SMALL FOR GESTATIONAL AGE BABIES AFTER 37 WEEKS: AN IMPACT STUDY OF A RISK STRATIFICATION PROTOCOL

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ABSTRACT

Objectives

Although no clear evidence exists, many international guidelines advocate early term

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delivery of small for gestational age (SGA) fetuses. The aim of this study was to determine whether a protocol that included monitoring SGA fetuses beyond 37 weeks affected perinatal and maternal outcomes.

Methods

The impact of the introduction in 2014 of a protocol for management of SGA, which included risk stratification with surveillance and expectant management after 37 weeks for lower risk babies (Group 2), was compared with the previous strategy, which recommended delivery at around 37 weeks (Group 1). Data from all referred SGA babies over a 39 month period were analyzed.

Results

In group 1 there were 138 SGA babies; in group 2 there were 143. The mean gestation at delivery was 37+4 and 38+2 weeks respectively (p=0.04). The incidence of neonatal composite adverse outcomes was lower in Group 2 (9% v 22% v; p<0.01) as was neonatal NNU admission (13% v 42%; p<0.01). Induction of labour and caesarean section rates were lower, and vaginal delivery (83% v 60%; p<0.01) was higher in group 2. Most of the differences were due to delayed delivery of SGA babies that were stratified as low risk.

Conclusions

This study suggests that protocol-based management of SGA babies may improve outcomes and that identification of moderate SGA should not alone prompt delivery. Larger numbers are required to assess any impact on perinatal mortality.

INTRODUCTION

The small for gestational age (SGA) fetus is at increased risk of perinatal complications including stillbirth[1-4]. Its identification remains a cornerstone of antenatal care. Several

authors report improved outcomes of such babies if they are identified in utero, largely as result of expedited delivery[5,6], although this is still debated[7-9]. The DIGITAT study[10] and subsequent Cochrane review[11] concluded that intervention did not alter perinatal outcomes, nor indeed caesarean section rates, but was underpowered to detect an impact on stillbirth rates. On this basis the current UK Guidelines recommend delivery at 37 weeks for all fetuses with an estimated fetal weight below the 10th centile even where the pregnancy is otherwise uncomplicated and fetal/placental Dopplers are normal[12]; US guidelines[13] are less prescriptive and uncertainty surrounds the optimal management and timing of delivery[14].

A principal difficulty is that many SGA fetuses are merely constitutionally small and therefore probably not at increased risk; equally a fetus may have impaired growth or placental function (fetal growth restriction: FGR) but not have a fetal weight below the 10th centile[15-17]. Curtailment of pregnancy three weeks before term should prevent later stillbirth, whether the fetus is SGA or not. However, this has to be compared to the risks of obstetric intervention, possibly increased infant mortality[18] and potentially greater neonatal unit admission[7] rate and even long term morbidity[19,20].

Recent data suggest that the risk of adverse outcome can be better determined using multiple factors including the cerebroplacental ratio (CPR)[21] and that conservative management of SGA fetuses with normal parameters is reasonable[22].

Delivery at 37 weeks for SGA was recommended in our unit prior to 2014, when we introduced a protocol that included conservative management of SGA babies not considered FGR beyond 37 weeks. The aim of this study is to compare the impact of this protocol with historical data in order to determine the effects it had on the obstetric and perinatal outcomes of antenatally diagnosed SGA babies.

METHODS

This is an impact study examining data collected over a 39-month period (January 2013-April 2016). The study was conducted in the John Radcliffe Hospital, Oxford, UK, a large tertiary referral unit with > 8000 deliveries per annum. Throughout the time period, growth scanning was not routine and was performed according to risk factors and abdominal palpation. Eligible women were those referred to the Fetal Medicine Unit (FMU), with a singleton non-anomalous fetus antenatally diagnosed as small for gestational age (SGA) from 36+0 weeks of gestation, but with a normal umbilical artery Doppler pulsatility index (UmbA PI) prior to referral. Small for gestational age was defined as an estimated fetal weight (EFW) <10th centile using Hadlock charts[23].

Protocol-based management of SGA pregnancies was introduced in October 2014, with a dedicated clinic for those pregnancies.

Group 1: Women referred to the FMU between January 2013 and September 2014, managed in an ad hoc manner according to clinicians' preference, broadly based on the national guidelines (RCOG)[12], which recommend delivery at 37 weeks.

Group 2: Women referred from October 2014 to April 2016, managed in accordance with a protocol as follows:

On the first appointment the gestational age (GA) was confirmed based on the first-trimester crown-rump length (CRL); the maternal serum level of the PAPP-A and the second trimester Uterine Arteries Doppler (UtA) were reviewed where available. Blood pressure (BP) and urinalysis were also assessed. Ultrasound measurements were re-taken, the umbilical artery and middle cerebral artery pulsatility index measured and the cerebro-placental ratio was calculated.

All examinations were performed by an experienced operator (MV or AC) using a Voluson E8 (GE Medical Systems, Zipf, Austria) machine, equipped with a 6-2-MHz linear curved-array transducer. The liquor volume was assessed measuring the deepest vertical pool. The umbilical artery pulsatility index (UmbA-PI) was calculated from a free-floating portion of the umbilical cord. The middle cerebral artery pulsatility index (MCA-PI) was measured in a transverse view of the fetal head, at the level of its origin from the circle of Willis. The cerebro-placental ratio (CPR) was calculated as the ratio MCA-PI/UmbA-PI, and was considered abnormal when < 5th centile for gestational age[24]. Doppler recordings were performed in the absence of fetal movements and voluntary suspended maternal breathing. All pulsed Doppler parameters were recorded automatically from at least three consecutive waveforms, with the angle of insonation as close to 0° as possible, and always below 30°.

Based on the EFW, Doppler measurement and risk factors, women were stratified and underwent a tailored follow up and timing of delivery according to the clinic protocol: Delivery, by induction of labour, was advised at 37+0 weeks and not before, in "high risk" babies, defined as EFW <3rd centile; or CPR <5th centile; or mean uterine artery PI at the anomaly scan was >95th centile[25]; or if the PAPP-A had been <0.3MoMs in the first trimester, or if there was pregnancy-induced hypertension (≥140/90). If the above risk factors were absent ("low risk" babies), the US scan was repeated in one week if the EFW was between the 3rd and 5th, or in two weeks if it was between the 5th and the 10th centile. Where the EFW was between the 5th and 10th centile, patients were advised to deliver by 40+0 weeks; when it was between the 5th and 10th centile delivery was recommended by 41+0 weeks.

Ultrasound and pregnancy outcomes were compared between the two periods. Ultrasound data were collected retrospectively for Group 1 and prospectively for Group 2, via an

electronic database system (Viewpoint); these were merged with demographic, obstetric details and neonatal outcomes via electronic patients record systems (Cerner Millenium and Badger). The last evaluation, performed within one week of delivery, was considered for analysis.

The primary outcome was a neonatal composite adverse outcome (NCAO) defined as the presence of at least one of the following conditions: intrauterine or neonatal death, Apgar < 7 at 5 min, cord arterial pH < 7.10, hypoglycemia (blood glucose <2.5mmol/l), and ventilation or cooling. Secondary outcomes were: admission to the neonatal admission to the neonatal unit (NNU), gestational age at delivery, mode of delivery and caesarean section rates. Neonatal policy remain unchanged during the time period and there was no policy for automatic neonatal unit admission simply because of gestation or birthweight.

Interventions and outcomes were compared between the two groups and according to the risk stratification described above. Categorical variables are presented by number and percentage. Continuous variables are presented by mean with standard deviation or median with interquartile range. The Chi-square or Fisher's exact test was performed for categorical variables and odds ratios (OR) with 95% confidence intervals were calculated; the independent-samples t-test was used for continuous variables. Institutional review board approval was granted in September 2005 (05/Q1605/110) and updated on Feb.1, 2017.

RESULTS

Study population

Patient selection for analysis is summarized in Figure 1. During 39 months, 363 women attended the Fetal Medicine Unit at the John Radcliffe Hospital having had at least one

scan showing a non-anomalous fetus with an EFW < 10th centile for the gestational age at beyond 36 weeks: 185 (51%) between January 2013 and September 2014 and 178 (49%) between October 2014 and April 2016. These represented 1.6% and 1.8% respectively of the singleton pregnancies >36 weeks delivered during this time at the John Radcliffe Hospital. After exclusion of babies whose EFW was found to be >10th centile and those without follow up data, there were 138 (49%) pregnancies in Group 1 and 143 (51%) in Group 2.

Maternal baseline characteristics are shown in Table 1. There were no significant differences between the two groups. There were also no significant differences in the incidence of risk factors for SGA. Ultrasound findings are summarised in Table 2. There were no significant differences between the two groups, although there was a trend towards a greater proportion of high risk babies in Group 1.

Overall maternal pregnancy outcomes are shown in Table 3. Data are given as mean ± SD, n (%) or median (interquartile range). In Group 2, the gestational age was significantly higher than in Group 1 compared to group 2; the induction of labour and caesarean section rate was lower, and the vaginal delivery rate higher. Overall neonatal outcomes are shown in Table 4. The birthweight was significantly higher in Group 2. Although no significant difference was observed between the two groups of neonates in terms of Apgar score, umbilical arterial pH and base-excess alone, the incidence of neonatal unit admission was higher, and the neonatal composite adverse outcome (NCAO) was more than twice as high in Group 1 as in Group 2.

The odds ratios with 95% CI of the main maternal and neonatal outcomes for Group 2 with Group 1 as reference are shown in Figure 2.

In Table 5 the interventions and major outcomes are stratified according to the allocated risk level. High risk babies, probably FGR, with either EFW < 3rd centile, or CPR < 5th centile, or uterine arteries PI > 95th centile, or PAPP-A < 0.3MoMs, or maternal hypertension, encompassed 58.7% of babies in Group 1 and 48.3% of babies in Group 2.

In low risk SGA babies, there was a small but significant increase in gestation, with a significant increase in spontaneous onset of labour and greater birthweight. The low incidence of the composite adverse outcome in these babies was not significantly altered but the neonatal unit admission rate was significantly reduced. In high risk SGA babies, there were largely non-significant decreases in intervention in Group 2, a higher mean birthweight and a significant decrease in the incidence of NNU admission and the composite adverse outcome.

There was one intrauterine death (IUD) in each group. In group 1 an IUD occurred at 37+2 weeks, which as diagnosed at the first FMU appointment. The birthweight was <3rd centile; in group 2 a fetal death occurred in a pregnancy first identified to be SGA at 38 weeks. The EFW was on the 3rd centile and the CPR was abnormal. Elective caesarean section was booked, because of a previous caesarean section, but was delayed by three days. The IUD was diagnosed the day before planned delivery.

DISCUSSION

There is an increasing trend towards early term delivery of small for gestational age babies[12,13]. Term neonatal unit admission rates are increasing in many countries[26]; early term delivery, also increasing[27] in an attempt to prevent stillbirth, may be a major risk

factor. Our data suggest that a prescriptive protocol for management, including risk stratification with conservative management for those considered at 'low risk', allows less intervention to be accompanied by less neonatal morbidity.

The data suggests that for the time period of Group 1, prior to the protocol, some risk stratification was already occurring in that babies that would have been 'lower risk'. They were not all being delivered, as at least UK guidelines recommend, at 37 weeks. Some of this is because they were identified until after 37 weeks. If they had been, the differences in intervention between the 2 groups would have been greater. Nevertheless, a more conservative protocol-based management allowed significantly more to reach 39 weeks, to labour spontaneously and when delivery was considered indicated, to not be delivered by caesarean section. This was followed by a considerable reduction in NNU admission, although no alteration in the composite outcome which, in these 'low risk' babies, was relatively rare. Although the numbers are too small to make conclusions about perinatal mortality, this does suggest that reduced intervention in SGA babies that are likely to be constitutionally small is reasonable and may even improve outcomes.

In babies considered 'high risk', there are also improvements in neonatal outcomes. The data do not allow firm conclusions as to why, and it is possible that the babies in Group 1 were simply more high risk. However, it was not that the incidence of detected SGA differed between the 2 groups: (1.6 and 1.8% respectively). These are in accordance with expectations: approximately 5% of our babies are <10th centile by Hadlock charts and detection rates of SGA in the UK are around 30%[6]. Indeed, the differences could also be related to the protocol which stipulated induction as opposed to caesarean, and not before 37 weeks, even in these higher risk babies.

The intrauterine death in group 2 was in a baby whose condition was diagnosed late, but met criteria for expedited delivery. Thus, this IUD would have occurred even under the former protocol. This highlights the need for identification of SGA, and FGR among non-SGA babies, which were not the intention of this protocol.

Previous reports have shown variable or increased morbidity with earlier delivery[7,9]. This, particularly neonatal unit admission, is to be expected if SGA but otherwise healthy babies are delivered even mildly preterm. The risk stratification part of the protocol, attempting to differentiate between constitutionally small fetuses and FGR fetuses, was an adaptation of a published protocol[28], although we delayed induction of labour to 41 weeks in babies considered at least risk. This was because a key aim of our protocol was to limit induction of labour, and the gestation window of 40-41 weeks is one where a large number of women should deliver spontaneously.

Other risk factors that may help determine risk in SGA babies include uterine artery Doppler in the third trimester [29], abdominal circumference trajectory[30] and maternal age[31]. Using these may further reduce the risk of serious adverse outcomes; ideally, modelling of independent risk factors would allow a risk assessment tool.

Our data also suggest that the introduction of a protocol-based management may improve maternal outcomes. This is in contrast to the conservatively managed arm of DIGITAT[10]. Although routine induction of labour at 39 weeks has not been shown to increase intrapartum intervention in many RCTs of higher risk pregnancies, overall caesarean section rates are often very high[32], and induction is not viewed well by women[33].

We acknowledge a number of limitations. As discussed, we cannot exclude the possibility, in the babies considered high risk, that, despite the similar demographics, incidence of risk factors and detection rate of SGA babies, the improved neonatal outcomes are because

Group I contained higher risk babies. This does not, however, prevent conclusions being drawn about the low risk babies. It highlights the drawbacks of an impact study, but the RCT[10] that has addressed early term delivery did not use a prescriptive risk stratification protocol like ours. Our findings are also limited by the retrospective nature of data collection, particularly in group 1, and the consequent missing outcomes. Finally, we are unable to draw conclusions about stillbirth and long term morbidity: to do this would require vast numbers.

The potential benefit of early term labour delivery is the prevention of later stillbirth. Indeed, curtailment of a pregnancy at any gestation will prevent stillbirth beyond the gestation of delivery, so this outcome cannot be considered in isolation: at the very least, neonatal and infant mortality must be considered. Late-onset FGR is also associated with increased perinatal morbidity in the form of fetal distress, hypoglycaemia, seizures, behavioural problems, cerebral palsy and cardiovascular disease[35-37]. There are, however, other potential risks, including increased neonatal unit admission[7] and childhood morbidity[19,20], and increased 'medicalisation'. What is not clear is the respective roles of the gestation or birthweight and of the pregnancy characteristics associated with early term delivery.

CONCLUSIONS

The ACOG Practice Bulletin[13] states: "Size alone is not an indication of a complication. As a result of this confusion, under-intervention and over-intervention can occur." The

prevention of over-intervention will become even more important if, as has been recommended in the UK[38], detection rates of SGA increase. This means risk stratification is essential and we show it is effective. Although our study was too small to demonstrate an effect on stillbirth, it is uncertain if a large reduction in near term stillbirth is achievable by routine delivery of small babies, even if they are identified. A version of the protocol we have described in all pregnancies might yet achieve this.

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Legends

Table 1: Demographic details. Group 1 : pre-SGA clinic population; Group 2: SGA clinic population.

Table 2: Risk stratification of Groups. Group 1: pre-SGA clinic population; Group 2: SGA clinic population; EFW: estimated fetal weight; CPR: cerebro-placental ratio; UtA: uterine arteries.

Table 3: Maternal outcomes. Group 1: pre-SGA clinic population; Group 2: SGA clinic population; GA: gestational age; LSCS: lower segment caesarean section.

Table 4: Neonatal outcomes. Group 1: pre-SGA clinic population; Group 2: SGA clinic population. Hypoglycaemia: blood glucose <2.5mmol/l; NNU: neonatal unit admission; NCAO: neonatal composite adverse outcome.

Table 5: Major interventions and outcomes stratified according to risk categories
Group 1: pre-SGA clinic population; Group 2: SGA clinic population. LSCS: low segment caesarean section; NNU: neonatal unit admission; NCAO: neonatal composite adverse outcome.

Figure 1. Flow chart: multi-step process of patients selection for the analysis of the study groups. Group 1: pre-SGA clinic population; Group 2: SGA clinic population.

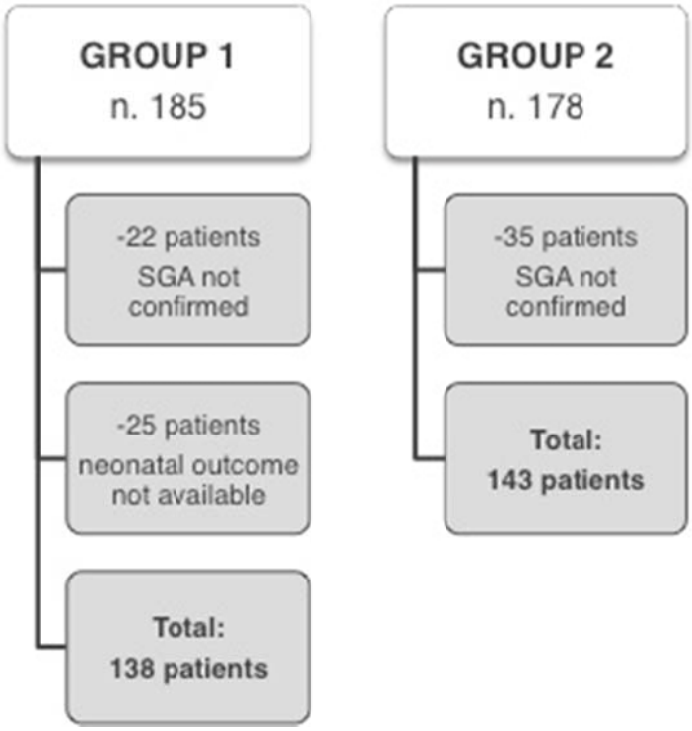

Figure 2. Odds ratios with 95% CIs for the risk for the main maternal and neonatal outcomes for Group 2 with Group 1 as reference (dashed line): gestational age at delivery ≥ 39 weeks; vaginal delivery; labor induction, caesarean section, neonatal unit admission (NNU); neonatal composite adverse outcome (NCAO).

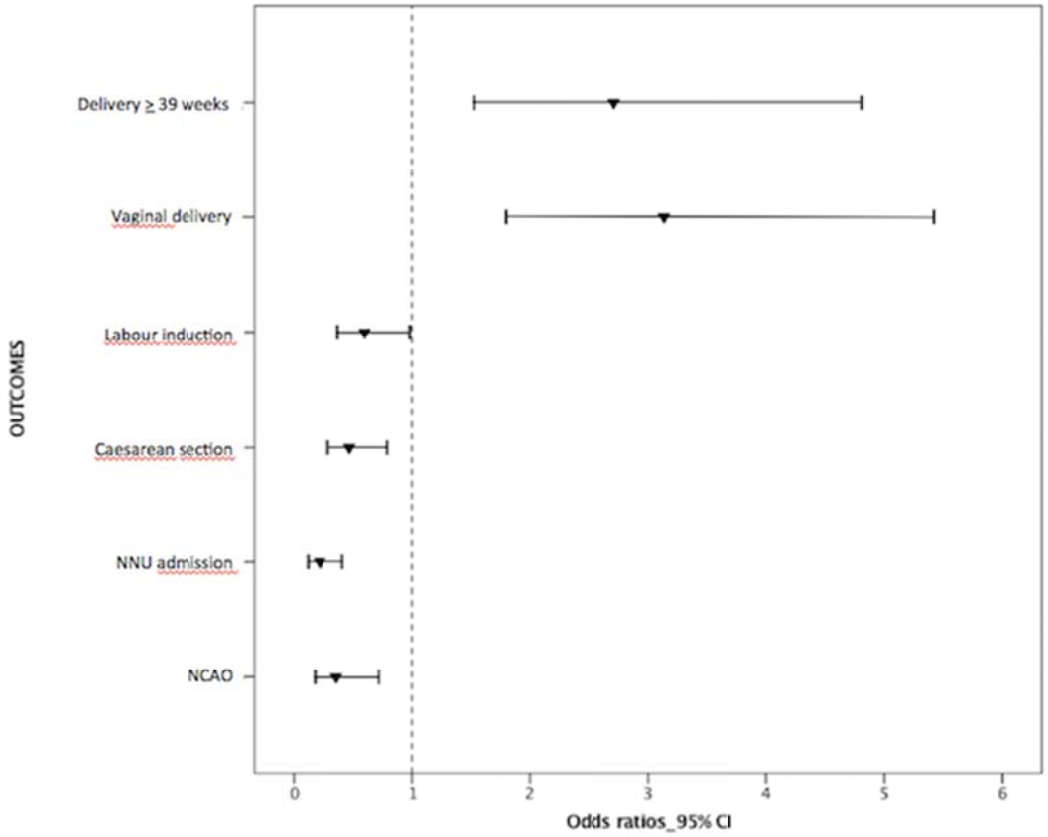

Table 1: Demographic details

	Group 1	**Group 2**	**P value**
	n (%) / mean (SD)	n (%) / mean (SD)	
Total	138	143	
Age	28.24 (5.76)	29.58 (5.76)	0.63
BMI	24.1 (5.69)	23.6 (4.5)	0.36
Nulliparous	69 (50)	69 (48)	0.16
Hypertensive disorders	11 (8.5)	11 (7.3)	0.70
Gestational diabetes	7 (5.7)	6 (4.3)	0.60
Smoking	16 (13.1)	26 (17.7)	0.23
Drug misuse	5 (4.1)	5 (3.6)	0.82
Previous SGA baby	20 (15.7)	34 (23.8)	0.10

Table 2: Risk stratification of Groups

	Group 1	**Group 2**	**P value**
	n (%)	n (%)	
Total	138	143	
High Risk*	**81 (58.7)**	**69 (48.3)**	**0.08**
- EFW < 3rd	54 (39.1)	47 (32.9)	0.22
- CPR < 5th	30 (21.7)	25 (17.0)	0.18
- UtA mean PI > 95th **	15/43 (35)	14/50 (28)	0.5
- PAPP-A < 0.3 MoMs	6 (4.3)	8 (5.6)	0.4
Low Risk	**57 (41.3)**	**74 (51.7)**	**0.08**
- 3rd < EFW < 5th c	30 (21.7)	36 (25.2)	0.5
- 5th < EFW < 10th c	27 (19.6)	38 (26.6)	0.17

* inclusion criteria not mutually exclusive

** not all women had 2nd trimester uterine artery Dopplers

Table 3: Maternal outcomes

Outcome	Group 1	Group 2	OR (95% CI)	P value
	n (%) / med (IQR)	n (%) / med (IQR)		
Total	138	143		
Vaginal delivery	83 (60.1)	118 (82.5)	3.13 (1.80-5.42)	<0.01
Instrumental deliver	15 (10.9)	17 (11.9)	1.11 (0.53-2.31)	0.79
Labour Induction	91 (66)	77 (53.8)	0.60 (0.37-0.98)	0.04
Elective LSCS	31 (22.5)	17 (11.9)	0.47 (0.24-0.89)	0.02
Emergency LSCS	24 (17.4)	18 (12.6)	0.68 (0.35-1.33)	0.26

Table 4: Neonatal outcomes

Outcome	Group 1	Group 2	OR (95% CI)	P value
	n(%)/mean(SD)	n(%)/mean(SD)		
Total	138	143		
Birthweight (g)	2328 (335)	2544 (337)		<0.01
Perinatal mortality	1 (0.7)	1 (0.7)	1.09 (0.07-17.67)	1.00
Gestation at delivery	37.4 (1,7)	38.2 (1,9)		0.04
Delivery >39 weeks	27 (19.6)	50 (35.0)	2.28 (1.33-3.94)	<0.01
Arterial pH < 7.1	4/51 (7.8)	1/47 (2)	0.26 (0.03 – 2.37)	0.36
Arterial pH	7.25 (0.09)	7.25 (0.08)		0.77
Hypoglycaemia	14/121 (11.5)	11/119 (9.2)	0.78 (0.34 – 1.79)	0.51
Apgar 5 min < 7	3 (2.3)	0 (0)		
NNU admission	54 (42.2)	18 (12.6)	0.22 (0.12 – 0.41)	<0.01
Assisted ventilation	20 (14.5)	8 (5.6)	0.32 (0.14 – 0.76)	<0.01
NNU total days	268 (1.94)	152 (1.06)		0.07
NCAO	30 (21.7)	13 (9.1)	0.36 (0.18 – 0.72)	<0.01

Table 5: Major interventions and outcomes stratified according to risk categories

	Group 1	**Group 2**	**OR (95%CI)**	**P value**
Total babies	138	143		
High risk babies	**81 (58.7)**	**69 (48.3)**		
	n (%) / mean (SD)	**n (%) / mean (SD)**		
Gestation	37.0 (1.3)	37.6 (1.2)		0.01
Gestation >39 weeks	7 (8.6)	8 (11.6)	1.39 (0.48-4.04)	0.36
Birthweight	2173 (294)	2355 (342)		<0.01
Spontaneous labour	3 (3.7)	11 (15.9)	4.93 (1.32-18.5)	0.01
Induction	52 (64.2)	42 (60.9)	0.86 (0.45-1.68)	0.67
Elective LSCS	23 (28.4)	14 (20.3)	0.64 (0.3-1.37)	0.25
Emergency LSCS	18 (22.2)	9 (13.0)	0.52 (0.21-1.26)	0.15
NCAO	22 (27.2)	9 (13.0)	0.39 (0.16-0.92)	0.03
NNU	38 (46.9)	16 (23.2)	0.34 (0.17-0.69)	<0.01
Low risk babies	**57 (41.3)**	**74 (51.7)**		
	n (%) / mean(SD)	**n (%) / mean (SD)**		
Gestation	38.4 (1.17)	39.1 (1.25)		<0.01
Gestation >39 weeks	20 (35.1)	42 (56.8)	2.43 (1.19-4.95)	0.01
Birthweight	2573 (237)	2720 (321)		<0.01
Spontaneous labour	9 (15.8)	34 (45.9)	4.53 (1.95-10.57)	<0.01
Induction	39 (68.4)	35 (47.3)	0.41 (0.20-0.85)	0.02
Elective LSCS	8 (14.0)	3 (4.1)	0.26 (0.07-1.03)	0.06
Emergency LSCS	6 (10.5)	9 (12.1)	1.18 (0.39-3.52)	0.77
NCAO	8 (14.0)	4 (5.4)	0.35 (0.10-1.23)	0.09
NNU	16 (28.1)	2 (2.7)	0.07 (0.02-0.33)	<0.01