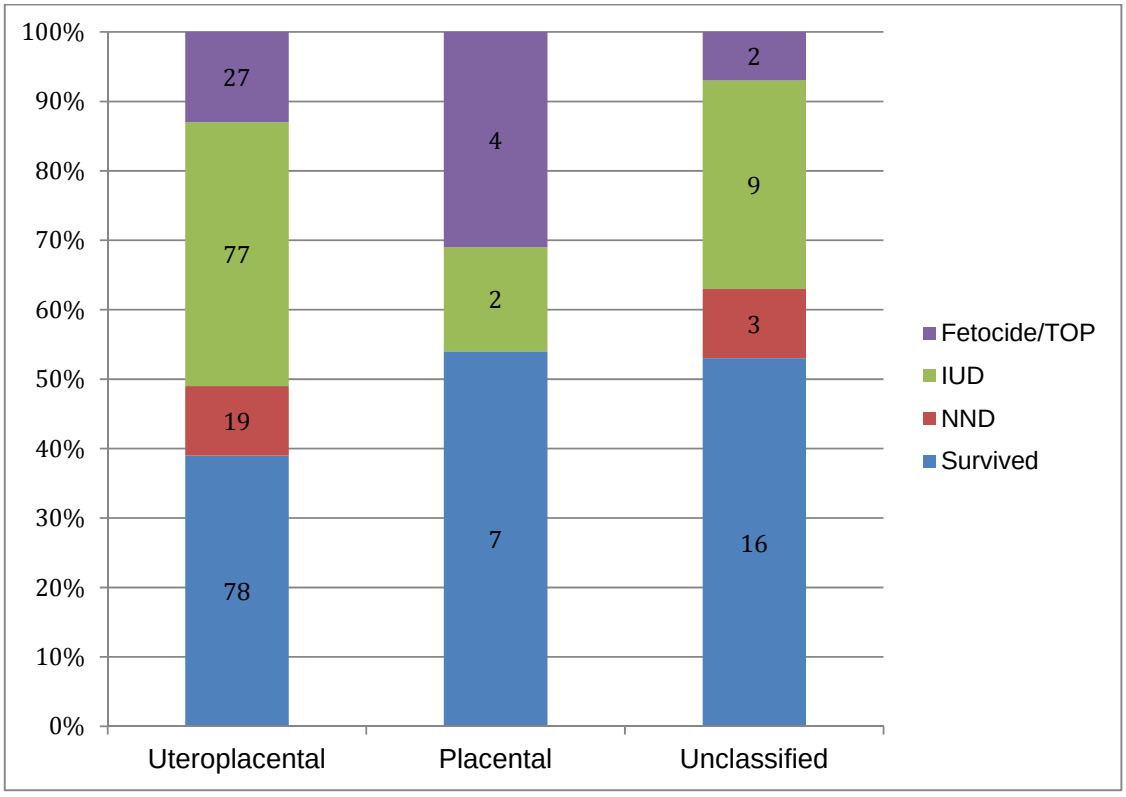


Figure 2:

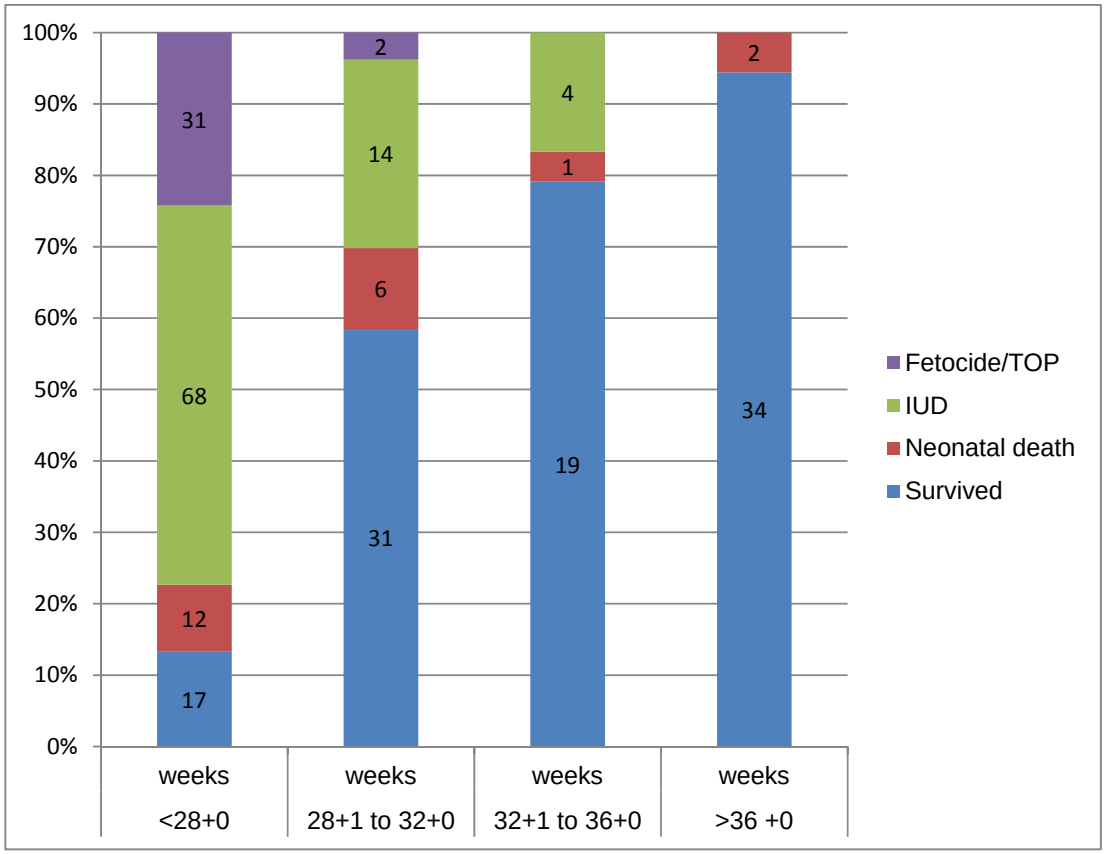
Fetal outcome by antenatal categorisation



Fetal outcome by antenatal categorisation at sentinel scan (uteroplacental n= 201; placental n= 13; unclassified n= 30). (viral category not shown as n=1)

Figure 3:

Fetal outcome by gestational age



Fetal outcome by gestational age in weeks at delivery (≤28 weeks n= 128; 28+1 – 32 weeks n= 53; 32+1 – 36 weeks n= 24; >36 weeks n= 36). (unknown gestation n= 4; IUD n= 3; NND n= 1)