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Prediction of adverse perinatal outcome at midgestation

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KEYWORDS: competing-risks model; neonatal death; neonatal morbidity; neonatal unit admission; precision medicine; pyramid of prenatal care; small-for-gestational age; stillbirth; stratification

CONTRIBUTION

What are the novel findings of this work?
Women identified by the competing-risks model applied at midgestation as being at high risk of delivering small-for-gestational-age (SGA) neonates are also at increased risk of delivering babies requiring admission to neonatal unit for ≥ 48 h, perinatal death and major neonatal morbidity.

What are the clinical implications of this work?
Women with increased midgestation risk for SGA should be informed about their increased risk for adverse neonatal outcomes. A risk-based personalized stratification of pregnancy care for SGA may potentially reduce the rate of adverse neonatal outcomes, but this remains to be proven.

ABSTRACT

Objectives *First, to investigate the association between adverse neonatal outcomes and birth weight and gestational age at delivery. Second, to describe the distribution of adverse neonatal outcomes within different risk strata derived by a population stratification scheme based on the midgestation risk assessment for small-for-gestational-age (SGA) neonates using a competing-risks model.*

Methods *This was a prospective observational cohort study in women with a singleton pregnancy attending a routine hospital visit at 19 + 0 to 23 + 6 weeks' gestation. The incidence of neonatal unit (NNU) admission for ≥ 48 h was evaluated within different birth-weight-percentile subgroups. The pregnancy-specific risk of delivery with SGA < 10th percentile at < 37 weeks was estimated by the competing-risks model for SGA, combining maternal factors and the likelihood functions of Z-score of sonographically estimated fetal weight and uterine artery pulsatility index multiples of the median. The population was stratified into six risk categories: > 1 in 4, > 1 in 10 to ≤ 1 in 4, > 1 in 30 to ≤ 1 in 10, > 1 in 50 to ≤ 1 in 30, > 1 in 100 to ≤ 1 in 50 and ≤ 1 in 100. The outcome measures were admission to the NNU for a minimum of 48 h, perinatal death and major neonatal morbidity. The incidence of each adverse outcome was estimated in each risk stratum.*

Results *In the study population of 40 241 women, 0.8%, 2.5%, 10.8%, 10.2%, 19.0% and 56.7% were in the risk strata > 1 in 4, > 1 in 10 to ≤ 1 in 4, > 1 in 30 to ≤ 1 in 10, > 1 in 50 to ≤ 1 in 30, > 1 in 100 to ≤ 1 in 50 and ≤ 1 in 100, respectively. Women in higher-risk strata were more likely to deliver a baby that suffered an adverse outcome. The incidence of NNU admission for ≥ 48 h was highest in the > 1 in 4 risk stratum (31.9% (95% CI, 26.9–36.9%)) and it gradually decreased until the ≤ 1 in 100 risk stratum (5.6% (95% CI, 5.3–5.9%)). The mean gestational age at delivery in SGA cases with NNU admission for ≥ 48 h was 32.9 (95% CI, 32.2–33.7) weeks for risk stratum > 1 in 4 and progressively increased to 37.5 (95% CI, 36.8–38.2) weeks for risk stratum ≤ 1 in 100. The incidence of NNU admission for ≥ 48 h was highest for neonates with birth weight below the 1st percentile (25.7% (95% CI, 23.0–28.5%)) and decreased progressively until the 25th to < 75th percentile interval (5.4% (95% CI, 5.1–5.7%)). Preterm SGA neonates < 10th percentile had significantly higher incidence of NNU admission for ≥ 48 h compared with preterm non-SGA neonates (48.7% (95% CI, 45.0–52.4%)* vs *40.9% (95% CI, 38.5–43.3%); P < 0.001). Similarly, term SGA neonates < 10th percentile had significantly higher incidence of NNU admission for ≥ 48 h compared with term non-SGA neonates (5.8% (95% CI, 5.1–6.5%)* vs *4.2% (95% CI, 4.0–4.4%); P < 0.001).*

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Conclusions *Birth weight has a continuous association with the incidence of adverse neonatal outcomes, which is affected by gestational age. Pregnancies at high risk of SGA, estimated at midgestation, are also at increased risk for adverse neonatal outcomes.* © *2023 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

It is believed that small-for-gestational-age (SGA) fetuses are at increased risk of stillbirth and adverse perinatal outcome[1–6]. However, data that support this notion are, first, historical and do not take into account the major improvements in neonatal care with time; second, are focused mainly on term pregnancies; and, third, are available mainly for stillbirth and do not cover the whole range of reported neonatal outcomes. It is also generally accepted that early prediction may lead to timely and effective recognition of smallness and improved outcome[6–8]. However, the association between early prediction and adverse neonatal outcome has not been investigated systematically.

In a series of publications, a new competing-risks model for SGA has been developed and validated[9–15]. This model is based on the concept that SGA is more severe the smaller the baby is and the earlier it is delivered. The new approach is superior to the traditional methods, and it is also effective for the prediction of stillbirth[16,17]. We have shown that patient-specific stratification of care has the potential to enhance clinical management, as knowing that a pregnancy is high risk is not enough and a structured antenatal plan for follow-up visits is required[18]. There is a lack of updated evidence for the continuous association between birth-weight distribution and the incidence of adverse neonatal outcomes. Moreover, the incidence of adverse perinatal outcome related to SGA is unclear, in general and after factoring in disease severity expressed in risk profiling, according to our newly established continuous competing-risks approach.

The objective of this non-interventional observational study of singleton pregnancies was, first, to examine the incidence of adverse neonatal outcomes in relation to neonatal size and gestational age at delivery and, second, to describe the distribution of adverse neonatal outcomes within different risk strata derived by a population stratification scheme based on the midgestation risk assessment for SGA by a competing-risks model.

METHODS

Study population and design

The study population was derived from a prospective study for adverse obstetric outcomes in an unselected cohort of women with a singleton pregnancy attending for routine pregnancy care at 19 + 0 to 23 + 6 weeks' gestation at King's College Hospital, London, UK (October 2011 to January 2014 and October 2016 to March 2020) and Medway Maritime Hospital, Gillingham, UK (January 2012 to January 2014 and October 2016 to March 2020).

In the present study, we used information from maternal characteristics and medical history, together with the midgestation measurements of uterine artery pulsatility index (UtA-PI) and fetal biometry. We measured the left and right UtA-PI using transvaginal or transabdominal color Doppler ultrasound and calculated the mean value for the two arteries[19,20]. The majority of UtA-PI measurements were carried out transvaginally because cervical length was being measured at that time; the transabdominal approach was used when women declined transvaginal sonography. Fetal head circumference, abdominal circumference and femur length were measured, and estimated fetal weight (EFW) was calculated using the Hadlock's formula[21] because a systematic review identified this as being the most accurate model[22]. Ultrasound scans were carried out by sonographers who had extensive training in ultrasound imaging and had obtained the appropriate Fetal Medicine Foundation Certificate of Competence in ultrasound and Doppler examinations (http://www.fetalmedicine.com). Pregnant women or healthcare providers were not aware of the results of this assessment. Gestational age was determined by measurement of fetal crown–rump length at 11–13 weeks' gestation or fetal head circumference at 19 + 0 to 23 + 6 weeks' gestation[23,24].

Inclusion criteria for this analysis were a singleton pregnancy and delivery of a non-malformed liveborn or stillborn at ≥ 24 weeks. Pregnancies with major fetal abnormality, termination or fetal death before 24 weeks were excluded. All women gave written informed consent to participate in the study. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the NHS research ethics committee (REC reference: 02-03-033 on 11 March 2003).

Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or general medical practitioners of the women. The examined perinatal outcomes included neonatal unit (NNU) admission for ≥ 48 h, perinatal death, which was defined as stillbirth or neonatal death prior to hospital discharge, and major neonatal morbidity. The following outcomes related to major neonatal morbidity were collected, as indicated in the BadgerNet Neonatal discharge summary: need for ventilation (i.e. continuous positive airway pressure or nasal continuous positive airway pressure or intubation), respiratory distress syndrome (i.e. need for surfactant and ventilation), brain injury (i.e. hypoxic ischemic encephalopathy, intraventricular hemorrhage Grade ≥ 2 or periventricular leukomalacia), sepsis (based on positive blood culture), anemia treated with blood transfusion or necrotizing enterocolitis requiring surgical intervention. Ultimately, major neonatal morbidity was defined as a composite of brain injury, sepsis, anemia and necrotizing enterocolitis. Ventilation and respiratory distress

syndrome were not included in the composite outcome because they were associated with NNU admission for ≥ 48 h. The Fetal Medicine Foundation (FMF) fetal and neonatal population weight charts were used to convert birth weight and EFW into percentiles and *Z*-scores[25].

Statistical analysis

We divided the population according to birth-weight-percentile interval and examined the incidence of NNU admission for ≥ 48 h with corresponding 95% CI within the different percentile subgroups. We examined the incidence of NNU admission for ≥ 48 h in SGA and non-SGA pregnancies with delivery before and after 37 weeks' gestation. The next step was to stratify our population according to the risk assessment for SGA at midgestation. In detail, the competing-risks model, combining the prior joint distribution of birth-weight *Z*-scores and gestational age at delivery with the likelihood functions of UtA-PI multiples of the median (MoM) and EFW *Z*-scores, was used to estimate the risk of delivery of a SGA neonate < 10th percentile < 37 weeks' gestation for each pregnancy in the study population[9,11,12]. The patients were then grouped into one of six risk categories: > 1 in 4, > 1 in 10 to ≤ 1 in 4, > 1 in 30 to ≤ 1 in 10, > 1 in 50 to ≤ 1 in 30, > 1 in 100 to ≤ 1 in 50 and ≤ 1 in 100. NNU admission for ≥ 48 h, major neonatal morbidity and perinatal death were summarized as *n* (%) across the risk strata. Among SGA cases, gestational age at delivery was compared between cases with and those without NNU admission for ≥ 48 h in the different risk strata. Screen-positive rates and detection rates of SGA with NNU admission for ≥ 48 h were also estimated. The statistical software package R was used for data analysis[26].

RESULTS

Study participants

The maternal and pregnancy characteristics of the study population including 40 241 singleton pregnancies are given in Table 1. In the SGA < 10th percentile group, compared with the non-SGA group, there was a lower median maternal age, weight, height and body mass index, a lower prevalence of white women and a higher prevalence of women of black, South Asian, East Asian or mixed racial origin, women with a history of chronic hypertension, systemic lupus erythematosus or antiphospholipid syndrome, women with a family history of PE, smokers, nulliparous women and parous women who had previously developed PE or delivered a SGA neonate. Among parous women, in the SGA group,

Table 1 Maternal and pregnancy characteristics in study population, overall and according to delivery of small-for-gestational-age (SGA) neonate with birth weight < 10th percentile

Variable	*Total* (n = *40 241*)	*Non-SGA* (n = *35 468*)	*SGA* (n = *4773*)	P
Age (years)	31.9 (27.9–35.5)	32.0 (28.0–35.5)	31.4 (27.0–35.3)	< 0.0001
Weight (kg)	67.2 (59.9–78.1)	68.0 (60.0–79.0)	63.8 (56.4–73.8)	< 0.0001
Height (cm)	165 (161–170)	165 (161–170)	163 (158–167)	< 0.0001
Body mass index (kg/m^2)	24.6 (22.0–28.5)	24.7 (22.1–28.6)	24.0 (21.4–27.6)	< 0.0001
GA at assessment (weeks)	21.6 (21.1–22.0)	21.6 (21.1–22.0)	21.6 (21.1–22.0)	0.241
Racial origin				
White	31 195 (77.5)	28 036 (79.0)	3159 (66.2)	< 0.0001
Black	5226 (13.0)	4334 (12.2)	892 (18.7)	< 0.0001
South Asian	1923 (4.8)	1487 (4.2)	436 (9.1)	< 0.0001
East Asian	784 (1.9)	669 (1.9)	115 (2.4)	0.016
Mixed	1113 (2.8)	942 (2.7)	171 (3.6)	0.0003
Conception				
Natural	38 433 (95.5)	33 897 (95.6)	4536 (95.0)	0.101
Ovulation induction	295 (0.7)	255 (0.7)	40 (0.8)	0.415
In-vitro fertilization	1513 (3.8)	1316 (3.7)	197 (4.1)	0.167
Medical history				
Chronic hypertension	425 (1.1)	323 (0.9)	102 (2.1)	< 0.0001
Diabetes mellitus	354 (0.9)	315 (0.9)	39 (0.8)	0.681
SLE/APS	85 (0.2)	68 (0.2)	17 (0.4)	0.031
Cigarette smoker	3016 (7.5)	2324 (6.6)	692 (14.5)	< 0.0001
Family history of PE	1451 (3.6)	1246 (3.5)	205 (4.3)	0.007
Parity				
Nulliparous	18 954 (47.1)	16 241 (45.8)	2713 (56.8)	< 0.0001
Parous, previous SGA	2818 (7.0)	2033 (5.7)	785 (16.4)	< 0.0001
Parous, previous PE and/or SGA	3563 (8.9)	2701 (7.6)	862 (18.1)	< 0.0001
Interpregnancy interval (years)	2.7 (1.7–4.7)	2.7 (1.7–4.6)	3.2 (1.8–5.8)	< 0.0001
PE	1197 (3.0)	846 (2.4)	351 (7.4)	< 0.0001
Gestational hypertension	1095 (2.7)	859 (2.4)	236 (4.9)	< 0.0001

Data are given as median (interquartile range) or *n* (%). Comparisons between outcome groups were performed by chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

compared with the non-SGA group, there was a higher interpregnancy interval.

Incidence of NNU admission for ≥ 48 h according to birth weight and gestational age at delivery

The incidence of NNU admission for ≥ 48 h was highest in the group with birth weight below the 1st percentile (25.7% (95% CI, 23.0–28.5%)), decreased progressively until the 25th to < 75th percentile interval (5.4% (95% CI, 5.1–5.7%)) and then increased for larger babies, following a U-shaped association (Figure 1).

For preterm deliveries < 37 weeks' gestation, SGA neonates < 10th percentile had significantly higher incidence of NNU admission for ≥ 48 h compared with non-SGA neonates (48.7% (95% CI, 45.0–52.4%) *vs* 40.9% (95% CI, 38.5–43.3%); $P < 0.001$) (Figure 2). Similarly, for term deliveries ≥ 37 weeks' gestation, SGA neonates < 10th percentile had significantly higher incidence of NNU admission for ≥ 48 h compared with non-SGA neonates (5.8% (95% CI, 5.1–6.5%) *vs* 4.2% (95% CI, 4.0–4.4%); $P < 0.001$) (Figure 2).

Incidence of pregnancy complications in different risk strata

In the study population of 40 241 women, 0.8%, 2.5%, 10.8%, 10.2%, 19.0% and 56.7% were in the risk strata > 1 in 4, > 1 in 10 to ≤ 1 in 4, > 1 in 30 to ≤ 1 in 10, > 1 in 50 to ≤ 1 in 30, > 1 in 100 to ≤ 1 in 50 and ≤ 1 in 100, respectively. Women in higher-risk strata were more likely to deliver neonates admitted to NNU for ≥ 48 h and have babies that had major morbidity or suffered a perinatal death (Table 2, Figures 3 and 4). The incidence of NNU admission for ≥ 48 h, perinatal death and major neonatal morbidity was highest in the > 1 in 4 risk stratum and it gradually decreased until the ≤ 1 in 100 risk stratum.

Gestational age at delivery of SGA neonates in relation to NNU admission in different risk strata

The mean gestational age at delivery in cases with SGA and NNU admission for ≥ 48 h was 32.9 (95% CI, 32.2–33.7) weeks for risk stratum > 1 in 4, 34.4 (95% CI, 33.7–35.1) weeks for risk stratum > 1 in 10 to ≤ 1 in 4, 36.0 (95% CI, 35.4–36.5) weeks for risk stratum > 1 in 30 to ≤ 1 in 10, 36.3 (95% CI, 35.5–37.1) weeks for risk stratum > 1 in 50 to ≤ 1 in 30, 37.2 (95% CI, 36.5–37.8) weeks for risk stratum > 1 in 100 to ≤ 1 in 50 and 37.5 (95% CI, 36.8–38.2) weeks for risk stratum ≤ 1 in 100 (Figure 5).

The respective figures in SGA cases without NNU admission for ≥ 48 h were 36.9 (95% CI, 36.2–37.5), 38.5 (95% CI, 38.3–38.7), 39.0 (95% CI, 38.9–39.1), 39.2 (95% CI, 39.0–39.3), 39.4 (95% CI, 39.3–39.5) and 39.4 (95% CI, 39.3–39.5) weeks (Figure 5).

Prediction of SGA-related NNU admission for ≥ 48 h and stratification of pregnancy care

Table 3 summarizes the prediction of neonatal morbidity related to SGA in the form of NNU admission for ≥ 48 h.

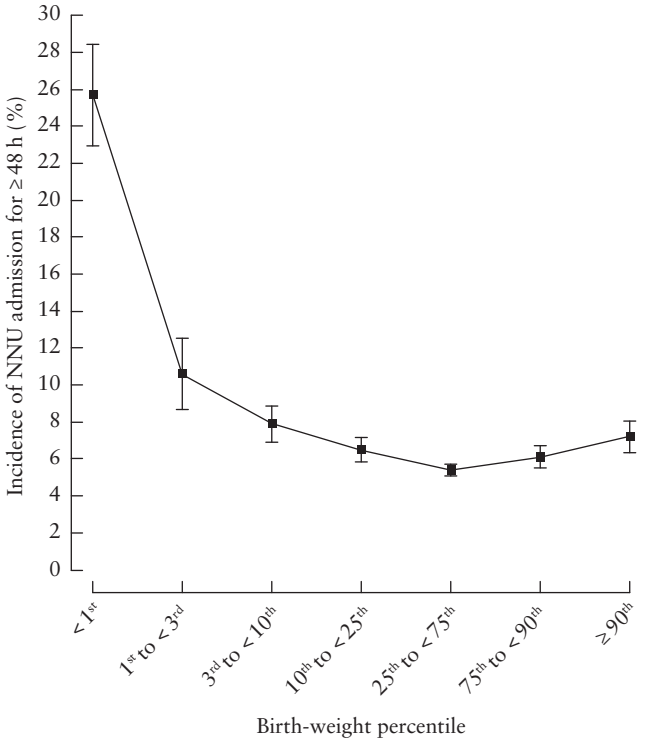

Figure 1 Incidence of neonatal unit (NNU) admission for ≥ 48 h according to birth-weight percentile. Bars are 95% CI.

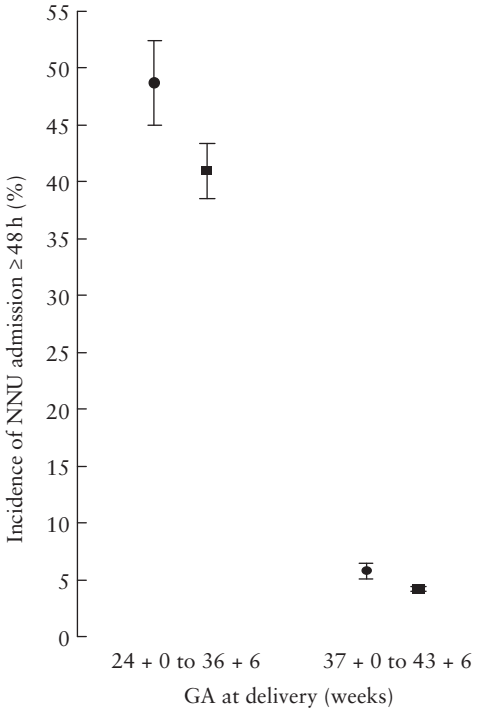

Figure 2 Incidence of neonatal unit (NNU) admission for ≥ 48 h in small-for-gestational-age neonates < 10th percentile (●) and non-small-for-gestational-age neonates (■) according to gestational age (GA) at delivery. Bars are 95% CI.

Table 2 Incidence of adverse pregnancy outcome according to estimated risk of delivery with small-for-gestational age (SGA) < 10th percentile at < 37 weeks

		Risk of delivery with SGA < 10th percentile at < 37 weeks					
Outcome	*Total (n = 40 241)*	*> 1 in 4 (n = 339)*	*> 1 in 10 to ≤ 1 in 4 (n = 998)*	*> 1 in 30 to ≤ 1 in 10 (n = 4327)*	*> 1 in 50 to ≤ 1 in 30 (n = 4101)*	*> 1 in 100 to ≤ 1 in 50 (n = 7654)*	*≤ 1 in 100 (n = 22 822)*
NNU admission for ≥ 48 h	2662 (6.62)	108 (31.86)	131 (13.13)	363 (8.39)	289 (7.05)	490 (6.40)	1281 (5.61)
Perinatal death*	131 (0.33)	18 (5.31)	16 (1.60)	14 (0.32)	12 (0.29)	19 (0.25)	52 (0.23)
Composite major neonatal morbidity†	204 (0.51)	19 (5.60)	16 (1.60)	30 (0.69)	30 (0.73)	31 (0.41)	78 (0.34)

Data are given as *n* (%). *Perinatal death was defined as stillbirth or neonatal death prior to hospital discharge. †Composite major neonatal morbidity included: brain injury (i.e. hypoxic ischemic encephalopathy, intraventricular hemorrhage Grade ≥ 2 or periventricular leukomalacia), sepsis (based on positive blood culture), anemia treated with blood transfusion or necrotizing enterocolitis requiring surgical intervention. NNU, neonatal unit.

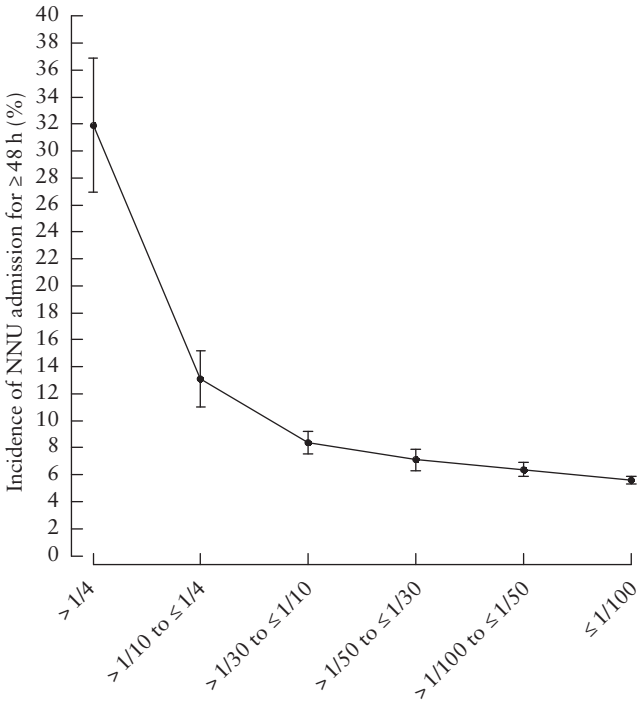

Figure 3 Incidence of neonatal unit admission (NNU) for ≥ 48 h according to estimated mid-trimester risk for delivery with small-for-gestational age (SGA) < 10th percentile at < 37 weeks' gestation. Bars are 95% CI.

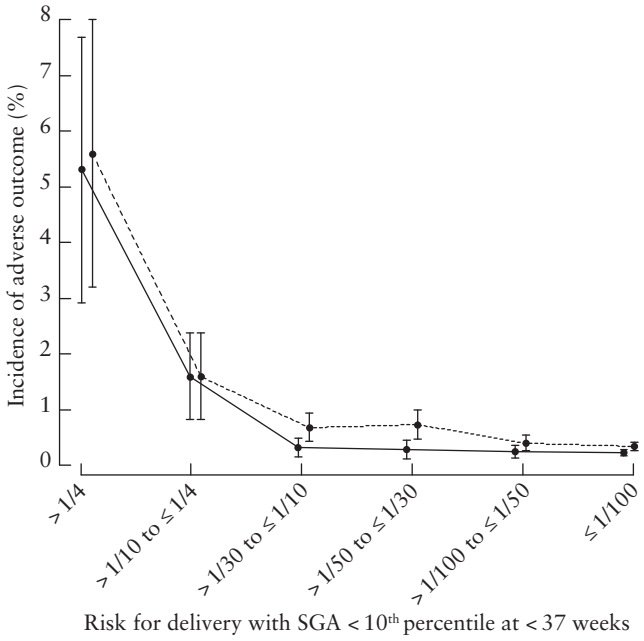

Figure 4 Incidence of perinatal death (—●—) and major neonatal morbidity (--●--) according to estimated mid-trimester risk for delivery with small-for-gestational age (SGA) < 10th percentile at < 37 weeks' gestation. Bars are 95% CI.

The screen-positive rates for risk cut-offs of > 1 in 10, > 1 in 30 and > 1 in 50 were 3.3%, 14.1% and 24.3%, respectively, yielding a detection rate of about 80% for SGA < 10th percentile with NNU admission for ≥ 48 h delivered at < 28, < 32 and < 37 weeks' gestation, respectively (Table 3). The stratification plan deduced from these results would be to start early assessment at 24 weeks for 3.3% of the population (risk > 1 in 10), 28 weeks for 10.8% of the population (risk > 1 in 30 to ≤ 1 in 10), 32 weeks for 10.2% of the population (risk > 1 in 50 to ≤ 1 in 30) and after 35 weeks for the remaining strata with lower risk.

DISCUSSION

Main findings

There are four principal findings of this large prospective observational cohort study on the incidence of adverse neonatal outcomes. First, neonates with a low birth weight are at higher risk for NNU admission and the risk increases with lower birth weight (Figure 1). The baseline risk for NNU admission is much lower in term pregnancies, but the risk in the SGA group is always higher than that in the non-SGA group (Figure 2). Second, in SGA neonates with high midgestation estimated risk of delivery with SGA < 10th percentile at < 37 weeks, there is also increased risk for other neonatal complications, including perinatal death, admission to NNU for ≥ 48 h and major neonatal morbidity (Table 2, Figures 3 and 4).

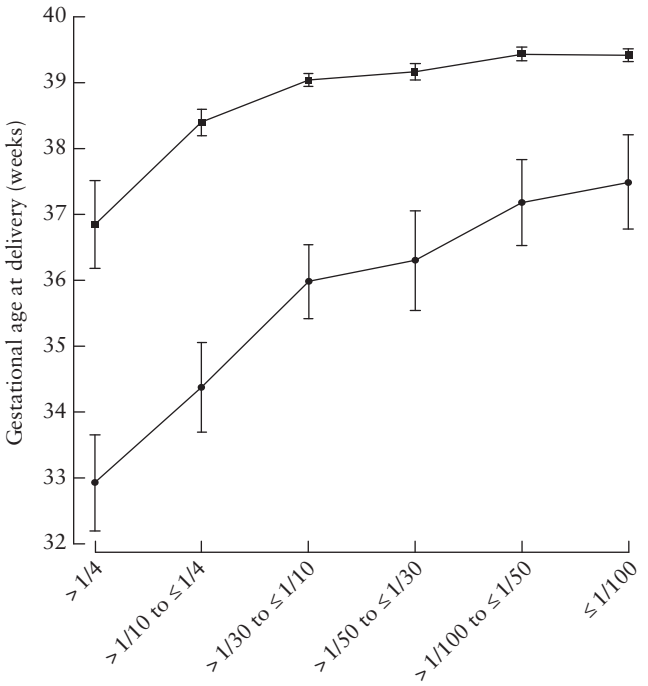

Figure 5 Mean (95% CI) gestational age at delivery in cases with small-for-gestational age (SGA) < 10th percentile with (•) and those without (▪) neonatal unit admission for ≥ 48 h, according to estimated mid-trimester risk for SGA < 10th percentile at < 37 weeks' gestation.

Table 3 Detection rates and screen-positive rates for small-for-gestational age (SGA) with neonatal unit (NNU) admission for ≥ 48 h for different estimated risk cut-offs

	Risk of delivery with SGA < 10th percentile at < 37 weeks		
Outcome	*> 1 in 10*	*> 1 in 30*	*> 1 in 50*
Screen-positive rate (%)	3.3	14.1	24.3
Detection rate (%)			
SGA < 10th percentile < 37 weeks + NNU admission ≥ 48 h	41.4	68.3	80.2
SGA < 10th percentile < 32 weeks + NNU admission ≥ 48 h	55.7	80.4	89.6
SGA < 10th percentile < 28 weeks + NNU admission ≥ 48 h	80.0	90.0	95.0

Third, SGA neonates with increased midgestation risk of delivery with SGA < 10th percentile at < 37 weeks are delivered earlier (Figure 5). Fourth, the higher the risk stratum for the SGA neonates that are admitted to the NNU for ≥ 48 h, the earlier the delivery and the admission to NNU occur (Figure 5).

Interpretation of results and implications for clinical practice

This study demonstrates clearly that birth weight has a continuous association with the incidence of NNU admission for ≥ 48 h (Figure 1). Our data underline the fact that the association between birth weight and adverse neonatal outcome is dependent on gestational age at delivery (Figure 2). This is in alignment with the two-dimensional structure of the SGA model that we have developed. The findings of this study establish the concept that SGA is a tangible and clinically relevant surrogate for placenta-related growth restriction, which is indeed a spectrum condition. The competing-risks model captures effectively the nature of growth restriction; SGA pregnancies at higher risk according to the model are at higher risk of adverse neonatal outcome (Figures 3 and 4). Furthermore, in SGA pregnancies with higher risk, NNU admission for ≥ 48 h occurs earlier in pregnancy and mainly at preterm gestational ages (Figure 5). Therefore, the increasing personalized risk according to the competing-risks approach reflects continuously the increasing severity of the condition.

The results of this study may have a profound effect on the management of growth restriction. We are shifting from an arbitrary and vague way of thinking to a risk-based stratification that integrates the outcomes that we aim to alleviate. The first crucial step is to identify effectively the condition early so that growth-restricted fetuses are diagnosed promptly and receive evidence-based care. This can be achieved by our model, as we have proved in several studies[9–14]. We propose that effective identification should be linked with, first, an appropriate stratification scheme that aims to personalize the timing when third-trimester assessment should be initiated and, second, the timing for delivery, balancing the need for early delivery to avoid the risk of stillbirth and hypoxia, but not too early so that the incidence of adverse neonatal outcomes due to prematurity can be minimized.

In practical terms, the alternative strategy that is shaped by the findings of our study would be to undertake screening for SGA at 19–24 weeks' gestation, stratify the population into risk categories as demonstrated in the current study and plan early assessment at 24 weeks for 3.3% of the population (those with risk > 1 in 10), at 28 weeks for 10.8% of the population (those with risk > 1 in 30 to ≤ 1 in 10), at 32 weeks for 10.2% of the population (those with risk > 1 in 50 to ≤ 1 in 30) and after 35 weeks for the remaining strata with lower risk. Therefore, 24.3% of the population would be examined before the proposed universal assessment at 35–37 weeks at a different and appropriate timing, saving resources and detecting about 80% of cases at risk of SGA-related morbidity (Table 3). The interventions in this high-risk group may include: first, timely administration of steroids, considering their temporal effect close to delivery; second, profiling with fetal growth and Doppler assessments that may prevent hypoxia and stillbirth with timely iatrogenic delivery; third, transfer to a unit with high-level neonatal care; and fourth, deferred delivery, under increased surveillance, beyond the gestational age at which adverse outcomes occur per risk group: 34 weeks for risk stratum > 1 in 4, 35 weeks for risk stratum > 1 in 10 to ≤ 1 in 4, 36.5 weeks for risk stratum > 1 in 30

to ≤ 1 in 10, 37 weeks for risk stratum > 1 in 50 to ≤ 1 in 30 and at about 38 weeks for the remaining strata with lower risk (Figure 5). Therefore, risk-based management may also inform an individualized decision for delivery. The extent to which such a stratification strategy would improve SGA-related neonatal outcomes should be the subject of a future trial.

Strengths and limitations

The main strengths of the study are, first, prospective examination of a large population of women with a singleton pregnancy attending for routine pregnancy care at 19–24 weeks' gestation; second, establishment of the appropriate infrastructure for collection of data on several adverse neonatal outcomes; and, third, the non-interventional nature of the study, allowing reliable conclusions regarding perinatal morbidity and mortality with potential room for improvement for these outcomes. An important strength of our modeling is that the presented stratification scheme is not a fixed one, but it can be tailored to the needs of healthcare systems by simply changing the risk cut-offs. We can also inform a week-by-week personalized timing for the following up of high-risk pregnancies identified at midgestation, customizing pregnancy care on an individual basis[18].

An important limitation of the study is that data were restricted to women with a singleton pregnancy. Therefore, our findings may not necessarily apply to women with a multiple pregnancy. The available information did not allow us to perform a proper health economic analysis. In such an analysis, major cost components, including NNU admission and necessary treatment, would be balanced against a model without any additional cost and a limited number of extra ultrasound scans in the high-risk pregnancies.

Conclusion

Pregnancies with high midgestation estimated risk for delivery of a SGA neonate are also at increased risk for adverse perinatal outcomes. The potential reduction in SGA-related perinatal adverse outcomes by a risk-based stratification plan that promotes appropriate and timely interventions is an important subject of future investigation.

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