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Effects of antenatal recognition and follow-up on perinatal outcomes in small-for-gestational age infants delivered after 36 weeks

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Key words
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Conflict of interest
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Abstract

Objective. To compare perinatal outcomes of late small-for-gestational age (SGA, birthweight <10th percentile) infants, according to antenatal recognition. *Design.* Retrospective study. *Setting.* Tertiary referral center. *Population.* All singleton pregnancies with SGA (birthweight <10th percentile) infants born ≥36 weeks' gestation from January 2007 to April 2009. *Methods*: Chart review of 771 pregnancies. SGA infants identified prior to delivery (group A) were compared with those not identified (group B). *Main outcome measures.* Mode of delivery, perinatal complications, admission to neonatal intensive care unit (NICU). In group A, receiver operating characteristic (ROC) analysis and area under the curve (AUC) of antenatal tests to predict NICU admission were calculated. *Results.* In 17% of infants, SGA was recognized before birth (group A), whereas in 83% it was recognized only at birth (group B). Infants with the most severe degree of SGA (birthweight <3rd percentile) were more frequently diagnosed antenatally (30%). Admission to NICU (14 vs. 3%, $p < 0.001$) and cesarean delivery (42 vs. 26%; $p < 0.001$) were more likely in group A. Adverse outcomes related to hypoxia were all observed in group B, but the difference was not significant. In antenatally detected fetuses a combination of fetal abdominal circumference, umbilical artery pulsatility index and middle cerebral artery pulsatility index z-scores was useful for prediction of NICU admission (AUC = 0.94). *Conclusion.* Antenatal recognition of late SGA may improve perinatal outcomes. However, admission to neonatal intensive care and cesarean delivery were more frequent among SGA infants recognized antenatally.

Abbreviations: AC, abdominal circumference; AUC, area under the ROC curve; CI, confidence interval; IQR, interquartile range; IUD, intrauterine death; IUGR, intrauterine growth restriction; MCA PI, middle cerebral artery pulsatility index; NICU, neonatal intensive care unit; OR, odds ratio; ROC, receiver operating characteristic; SGA, small-for-gestational age; STV, short-term variation; UA PI, umbilical artery pulsatility index; UtA RI, uterine arteries mean resistance index.

Introduction

Small-for-gestational age (SGA) commonly refers to a fetus that has failed to achieve the 10th percentile for abdominal circumference and estimated birthweight (1). Most term SGA infants have no appreciable morbidity or mortality (2) and the reason why studies on SGA fetuses have shown poor perinatal outcome is likely to be the high incidence of intrauterine growth restriction (IUGR) in this group (3). According

Key Message

Antenatal recognition of late small-for-gestational age may improve perinatal outcomes. However, admission to neonatal intensive care unit and cesarean delivery were more frequent among small-for-gestational age infants recognized antenatally.

to available guidelines, antenatal surveillance should be undertaken in SGA fetuses to minimize the risk of intrauterine death (IUD) (4). While umbilical artery Doppler is effective in reducing perinatal death in pregnancies with preterm IUGR, it loses its predictive ability when approaching term (5), and the optimal management strategy to reduce neonatal mortality and morbidity in SGA fetuses in the late third trimester has not yet been determined (6–8). A study comparing neonatal outcome between identified and unidentified cases of SGA already demonstrated that an awareness of SGA before delivery, in combination with a structured program of surveillance, was related to a fourfold lowered risk of adverse fetal outcome (9). However, this study included both term and preterm SGA which were followed up using umbilical artery Doppler velocimetry. The results of this study might not be applied to SGA cases approaching term because normal umbilical artery Doppler results are common in IUGR late in pregnancy, and sequential deterioration of Doppler indices is rare beyond 34 weeks' gestation (10,11).

The aim of our study was to evaluate whether antenatal recognition improves perinatal outcome in SGA infants delivered ≥36 weeks' gestation.

Material and methods

This retrospective study was performed in a tertiary referral center. The nature of the study did not require ethical committee approval according to national regulations. We searched our labor ward database to identify all singleton infants delivered ≥36 weeks' gestation between January 2007 and April 2009 with a birthweight <10th percentile according to published normograms (12). Pregnancies were dated by a certain last menstrual period in women with regular cycles, and gestational age was confirmed on the basis of ultrasonographic examination before 20 weeks of gestation. National guidelines in use at the time of the study and applied to our population recommended a growth scan between 28 and 32 weeks' gestation in all pregnancies (13). Pregnancies complicated by chromosomal or structural abnormalities, infections or metabolic disorders were excluded. Group A included fetuses in which abdominal circumference was known to be <10th percentile before birth (14). These patients were managed expectantly and antenatal surveillance was performed using feto-maternal Doppler velocimetry, amniotic fluid evaluation and computerized cardiotocography. Appointments were scheduled at least every two weeks, and even up to three times a week depending on the severity of growth restriction, oligohydramnios and Doppler flow changes. Biometry was assessed every two weeks: fetal head circumference, biparietal diameter, abdominal circumference (AC) and femur length were measured. Left and right maternal uterine arteries were examined at their apparent crossover with the external iliac arteries, and the mean resistance index (UtA RI) was calculated.

The following variables were assessed at each fetal monitoring session. First, the amniotic fluid index was calculated as the sum of the deepest vertical pools without fetal parts or cord, measured sonographically in each quadrant of the uterus (15). Secondly, the pulsatility index for the umbilical artery (UA PI) and the middle cerebral artery (MCA PI) was determined. The umbilical artery was examined at a mid-region between the fetal abdominal wall and placental insertion. The middle cerebral artery was identified using color flow mapping and interrogated in its midportion. The pulsatility index was considered abnormal when it was above the 95th percentile for gestational age in the umbilical artery and below the 5th percentile for gestational age in the middle cerebral artery (16). We attempted to achieve an angle close to 0° between the Doppler ultrasound beam and the direction of blood flow in each vessel. Measurements of fetal Dopplers were taken during periods of fetal quiescence. Thirdly, computerized cardiotocography was recorded with the fetal heart rate for a minimum of 40 min and analyzed by a computerized system (Oxford Sonicaid System 8002, Oxford Instruments, Abingdon, UK), which fits a baseline to the fetal heart rate trace and calculates short-term variation (STV) in milliseconds (msec) as fetal pulse interval differences averaged over successive periods of 3.75 seconds, after exclusion of decelerations (17).

Indications for delivery in group A were: UA PI >95th percentile (16) on two occasions 24 hours apart, nonreactive cardiotocography with STV <5 msec or repeated decelerations, amniotic fluid index <5 cm on two occasions 24 h apart; preeclampsia (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg with proteinuria ≥0.3 g/24 hours) or poorly controlled maternal hypertension, gestational age ≥40 weeks' gestation and other maternal indications. Results of Doppler waveform analysis of the middle cerebral artery were not used for patient management.

Group B included infants with birthweight <10th percentile (12) in which diagnosis of SGA was unknown before birth. Pregnancy outcome and neonatal follow-up were obtained in all cases from review of patients' and infants' notes.

Statistical analysis

For descriptive statistics, median and interquartile range (IQR) were used. The Mann–Whitney test was used for the comparison of continuous not normally distributed variables. The chi-squared or Fisher's exact test was used for comparison of categorical variables. Maternal and neonatal characteristics, gestational age at delivery and rates of preeclampsia, induction of labor and cesarean section were

compared between antenatally (group A) and postnatally (group B) recognized SGA. Occurrence of IUD, admission to neonatal intensive care unit (NICU), respiratory distress requiring respiratory support for longer than 24 hours, intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and retinopathy of prematurity were compared between groups A and B. Umbilical artery pH at birth and occurrence of umbilical artery pH <7.10 at birth were also compared between the two groups. Relative risks were estimated by odds ratio (OR) with 95% confidence intervals (CI). Bivariate ORs were calculated with cross-tabulation and 95% CI. Birthweight percentile, AC, mean UtA RI, UA PI, MCA PI and STV were converted into z-scores using published normograms (12,14,16–18). Receiver operating characteristic (ROC) curves were constructed for birthweight, AC, STV and Doppler variables. The area under the ROC curve (AUC) was measured to evaluate the ability of each parameter to discriminate between SGA infants that were admitted to NICU and those who were not admitted, both in groups A and B, and in the whole study population. The logistic regression analysis computing interaction term was used to correlate birthweight z-score and antenatal diagnosis of SGA to admission to NICU. Logistic regression analysis was also performed, limited the antenatally recognized (group A) SGA infants to predict the probability of admission to NICU in this group using AC, UA PI and MCA PI z-scores. The AUC was measured. The data were analyzed using STATA SE 10.0 (StataCorp LP, College Station, TX, USA). All tests were performed with two-sided alternatives and p-values <0.05 were considered significant.

Results

During the study period, 8466 infants were delivered at Brescia University Hospital, 816 of whom were SGA and delivered at $\geq 36^{+0}$ weeks gestation. Forty-five were excluded because chromosomal or structural abnormalities, infections or metabolic disorders were present, leaving 771. In 132/771 infants (17%) abdominal circumference was known to be <10th percentile before birth (group A), whereas 639/771 (83%) cases of SGA were recognized only at birth (group B). Table 1 shows a comparison of clinical characteristics for groups A and B. Admission to NICU was more likely in group A than in group B (OR 4.95, 95%CI 2.5–9.6). Only 39/389 (10%) infants with birthweight between the 5th and 10th percentile were recognized before birth, while 27/158 (17%) infants with birthweight between the 3rd and 5th percentile and 66/223 (30%) infants with birthweight <3rd percentile were detected antenatally. There were two antepartum IUDs, both in group B, and both infants had a birthweight <3rd percentile. Neither woman had any relevant medical history, and the pregnancy had been uneventful until term, when IUD was diagnosed by ultrasound following a maternal report of reduced fetal movements. In one case a female stillborn fetus of 2600 g (birthweight z-score −2.13) was delivered at 40^{+1} weeks' gestation after induction of labor with vaginal prostaglandins. In the other case a male stillborn fetus of 2100 g (birthweight z-score −3.12) was delivered at 40^{+1} weeks' gestation after induction of labor with vaginal prostaglandins. The difference in stillbirth rate between groups A and B was not significant.

Admission to NICU was more likely among antenatally recognized SGA infants with birthweight <3rd percentile (16/66, 24.2%) than among those recognized at birth (8/157; 5.1%; $p < 0.001$). This difference was not significant for SGA infants with birthweight between the 3rd and 5th percentile (0/27, 0% for group A, 4/131, 3% for group B; $p = 1$) and birthweight between the 5th and 10th percentile (3/39, 7.7% for group A, 9/350, 2.6% for group B; $p = 0.11$). A summary of the incidence of the various indications did not differ significantly between the two groups, with the exception of infants delivered with acidosis (umbilical artery pH <7.20), in addition to clinical signs suspicious for perinatal asphyxia (none in group A vs. five in group B, $p = 0.049$). Main indications for admission to NICU in groups A and B are shown in Table 2. Grouping together these cases with those of antepartum IUD (presumably caused by hypoxia), adverse outcomes related to hypoxia were none in group A and seven in group B, but the difference did not reach significance ($p = 0.61$).

In the whole study population, delivery by cesarean section carried a higher risk of admission to NICU compared with vaginal delivery (30/220, 13.6% vs. 10/551, 1.8%; OR 8.5, 95%CI 4.15–17.55, $p < 0.001$). This risk persisted also considering separately group A [15/56 (27%) vs. 4/76 (5%); OR 6.58, 95%CI 2.13–20.12, $p < 0.001$] and group B [15/164 (9%) vs. 6/475 (1%); OR 7.86, 95%CI 3.09–19.99, $p < 0.001$]. Delivery by cesarean section was more likely among antenatally recognized SGA infants with birthweight <3rd percentile (33/66, 50%) than in those recognized at birth (45/157; 28.7%; $p = 0.002$). There were no significant differences in cesarean section rate in SGA infants with birthweight between the 3rd and 5th percentile (7/27, 25.9% for group A, 24/131, 18.3% for group B; $p = 0.37$) or with birthweight between the 5th and 10th percentile (16/39, 41% for group A, 95/350, 27% for group B; $p = 0.07$). Indications for performing cesarean section in groups A and B are reported in Table 3. The incidence of cesarean section for abnormal fetal heart rate was not significantly different between group A and B infants for birthweight <3rd percentile (14/33, 42.4% for group A, 28/45, 62.2% for group B; $p = 0.08$); between the 3rd and 5th percentile (3/7, 42.9% for group A, 10/24, 41.7% for group B; $p = 1$) and between the 5th and 10th percentile (2/16, 12.5% for group A, 22/95, 23.2% for group B; $p = 0.34$). As expected, an abnormal fetal biophysical profile was an indication for cesarean section almost exclusively

Table 1. Comparison of clinical characteristics for group A (antenatally recognized) and group B (recognized at birth) small-for-gestational age infants.

	Group A antenatally recognized $n = 132$	Group B recognized at birth $n = 639$	*p*-value
Nulliparous	84 (63%)	435 (68%)	0.32
Gestational age at delivery, weeks; median (IQR)	39 (38–40)	39.4 (38.6–40.1)	0.002
Birthweight, g; median (IQR)	2475 (2240–2675)	2690 (2530–2780)	<0.001
Birthweight z-score, median (IQR)	−1.89 (−2.33/−1.59)	−1.58 (−1.88/−1.33)	<0.001
Birthweight >5th percentile (*n*(%))	39 (30%)	350 (55%)	<0.001
Birthweight 3rd–5th percentile, *n* (%)	27 (20%)	131 (20%)	0.98
Birthweight <3rd percentile, *n* (%)	66 (50%)	157 (25%)	<0.001
Intrauterine death, *n*	0	2	0.52
Preeclampsia, *n*	7	20	0.22
Induction of labor, *n* (%)	113 (33%)	43 (18%)	<0.001
Cesarean section, *n* (%)	56 (42%)	164 (26%)	<0.001
Arterial cord pH, median (IQR)	7.27 (7.21–7.32), $n = 110$	7.25 (7.19–7.29), $n = 522$	0.02
pH <7.10 (*n* (%))	6 (5%) $n = 110$	32 (6%) $n = 524$	0.79
Admission to NICU (*n*, (%))	19 (14%)	21 (3%)	<0.001
RDS (*n*)	3	8	0.37
PVLM (*n*)	0	1	0.65
IVH (*n*)	0	0	1
NEC (*n*)	0	0	1
ROP (*n*)	0	0	1

IQR, interquartile range; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PVLM, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

Table 2. Indications for admission to neonatal intensive care unit (NICU) in groups A (antenatally recognized) and B (recognized at birth) small-for-gestational age infants.

	Group A Admitted to NICU, $n = 19$	Group B Admitted to NICU, $n = 21$	*p*-value
Respiratory distress syndrome	3/19	8/21	0.16
Hypoglycemia	1/19	4/21	0.35
Hypocalcemia	2/19	0/21	0.48
Feeding difficulties	2/19	0/21	0.22
Arterial cord pH <7.20 plus clinical suspicion of perinatal asphyxia	0/19	5/21	0.049
Low birthweight only	3/19	3/21	1
Neonatal withdrawal syndrome (methadone)	0/19	1/21	1
Jaundice	1/19	0/21	0.48
Anemia	1/19	0/21	0.48
Atrial septal defect	3/19	0/21	0.10
Patent foramen ovale	1/19	0/21	0.48
Patent ductus arteriosus	1/19	0/21	0.48
Persistent pulmonary hypertension	1/19	0/21	0.48

in group A, where fetal wellbeing assessment was systematically performed. On the contrary, we observed a significantly higher incidence of labor dystocia (arrest of dilation, arrest of progression) in group B.

Logistic regression analysis with interaction effect showed that birthweight z-score ($p = 0.03$), but not antenatal recognition ($p = 0.31$), was significantly associated with NICU admission ($p < 0.001$, pseudo $R^2 = 0.15$). There was no significant interaction effect between antenatal recognition and birthweight z-score ($p = 0.07$). AUC comparison showed that AC z-score estimated by ultrasound in SGA fetuses recognized antenatally (AUC 0.77, 95%CI 0.62–0.91) was as good as birthweight z-score (AUC 0.79, 95%CI 0.66–0.93) in correctly identifying infants who were admitted to NICU ($p = 0.65$).

Table 4 shows that in SGA infants recognized antenatally, cesarean section rate, UA PI z score, mean UtA RI z score and prevalence of amniotic fluid index <5 cm were significantly higher, whereas AC and MCA PI z-scores were significantly lower in infants admitted to NICU compared with those not admitted. The prevalence of preeclampsia and STV z-score were not significantly different between these two groups. Antenatally recognized SGA infants (group A) delivered by cesarean section and subsequently admitted to NICU were smaller (median birth weight z score −2.19 [IQR −2.74 to −1.64] vs. −1.59 [IQR −1.97 to −1.28], $p < 0.001$), had higher UA PI z scores [median 0.85 (IQR −0.42 to 1.64) vs. −0.41 (IQR −1.02 to −0.30), $p = 0.041$] and lower MCA PI z scores [median −1.00 (IQR −1.72 to 0.14) vs. median −0.01 (IQR −0.67 to 0.76), $p = 0.03$] when compared with group A infants delivered by cesarean section and not admitted to NICU. Logistic regression analysis showed that UA PI ($p = 0.03$) and MCA PI ($p = 0.05$) z-scores, but not AC z-score

Table 3. Indications for performing cesarean section in groups A (antenatally recognized) and B (recognized at birth) small-for-gestational age infants.

	Group A antenatally recognized $n = 56$	Group B recognized at birth $n = 164$	*p*-value
Fetal heart rate abnormalities	19/56	60/164	0.72
Abnormal fetal biophysical profile	6/56	0/164	<0.001
Failed induction of labor	1/56	0/164	0.26
Placental abruption	0/56	5/164	0.33
Previous cesarean section	13/56	47/164	0.43
Hypertensive complications of pregnancy	3/56	1/164	0.42
Breech presentation	10/56	17/164	0.14
Dystocia	0/56	19/164	5
Maternal disease	3/56	6/164	0.70
Placenta previa minor	0/56	1/164	1
Obstructing fibroid	0/56	1/164	1
Maternal request	1/56	7/164	0.68

($p = 0.11$), were independently associated with NICU admission in group A infants ($p < 0.001$, pseudo $R^2 = 0.46$). The AUC of a model incorporating these three variables for the prediction of NICU admission was 0.94 (95%CI 0.87–1.00).

Discussion

In our study, group A SGA infants (recognized antenatally) were smaller, and were more often delivered by cesarean section and admitted to NICU than were group B infants SGA infants (recognized at birth). Infants with the most severe degree of SGA (birthweight <3rd percentile) were more likely to be diagnosed antenatally.

Adverse outcomes related to hypoxia (two cases of IUD and five cases of NICU admission with peripartum hypoxia) were all observed in group B (no antenatal recognition of SGA), but absolute numbers were too small to achieve statistical significance. Occurrence of respiratory distress requiring respiratory support for longer than 24 hours and periventricular leukomalacia was not significantly different between groups A and B. There were no cases of intraventricular hemorrhage, necrotizing enterocolitis or retinopathy of prematurity in either group. It is likely that groups A and B contained both constitutionally small fetuses and fetuses with IUGR due to placental insufficiency, the latter being more represented in group A. Moreover, group A infants admitted to NICU were smaller and had higher UA PI and lower MCA PI when compared with group A infants not admitted to NICU. We hypothesize that this subgroup might have the highest incidence of IUGR due to placental insufficiency, although it is difficult, due to the small absolute numbers, to identify a typical pattern of neonatal complications related to the IUGR among the indications for NICU admission (19). Overall, our findings corroborate the observation that a birthweight <3rd percentile discriminates between SGA fetuses with a higher risk for adverse perinatal outcome and those with outcomes similar to those of normally grown fetuses (20). The difference in IUDs and neonatal morbidity between groups A and B was not significant, even though group A infants had a higher risk of adverse outcomes (21). In accordance with a previous study (9), this highlights the importance of a structured antenatal surveillance program to identify SGA fetuses before birth in order to lower the risk of adverse fetal outcome.

We observed that AC, UA PI and MCA PI z-scores, and the incidence of oligohydramnios were significantly worse in antenatally recognized SGA infants admitted to NICU. In a recent study UA PI percentile, gestational age at delivery and abdominal circumference were used to calculate the risk of adverse outcome in IUGR fetuses delivered >34 weeks' gestation (8). Our results suggest that middle cerebral artery

Table 4. Comparison of clinical, cardiotocographic, Doppler and ultrasound variables for group A (antenatally recognized) small-for-gestational age infants admitted and not admitted to the neonatal intensive care unit (NICU).

	Admitted to NICU $n = 19$	Not admitted to NICU $n = 113$	*p*-value
AC z score, median (IQR)	−2.23 (− 2.64/ − 1.76)	−1.65 (− 1.99/ − 1.42)	0.002
UA PI z score, median (IQR)	1.14 (− 0.07–1.79)	−0.03 (− 0.96–0.43)	0.003
MCA PI z score, median (IQR)	−0.74 (− 1.33–0.14)	0.20 (− 0.31–1.26)	0.002
UtA mean RI z score, median (IQR)	1.92 (0.99–2.5)	1.09 (0.48–1.90)	0.048
STV z score, median (IQR)	−1.04 (− 2.73/ − 0.37)	−0.57 (− 1.78–0.72)	0.142
AFI <5 cm, *n* (%)	6 (33%), $n = 18$	9 (9%), $n = 101$	0.004
Preeclampsia, *n* (%)	2 (11%)	5 (4%)	0.27
Cesarean section, *n* (%)	15 (79%)	41 (36%)	0.001

AC, abdominal circumference; AFI, amniotic fluid index; IQR, interquartile range; MCA PI, middle cerebral artery pulsatility index; STV, short-term variation; UA PI, umbilical artery pulsatility index; UtA mean RI, uterine artery mean resistance index.

Doppler evaluation might have a role, in addition to umbilical artery assessment, in the prediction for admission to NICU. These findings are in agreement with previous studies illustrating the importance of middle cerebral artery Doppler evaluation in the evaluation of SGA fetuses late in gestation (10,22). Whereas among preterm IUGR fetuses, absent or reversed diastolic flow in the umbilical artery is an important predictor (23), near term the diastolic flow is usually present in the umbilical artery and morbidity attributable to IUGR is possible in late gestation even with normal umbilical artery Doppler waveform (5,10,11). This might be due to increased fetal villous vascularization which, in response to the underlying uteroplacental ischemia, reduces umbilical artery vascular impedance (24).

In our study, 83% of SGA infants and 70% of those with birthweight <3rd percentile were not recognized before birth. In Italy, national guidelines in use at the time of the study and applied to our population recommended a growth scan between 28 and 32 weeks' gestation in all pregnancies (13), in order to identify the more severe cases of IUGR possibly requiring preterm delivery. Our study, in agreement with previous studies reporting sensitivities around 50% for the prediction of SGA by third trimester routine ultrasound in unselected populations (25–27), shows that such a policy has a low yield for the antenatal detection of term SGA fetuses. However, it allows antenatal identification of almost half (19/40) of the SGA infants requiring admission to NICU.

It might be argued that the increased cesarean delivery rate and NICU admission rates observed in the antenatally recognized SGA newborns might be due to an increase in fetal monitoring and medical interventions. In fact, 6/56 cesarean sections in group A were performed due to an abnormal fetal biophysical profile, and such an assessment was only performed in antenatally identified fetuses. However, the rate of cesarean section for fetal heart rate abnormalities was not different between the two groups. Moreover, logistic regression analysis showed that a lower birthweight, but not antenatal recognition, was significantly associated with NICU admission, with a non-significant interaction term between these two variables. These suggest that the chance of being admitted to NICU was more dependent on the severity of growth restriction rather than on any bias introduced by the antenatal recognition.

In conclusion, this study highlights the importance of antenatal recognition in late SGA. Possible limitations are the retrospective nature of the study and the unblinded evaluation of the diagnostic tests used. Early delivery triggered by the diagnostic tests is unlikely to have actually caused an increase in admissions to NICU and may have prevented adverse outcomes related to hypoxia. However, a much larger population is needed to prove such an effect. Only prospective studies can better define the role of antenatal identification of late SGA, and the best criteria for timing of delivery in this group of fetuses.

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