

ORIGINAL ARTICLE

Risk of stillbirth at extremes of birth weight between 20 to 41 weeks gestation

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Objective: To determine the risk of stillbirth between 20 to 41 weeks gestation, at highly detailed weight percentiles, including extreme degrees of small (SGA) and large (LGA) for gestational age birth weight.

Study Design: We completed a population-based study of all births in Ontario, Canada between 2002 and 2007. We included 767 016 liveborn and 4,697 stillborn singletons delivered between 20 and 41 weeks gestation. Smoothed birthweight percentile curves were generated for males and females, combining livebirths and stillbirths. Quantile regression was used to calculate sex-specific absolute birthweight differences and 95% confidence intervals (CI) between stillborns vs liveborns at various gestational ages. Logistic regression was used to calculate the odds ratios (OR) for stillbirth at various sex-specific birthweight percentiles, including <1st and ≥99th percentile. OR were adjusted for maternal age and parity.

Result: At the 10th percentile, stillborns weighed significantly less than liveborns starting at 24 weeks gestation. By 32 weeks, this difference was 590 g (95% CI 430 to 750) for males and 551 g (95% CI 345 to 448) for females. A reverse J-shaped association was observed between birthweight percentile and risk of stillbirth across all gestational ages. Relative to the 40th to 60th percentile referent, the adjusted OR for stillbirth was 9.63 (95% CI 8.39 to 11.06) at a birth weight <1st percentile. At ≥99th percentile, the adjusted OR was 2.24 (95% CI 1.76 to 2.86). The risk of stillbirth at extreme birthweight percentiles was robustly observed across gestational ages.

Conclusion: Substantial birthweight differences exist between stillborns and newborns. As a possible hallmark of impending intrauterine death, severe SGA and LGA may each be potential targets for future stillbirth prevention initiatives.

Journal of Perinatology (2012) 32, 829–836; doi:10.1038/jp.2012.60; published online 17 May 2012

Keywords: Stillbirth; birthweight; percentiles; small for gestational age; large for gestational age

Introduction

Infant¹ and maternal² mortality are important indicators of the overall health of a population and the status of its women. At a personal level, a postnatal infant death can carry a heavy emotional burden for both parents, including post-traumatic stress disorder.^{3,4} Similarly, fetal stillbirth has recently gained recognition as a major contributor to parental distress, anxiety and depression.^{5–8} The rate of stillbirth among industrialized nations is about 6 per 1000 total births, of which half occur after 27 weeks gestation.⁹ In poorer countries, the stillbirth rate is up to five times higher.⁶

Stillbirth is commonly defined as a fetal death arising ≥23 weeks gestation, and at a weight of 500 g or more.⁹ One major risk factor for stillbirth is fetal intrauterine growth restriction (IUGR).¹⁰ Though not one and the same, fetal intrauterine growth restriction is often proxied by small-for-gestational age (SGA) birth weight, usually defined by a sex- and gestational age-specific birth weight <10th percentile. Although stillborns weigh less at term than liveborns,¹⁰ less is known about weight discrepancies before 28 weeks, as most studies have only considered stillbirths after this period, and few before 23 weeks gestation.^{11,12} Moreover, no studies have applied more extreme weight percentiles (e.g., <1st) to define SGA. Rather, they have used dichotomous cut-points such as the third or tenth weight percentile. At the other end of the spectrum is the excessively large fetus, who may also be at higher risk of stillbirth, especially at term.^{13,14} However, few studies have applied formal percentile-based definitions of large for gestational age (LGA), and have instead used discrete cut-points of 4500 or 5000 g to define 'macrosomia', which are not standardized for gestational age and newborn sex.

In the study of stillbirths, it might be more appropriate to consider births ≥20 weeks gestation, the time at which the fully formed fetus is seen on level II anatomical ultrasonography, and maternal–fetal bonding is recognized.^{15,16} Moreover, including births ≥20 weeks, and at more extreme weight percentiles, may provide new information about the degree to which SGA and LGA are associated with the occurrence of stillbirths, including that before the point of viability.¹⁷ This might better inform

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Received 20 January 2012; revised 5 April 2012; accepted 24 April 2012; published online 17 May 2012

perinatologists about the competing risks of maintaining a pregnancy to permit fetal maturation *in utero* vs proceeding to delivery after 24 weeks gestation, in light of declining or excess fetal growth.

We examined the association between birth weight and stillbirth between 20 to 41 weeks gestation, at highly detailed weight percentiles, including extreme degrees of SGA and LGA. We also evaluated the relative weight differences between stillborns vs liveborns by gestational age.

Methods

Data source and participants

We completed a population-based study of all singleton livebirths and nonterminated stillbirths occurring within Ontario between 2002 and 2007. The province of Ontario provides free universal healthcare to all residents, including prenatal care and ultrasonography.

Births were identified using birth records provided by Vital Statistics (<http://www.statcan.gc.ca/pub/84f0210x/2002000/4068605-eng.htm> (accessed 15 June 2011)). A birth record requires that two documents be submitted to the Office of the Registrar General, which is part of the Ministry of Government Services of Ontario. The first record is from the attendant/certifier (e.g., physician or midwife) and the other from a parent. A stillbirth is defined as a newborn with no signs of life, whereas intrauterine fetal death refers to a fetus with no signs of life *in utero*. Both are recorded as a 'stillbirth'. A single cause of stillbirth is classified according to the International Statistical Classification of Diseases and Related Health Problems, tenth version (ICD-10). All other births ≥ 20 weeks are recorded as a livebirth.

The birth attendant fills out information on the clinical estimate of gestational age, in completed weeks. In the era of the current study, first trimester ultrasonography—the most accurate method for pregnancy dating¹⁸—is performed in $>75\%$ of pregnancies,¹⁹ 78% of women have a scan before 18 weeks, and 95% by 20 weeks gestation.²⁰ As a small proportion of births may be incorrectly dated for gestational age,²¹ we removed records with implausible birth weight for gestational age values based on cutoffs developed on the basis of clinical and statistical criteria.²² We included singletons born at 20 to 41 weeks' gestation, and excluded those whose birth weight was <250 g or whose sex was not recorded. We used a 250 g cut-off as a liveborn or stillborn fetus may weigh <500 g at ≥ 20 weeks gestation,²³ and one goal herein was to generate new information about extremely low birth weight that might otherwise be suppressed using a 500-g minimum cut-point.²⁴

We categorized each newborn as a livebirth or stillbirth according to the birth certificate record. A given woman may have contributed more than one birth during the period of study, but could not be identified. The primary cause of each stillbirth,

as detailed by its ICD-10 code, was then classified according to the Dutch Tulip classification system.²⁴

Data analysis

Birthweight percentiles. Smoothed birthweight percentile curves were derived using nonparametric quantile regression methods.^{25,26} When the distribution of the response variable is approximately normal, quantile regression produces virtually similar results to the lambda-mu-sigma method.²⁶ Curves were fitted using a cubic spline with four-degrees of freedom, with knots located at 23, 28, 36, 39 and 40 weeks, and the use of a smoothing algorithm. There were no differences between males and females in the location of the knots. The 1st, 3rd, 5th, 10th, 25th, 40th, 50th, 60th, 75th, 90th, 95th, 97th and 99th percentiles were derived from the smoothed curves.

Weight differences. Quantile regression was used to calculate sex-specific absolute birthweight differences and 95% confidence intervals (CI) between stillborns vs liveborns at 20, 22, 24, 26, 28, 32, 36 and 40 weeks gestation, for percentiles 10, 50 and 90.

Risk of stillbirth by gestational age. We plotted the frequency of stillbirth as the prevalence (percentage) of stillbirths at each gestational age, which reflects the probability of stillbirth among all infants born at a given gestational age.

Risk of stillbirth by birthweight percentile. Each newborn was assigned its sex-specific birthweight percentile band (<1 , 1 to <3 , 3 to <5 , 5 to <10 , 10 to <25 , 25 to <40 , 40 to <60 , 60 to <75 , 75 to <90 , 90 to <95 , 95 to <97 , 97 to <99 and ≥ 99) for its given gestational age at birth. Odds ratios (95% CI) were used to estimate the risk of stillbirth associated with each lower or higher percentile birthweight category, relative to the 40th to 60th percentile weight, which served as the referent.²⁷ Using multivariable logistic regression analysis, the odds ratios (OR) were adjusted for maternal age (<20 , 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40+ years) and parity (0 to 5, 5+), as each are risk factors for stillbirth⁹ and SGA,^{28,29} while SGA is a risk factor for stillbirth.⁹ The population attributable risk percent (PAR%) of stillbirth associated with each percentile category was calculated using the formula developed for multcategory exposures and adjusted ORs.³⁰

The crude and adjusted ORs were also presented, stratified by gestational age groups (20 to 27 weeks, 28 to 31 weeks, 32 to 36 weeks and 37 to 41 weeks). In addition, ORs were calculated in an analysis restricted to stillbirths excluding those due to a congenital anomaly or an infection. In a sensitivity analysis of all births between 20 and 40 weeks gestation, we reassigned all of the stillbirths to a gestational age at birth of 1 week earlier than in the main model, and then recalculated the crude, and adjusted OR of stillbirth according to birthweight percentile.

All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA).

Results

There were 772 297 singleton livebirths documented between the years 2002 and 2007. Of these, 5281 (0.68%) were excluded (including 3674 (0.48%) delivered after 41 weeks gestation), leaving 767 016 liveborn infants for analysis. There were 5102 singleton stillbirths, of which 405 (7.9%) were excluded for one or more of the following reasons: 2 were born before 20 weeks and 6 were born after 41 weeks; 15 had missing birth weight, 5 had missing gestational age and 133 had missing infant sex; and 259 had a birth weight under 250 g. Thus, there were 4697 stillbirths for analysis (Table 1). The overall rate of stillbirths was 6.1 stillbirths per 1000 singleton deliveries. The primary stillbirth causes are listed in Table 1.

Maternal age and parity were comparable between stillborns and liveborns (Table 1). Weight percentiles by gestational age and sex for combined liveborns and stillborns are shown in Supplementary Table S1.

Table 1 Characteristics of all 771 713 singleton liveborn and stillborn infants and their mothers delivered at 20 to 41 weeks gestation in Ontario between 2002 and 2007, as well as the primary cause of the stillbirths

Characteristic ^a	Stillbirths (n = 4697)	Livebirths (n = 767 016)
Percent of all deliveries	0.61	99.4
<i>Maternal</i>		
Mean (s.d.) age at delivery, years	30.3 (6.1)	30.0 (10.7)
Median (IQR) parity	2 (1, 2)	2 (1, 2)
<i>Newborn</i>		
Percent female	45.2	48.6
Mean (s.d.) gestational age at birth, weeks	28.7 (7.0)	39.0 (1.8)
Mean (s.d.) birthweight, g	1403 (1176)	3409 (553)
<i>Stillbirth cause^b</i>		
Congenital anomaly (chromosomal, syndrome and single- or multiple-organ system)	491 (10.5)	—
Infection (transplacental, ascending and not otherwise specified)	58 (1.2)	—
Placenta (placental bed, placental pathology, umbilical cord complication and not otherwise specified)	731 (15.6)	—
Prematurity (preterm prelabor rupture of membranes, preterm labour, cervical dysfunction, iatrogenic and not otherwise specified)	332 (7.1)	—
Other (fetal hydrops of unknown origin, maternal disease, trauma and out of the ordinary)	535 (11.4)	—
Unknown	2550 (54.3)	—
Total	4697 (100.0)	—

Abbreviation: IQR, interquartile range.

^aAll data are presented as number (%) unless otherwise indicated.

^bUsing the Dutch Tulip classification system.²⁴

Males were more likely than females to be stillborn between 20 and 23 weeks gestation (Figure 1a). Using this cross-sectional (prevalence) approach, stillbirths comprised about 86% of all male and 81% of all female births at 20 weeks gestation, 18% for each at 28 weeks, and about 0.09% of all births at 41 weeks. Using the fetuses-at-risk (incidence) approach, there was a U-shaped relation between gestational age and the stillbirth rate, which was especially prominent before 24 weeks and after 39 weeks gestation (Figure 1b).

At the 10th percentile, significant birthweight differences were observed between stillborns vs liveborns starting at 22 weeks gestation onward (Supplementary Figure S1a). By 32 weeks gestation, the absolute difference was 590 g (95% CI 430 to 750) for males—a relative difference of 41%—and 551 g (95% CI 345 to 448) for females—a 32% relative difference. At the 50th percentile birth weight, these differences were less pronounced, but smoothly followed a reverse J-shaped pattern from 22 weeks onward (Supplementary Figure S1b). At the 90th percentile birth weight, female (but not male) stillborns weighed about 112 g more than liveborns at 22 weeks gestation, but weight differences were either not significant or favored liveborns thereafter, and the reverse J-shaped pattern was negligible (Supplementary Figure S1c).

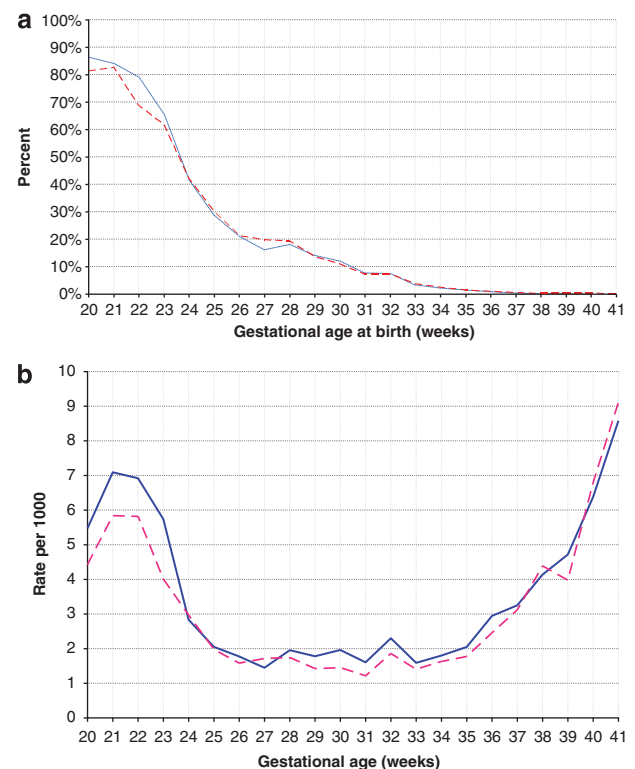


Figure 1 (a) Percentage of singleton stillbirths among all singleton livebirths and stillbirths (prevalence approach). Data are for males (solid blue line) and females (dashed red line), presented by gestational age. (b) Number of stillbirths per 1000 singleton livebirths and stillbirths combined (incidence approach). Data are for males (solid blue lines) and female (dashed red lines), presented by gestational age.

Table 2 Risk of stillbirth according to birthweight percentile among all 771 713 singleton newborns

Birthweight percentile	No. (prevalence (%)) with a given birthweight percentile		Odds ratio (95% CI) for stillbirth by birthweight percentile		Population attributable risk percent ^b
	Stillbirths (n = 4697)	Livebirths (n = 767 016)	Crude	Adjusted ^a	
<1	312 (6.6)	7522 (1.0)	9.82 (8.57–11.26)	9.63 (8.39–11.06)	6.0
1 to <3	292 (6.2)	15 445 (2.0)	4.48 (3.90–5.15)	4.40 (3.83–5.07)	4.8
3 to <5	205 (4.6)	15 157 (2.0)	3.20 (2.74–3.75)	3.22 (2.75–3.78)	3.0
5 to <10	394 (8.4)	37 967 (5.0)	2.46 (2.17–2.79)	2.47 (2.17–2.80)	5.0
10 to <25	822 (17.5)	115 491 (15.1)	1.69 (1.52–1.87)	1.70 (1.53–1.88)	7.2
25 to <40	620 (13.2)	113 504 (14.8)	1.29 (1.16–1.44)	1.30 (1.16–1.45)	3.1
40 to <60 (referent)	650 (13.8)	153 924 (20.1)	1.00 (referent)	1.00 (referent)	0
60 to <75	456 (9.7)	115 325 (15.0)	0.94 (0.83–1.06)	0.94 (0.84–1.06)	–0.62
75 to <90	486 (10.4)	115 183 (15.2)	1.00 (0.89–1.12)	1.00 (0.89–1.12)	0
90 to <95	174 (3.7)	39 136 (5.1)	1.05 (0.89–1.25)	1.04 (0.87–1.23)	0.14
95 to <97	85 (1.8)	15 099 (2.0)	1.33 (1.06–1.67)	1.32 (1.05–1.66)	0.44
97 to <99	127 (2.7)	15 573 (2.0)	1.93 (1.60–2.34)	1.88 (1.55–2.28)	1.3
≥99	74 (1.6)	7690 (1.0)	2.28 (1.79–2.90)	2.24 (1.76–2.86)	0.87

Abbreviations: CI, confidence interval.

^aAdjusted for maternal age (<20, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40+ years), and parity (0, 1, 2 to 5, 5+).^bCalculated by formula 5 in Rockhill *et al.*³⁰

A reverse J-shaped association was observed between birthweight percentile and risk of stillbirth among all newborns (Table 2, Figure 2a). Below the 1st birthweight percentile, the crude OR was 9.82 (95% CI 8.57 to 11.26), virtually unchanged after adjustment; the corresponding PAR% was 6%. Considering all births <5th percentile, the PAR% for stillbirth was 13.8%, and for all those <10th percentile, the PAR% was 18.8%. At ≥90th percentile, the OR for stillbirth increased in a linear manner, albeit with less pronounced effect sizes than at the lowest percentiles (Figure 2a), with a cumulative PAR% of 2.8% at ≥90th percentile (Table 2).

Upon excluding stillbirths, whose listed cause was a congenital anomaly or an infection, the effect sizes changed minimally, as noted by comparing Table 2 with Supplementary Table S2.

At more narrow ranges of gestational age, the associated risk of extreme birthweight percentiles and stillbirth was robustly observed across strata, and the reversed J-shaped association persisted (Figures 2b–e). The greatest effect size was among those born at 28 to 31 weeks at <1st percentile, with a crude OR of 43.0 (95% CI 17.7 to 104.4), and an adjusted OR of 50.6 (95% CI 22.9 to 111.8) (Figure 2c).

In the sensitivity analysis, where stillbirths were assigned a gestational age at birth of 1 week earlier, there remained a reverse J-shaped association between birthweight percentile and the risk of stillbirth (Supplementary Table S3), albeit slightly more attenuated than in the main mode (Table 2).

Discussion

In this population-based study of more than 770 000 liveborn and stillborn infants, about 85% of all male and 80% of all female

newborns were stillborn at 20 weeks gestation. Sizeable birthweight differences were observed between stillborns and newborns, starting at about 24 weeks gestation, and following a reverse J-shaped pattern. This same pattern was observed for the risk of stillbirth in association with the lower and upper extremes of birth weight, especially, at the very lowest percentile, and was not appreciably affected by maternal age or parity.

Weaknesses and strengths

In this data set of submitted birth records, we included newborns with a chromosomal or structural anomaly in our main analysis, like that by others,⁹ but a restricted analysis was also performed (Supplementary Table S2). We were limited to a single cause of death, and we neither possessed information about, nor control for, maternal weight, smoking, diabetes mellitus or hypertension—important risk factors for stillbirth.⁹ We had information about maternal diabetes and hypertension only when they were listed as the cause of fetal death. At the same time, we did control for some important predictors of fetal growth restriction and fetal death, such as maternal age and parity, and we determined sex-specific birthweight percentiles. We also limited our sample to singletons born up to 41 weeks gestation,^{9,31} but births after this gestation are now a minority in Ontario and other industrialized nations, comprising less than 0.5% of our sample. Although nearly 8% of stillbirths were excluded, just 6 (0.12%) were due to birth after 41 weeks. The most common reasons for exclusion were missing infant sex and a birth weight under 250 g, which should not have appreciably affected our observed association between severe SGA and intrauterine fetal death.

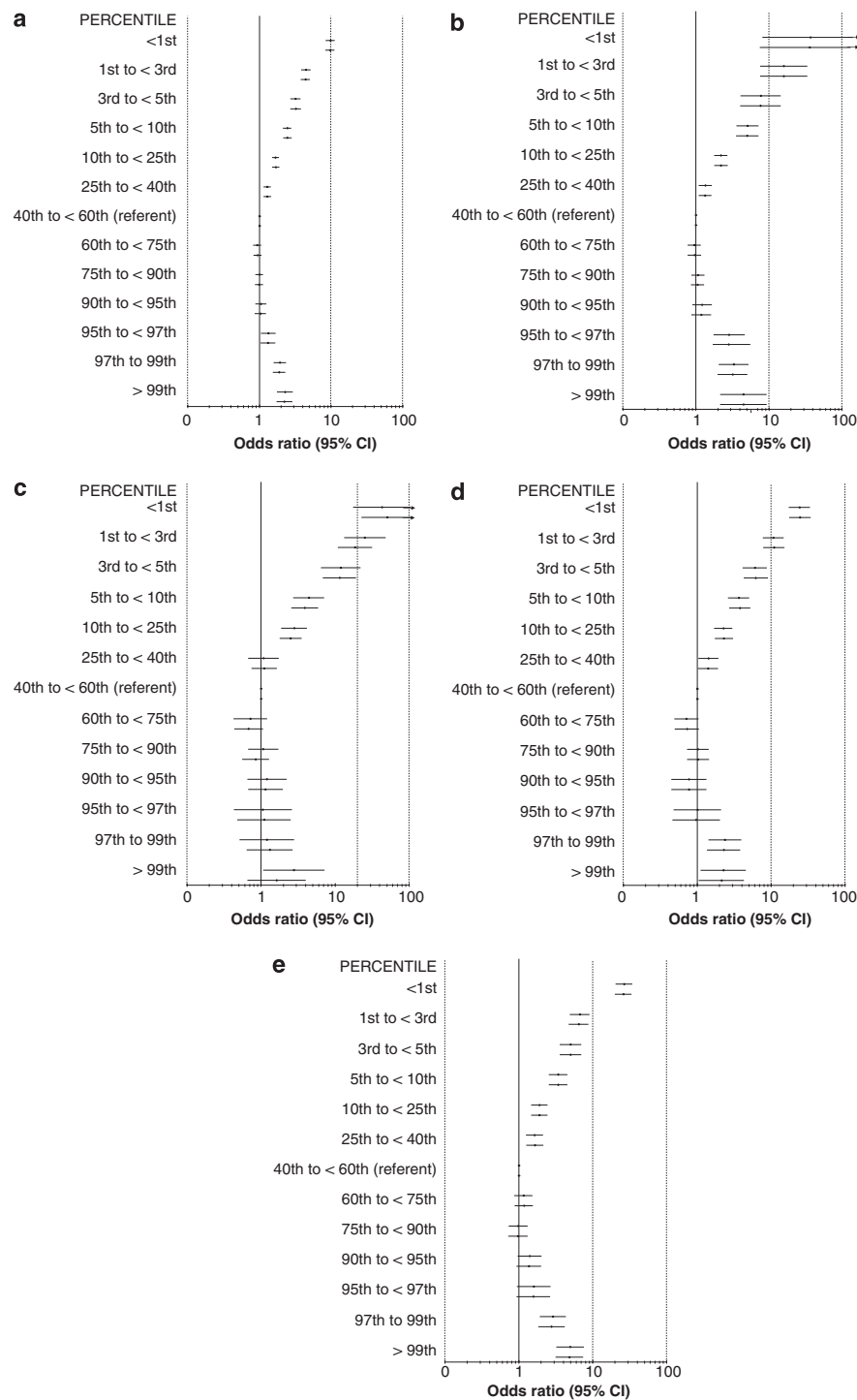


Figure 2 Risk of stillbirth according to birthweight percentile among singleton newborns. Data represent all newborns (**a**), and those born at 20 to 27 weeks (**b**), 28 to 31 weeks (**c**), 32 to 36 weeks (**d**) and 37 to 41 weeks gestation (GA) (**e**). The crude (upper) and adjusted (lower) odds ratios and 95% confidence intervals (CI) for stillbirth are provided at each percentile. Data are adjusted for maternal age and parity.

For multifetal pregnancies (not studied herein), in which the rate of stillbirth is higher, the cause of death may differ from singletons.

Our listed causes of stillbirth closely approximate the early pathophysiological classification system developed by Wigglesworth,

as discussed by Gardosi *et al.*³² However, there are limitations to the Wigglesworth system.³³ The more widely accepted Dutch Tulip criteria for classifying cause of death was evaluated by a prospective Dutch cohort study of 750 singleton intrauterine fetal deaths >20 weeks gestation.³⁴ Therein, 65% of deaths were due to placental

disease, whereas only 5% were due to anomalies and 2% due to infection; nearly one quarter was because of unknown cause. In our study, the respective proportions were 15.6%, 10.5%, 1.2% and 54.3%. One likely reason for this discrepancy is the less standardized and specific nature in which cause of death is recorded in Ontario birth certificates. For example, under the Dutch Tulip criteria, a 'maternal hypertensive disorder' affecting the placenta would be listed as placental disease, whereas, in our study, maternal hypertension would be the cause of death, as listed on the birth certificate.³³ Although our main goal was to examine the association between birth weight and stillbirth, the exclusion of two recognized causes of both SGA and stillbirth—infection and congenital anomalies—did not change that relation. The additional inclusion of fetuses with an unrecognized chromosomal or congenital disorder or an infection would not have likely changed our findings appreciably, in terms of the overall impact on SGA, fetal death and their interaction.^{35–37} Certainly, the future study of fetal weight and stillbirth should carefully assess for the presence of maternal, fetal and placental disease, as discussed below.

A retrospective study like ours is prone to misclassification bias, especially if the gestational age of some stillbirths is incorrectly assigned to a later date, thereby heightening the association between SGA and fetal demise. Although lack of antenatal care may be a strong risk factor for stillbirth,⁹ Ontario's universal health-care system includes comprehensive prenatal care, in which four or more visits are achieved by 90 to 95% of women, with little variation by socio-economic status.^{20,38} Moreover, our estimate of gestational age at delivery was likely very accurate. First, stillbirth and livebirth certification is completed by both a birth attendant and a parent. Second, in Ontario, 78% of women have a prenatal ultrasound before 18 weeks gestation, and 95% of women by 20 weeks gestation.²⁰ Third, although fetal death may occur days in advance of it being recognized, most stillborns are delivered in Ontario within a few days thereafter, as it occurs elsewhere.³⁹ Furthermore, in the current study, the largest difference in stillborn vs newborn weight was seen at about 36 weeks gestation (Supplementary Figure S1), and the risk of stillbirth in association with birthweight percentile persisted after 37 weeks (Figure 2e). At this later gestational age, maternal awareness of poor fetal movement, as well as lack of an audible fetal heartbeat at the weekly prenatal visit,^{20,38} would increase the likelihood that a fetal death is recognized with delivery soon thereafter. Even our sensitivity analysis, wherein stillbirths were reassigned a gestational age at birth of 1 week earlier, the effect sizes were pronounced (Supplementary Table S3). Finally, we did not find bimodal distributions of birth weight at early gestational ages due to errors in pregnancy dating, and we excluded implausible combinations of birth weight and gestational age using the method of Alexander *et al.*²² Thus, a delayed diagnosis of intrauterine fetal death probably does not explain the observed significant weight differences between liveborns and stillborns.

Mechanisms

We observed males to be at higher risk of death before 24 weeks gestation. Data have shown that male fetuses have a higher risk of placenta-mediated disease, including placental abruption, placenta praevia and preeclampsia.⁴⁰ Some argue that the 'sex of the placenta' should be considered in the evaluation of stillbirth risk, given that fetal growth and survival are mediated by the sex-specific function of the placenta.⁴¹ Clearly, a better understanding of the microscopic differences of the placentas of male and female stillborns is warranted, as well as serial study of the differences between male and female uterine artery Doppler flow, *in utero*.

A novelty of our study was the use of extreme percentile cut-points for SGA and LGA, the inclusion of births as early as 20 weeks gestation, the capture of all registered stillborns and liveborns at the population level, and our ability to precisely document the burden of stillbirth by gestational age and by birthweight percentile. When SGA was defined at <10th percentile birth weight, the PAR% for stillbirth was 19% (Table 2). This figure is in very close agreement with the PAR% provided by Flenady *et al.*⁹ in their meta-analysis of stillbirths in five high-income countries. However, using the 10th percentile as a threshold for SGA⁹ fails to appreciate the degree to which more extreme cut-points behave as indicators of stillbirth. Herein, in a cross-sectional manner, we established, with confidence, that this is so. Clearly, the PAR% for stillbirth is not equally distributed below the 10th percentile birth weight (Table 2). Rather, 6% of all stillbirths can be attributed to less than 1% of the lowest birth weights, while an equal percentage of stillbirths are attributed to the broader 5th to 10th percentile birth weights (Table 2). We did not evaluate the rate of antepartum vs intrapartum stillbirths, or that of early or late neonatal death among the livebirths in our study, but they are known to correlate with severe SGA.⁴² As we limited our data set to deliveries up to 41 weeks gestation, it is less likely that stillbirths were associated with post-term over-maturity of the placenta. We included deliveries up to 41 weeks, as early pregnancy-dating ultrasound is now commonly used in Western nations, thereby correctly assigning a slightly earlier gestational age to those previously miscategorized as 'post-term', when dating was based on last menstrual period.⁴³ This correct assignment of gestational age also enables accurate implementation of guidelines recommending delivery after 41 weeks gestation,⁴⁴ and lowers the likelihood that a stillbirth is incorrectly ascribed to a gestational age that is later than the true gestational age.⁴⁴

Relevance for policy makers and clinicians

We have shown that the most severe degrees of SGA reflect a major proportion of stillbirths across all gestational periods; severe LGA (>99th percentile) is also a significant, albeit, less prominent, risk factor. The risk of stillbirth persists at term, both at extreme SGA and at extreme LGA percentiles (Figure 2).

In many cases, severe SGA may signify looming intrauterine death that warrants clinical reflection and possible action.

The former can be aided by the sonographic assessment of the amniotic fluid index, fetal biophysical profile, and uterine artery and fetal blood flow Doppler indices.^{45,46} Among 15 low-quality randomized clinical trials, Doppler ultrasonography was compared with no Doppler ultrasonography in more than 9500 high-risk pregnancies.⁴⁶ Use of Doppler testing was associated with a pooled OR for stillbirth of 0.65 (95% CI 0.41 to 1.04).⁴⁶ Potential action in the presence of severe SGA with or without other markers of poor fetal well-being would certainly depend on gestational age as an indicator of neonatal viability. Our data suggest that delivery of a fetus with severe SGA or severe LGA close to, or at, term is sensible, and is in keeping with the DIGITAT study.⁴⁷ At earlier gestational ages, frequent sonographic assessment might aid the perinatologist in his/her reflection about the feasibility of early delivery in the face of dropping or rising weight percentiles, before the development of severe SGA or severe LGA, respectively.⁴⁵ The evidence for delivery of fetuses with preterm SGA is not convincing,⁴⁸ however, and must be established by a large-scale randomized clinical trial. Therein, careful consideration must be made as to the appropriate percentile cut-point that is selected to identify SGA, in that one would not want to expose fetuses with mild SGA to unnecessary preterm birth. Finally, as the process of fetal growth restriction may start in the first trimester of pregnancy,^{49,50} and as most women in the industrialized world receive a level II anatomical ultrasound by 22 weeks gestation, biometry at this time offers an indication of the presence of SGA or LGA, as well as a baseline for future comparison.

The global burden of stillbirths is well documented.^{6,9} Maternal, pregnancy surveillance and peripartum interventions are currently being considered for the prevention of stillbirths in both low-income and industrialized countries.^{46,51,52} Within new industrialized nations and industrialized nations, it is believed that a substantial proportion of stillbirths arise from placental pathology.⁹ Maternal features of the metabolic syndrome, including obesity, diabetes mellitus and hypertension introduce a higher risk of placental vascular disease,^{53,54} at both the lowest and highest percentiles of fetal growth.⁵⁴ Future stillbirth reduction initiatives—especially those aimed at reducing placental disease—may wish to also focus on the prevention and management of severe SGA and severe LGA.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This work was funded by the Canadian Foundation for the Study of Infant Deaths. We were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Disclaimer

No funding bodies had any role in the study design, data collection, analysis, decision to publish or preparation of the manuscript.

Ethics

Permission to complete the study was obtained from the Research Ethics Board of St. Michael's Hospital, Toronto, Ontario, February 2011.

Author contributions

Ray contributed to the study conception, design and analysis, drafting of manuscript, manuscript revision, approval of final version.

Urquia contributed to the study conception, design and analysis, drafting of manuscript, manuscript revision, approval of final version.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (<http://www.nature.com/jp>)