
Title: Ultrasound in Obstetrics & Gynecology
ArticleTitle: Large-for-gestational age and stillbirth: is there a role for antenatal testing?
ArticleAuthor: Carter
Vol: 54 No: 3 Date: September 2019 Pages: 334-337

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Ultrasound Obstet Gynecol 2019; **54**: 334–337
Published online 6 August 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20162

Large-for-gestational age and stillbirth: is there a role for antenatal testing?

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KEYWORDS: antenatal testing; diabetes; gestational diabetes; large-for-gestational age; LGA; stillbirth

ABSTRACT

Objective *To investigate the association between large-for-gestational-age (LGA) pregnancy and stillbirth to determine if the LGA fetus may benefit from antenatal testing with non-stress test or biophysical profile.*

Methods *This was a retrospective cohort study of singleton pregnancies that were ongoing at 24 weeks' gestation and that had undergone routine second-trimester anatomy ultrasound examination, during the period 1990 to 2009. Pregnancies complicated by fetal anomaly or aneuploidy, those with missing birth weight information and those that were small-for-gestational age were excluded. Appropriate-for-gestational age (AGA) and LGA were defined as birth weight between the 10th and 90th percentiles and > 90th percentile, respectively, according to the Alexander growth standard. The incidence of stillbirth was calculated as the number of stillbirths per 10 000 ongoing pregnancies. Adjusted odds ratios (aOR) with 95% CI for stillbirth in LGA compared with AGA pregnancies were estimated using logistic regression analysis, controlling for pre-existing and gestational diabetes. The incidence and aOR for stillbirth were estimated at 4-week intervals from ≥ 24 to ≥ 40 weeks' gestation.*

Results *Of 52 749 pregnancies ongoing at 24 weeks, 46 205 (87.6%) were AGA and 6544 (12.4%) were LGA at delivery. The incidence of stillbirth in LGA pregnancies was significantly higher than that in AGA pregnancies from 36 weeks' gestation (26/10 000* vs *7/10 000; aOR, 3.10; 95% CI, 1.68–5.70). When women with diabetes were excluded in stratified analysis, pregnancies complicated by LGA continued to be at increased risk for stillbirth ≥ 36 weeks (18/10 000* vs *7/10 000; OR, 2.63; 95% CI, 1.27–5.43).*

Conclusion *Pregnancies complicated by LGA are at significantly increased risk for stillbirth at or beyond 36 weeks, independent of maternal diabetes status, and may benefit from antenatal testing.* Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

In the USA, 1/200 pregnancies reaching 22 weeks' gestation will result in stillbirth[1]. There is a well-established association between small-for-gestational-age (SGA) pregnancies and stillbirth, but the risk of stillbirth in pregnancies with a large-for-gestational-age (LGA) fetus (birth weight > 90th percentile for gestational age) remains unclear[2]. Some population-based studies cite LGA as a possible hallmark of impending intrauterine death and therefore a potential target for stillbirth prevention initiatives[3–5], while others show no increased risk of stillbirth in LGA compared with appropriate-for-gestational-age (AGA) pregnancies[6,7].

In the setting of conflicting evidence, antenatal testing is not currently recommended in LGA pregnancies[8]. The aim of this study was to investigate the association between LGA and stillbirth. We hypothesized that LGA confers a significantly increased risk of stillbirth.

METHODS

This was a retrospective cohort study of singleton pregnancies that were ongoing at 24 weeks' gestation presenting at Washington University School of Medicine perinatal ultrasound units for routine second trimester anatomical survey during the period 1990 to 2009. The study was approved by the Washington University Institutional Review Board, ID no. 201206058, and informed consent was obtained. Our medical center is an academic tertiary care center that serves as a major regional and national referral center. The previously validated Washington University perinatal database was

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Accepted: 12 October 2018

used, a large system with dedicated research personnel for the collection and maintenance of data. Self-report questionnaires were used to collect maternal demographic information and medical and obstetric histories at the initial ultrasound visit. Follow-up information was obtained from medical records by trained research personnel. If the woman delivered outside the medical system, follow-up information was obtained via telephone contact with the woman or referring physician. Further details of data collection and management have been published previously[9].

Ultrasound was performed by certified sonographers dedicated to obstetric and gynecological examinations. The final diagnosis was made by the attending maternal–fetal medicine physician. Gestational age was determined by the best obstetrical estimate based on established American College of Obstetricians and Gynecologists (ACOG) guidelines at the time of the ultrasound examination. As per the inclusion criteria, all women had an ultrasound examination between 16 and 24 weeks; therefore, all pregnancies had dating performed or confirmed on first- or second-trimester ultrasound examination.

AGA and LGA were defined as birth weight between the 10th and 90th percentiles and > 90th percentile, respectively, according to the Alexander growth standard[10]. There was no standard practice or protocol guiding clinical management of fetuses with estimated fetal weight > 90th percentile at our institution during the study period. In general, women who had not undergone diabetes screening at the time of diagnosis were offered screening, but there was no standard approach regarding antenatal testing or timing of delivery. Women were identified as having gestational diabetes mellitus by the two-step screening test recommended by ACOG[11] using a 50-g oral glucose load with a 1-h blood sugar cut-off of 140 mg/dL and a 3-h glucose tolerance test using the National Diabetes Data Group diagnostic criteria[12]. Diagnosis of Type 1 or 2 diabetes was determined as self-reported by the patient or documented by the medical team. Pregnancies complicated by fetal anomaly or aneuploidy, those with missing birth weight information and those that were SGA were excluded.

The incidence of stillbirth was calculated as the number of stillbirths per 10 000 ongoing pregnancies. Within our database, stillbirth is defined as intrauterine fetal death ≥ 20 weeks' gestation, but deliveries < 24 weeks of gestation were excluded from the analysis in accordance with the aim of our study. The incidence of stillbirth was estimated at 4-week intervals from ≥ 24 to ≥ 40 weeks' gestation.

Baseline maternal characteristics were compared between LGA and AGA pregnancies. Variables were compared using descriptive and bivariate statistics by unpaired Student's *t*-test or the Mann–Whitney *U*-test for continuous variables and chi-square or Fisher's exact test for categorical variables. The Kolmogorov–Smirnov test was used to test the normality of the distribution of continuous variables. Univariate and multivariable logistic regression analyses were used to estimate the crude (OR) and adjusted (aOR) odds ratios with 95% CI for stillbirth in LGA pregnancies at 4-week intervals. Covariates for inclusion in the initial multivariable models were selected based on biological plausibility and the results of stratified analyses. Factors were removed in a backward stepwise fashion based on significant changes in the aOR. The final model was adjusted for pre-existing and gestational diabetes. Final models were tested using the Hosmer–Lemeshow goodness-of-fit test. Stratified analysis was conducted according to diabetes status. Statistical analysis was performed using Stata software (version 14, StataCorp LP, College Station, TX, USA).

RESULTS

A total of 52 749 singleton pregnancies that were ongoing at 24 weeks met the inclusion criteria. Of these, 46 205 (87.6%) delivered an AGA neonate and 6544 (12.4%) delivered a LGA neonate. Women with a LGA pregnancy were older and more often white and parous and had higher body mass index compared with an AGA pregnancy (Table 1). Diabetes (either pre-existing or gestational) complicated 6.6% of AGA pregnancies and 12.5% of LGA pregnancies ($P < 0.01$). Of the 17 stillbirths that occurred in LGA pregnancies, six (35%) were in women with diabetes.

The incidence of stillbirth ≥ 24 weeks was 21/10 000 among AGA pregnancies compared with 26/10 000 in LGA pregnancies (aOR, 1.07; 95% CI, 0.63–1.83) (Table 2). The incidence of stillbirth in LGA pregnancies was also greater than that in AGA pregnancies at ≥ 28 (26/10 000 *vs* 15/10 000) and ≥ 32 (26/10 000 *vs* 12/10 000) weeks. However, the differences were not statistically significant until ≥ 36 weeks. In LGA

Table 1 Maternal and pregnancy characteristics in 52 749 pregnancies, according to delivery of appropriate- (birth weight 10th–90th percentile; AGA) or large- (birth weight > 90th percentile; LGA) for-gestational-age neonate

Characteristic	*AGA (n = 46 205)*	*LGA (n = 6544)*	P
Age (years)	30.2 ± 6.3	31.6 ± 5.8	< 0.01
Race			
Black	10 393 (22.5)	870 (13.3)	< 0.01
White	28 527 (61.7)	4776 (73.0)	< 0.01
Other	7285 (15.8)	898 (13.7)	< 0.01
Nulliparous	18 046 (39.1)	1824 (27.9)	< 0.01
BMI (kg/m^2)	25.0 ± 9.3	26.3 ± 10.2	< 0.01
Diabetes			
Any	3069 (6.6)	817 (12.5)	< 0.01
Pre-existing	761 (1.6)	284 (4.3)	< 0.01
Gestational	2308 (5.0)	533 (8.1)	< 0.01
Pre-eclampsia	3501 (7.6)	408 (6.2)	< 0.01
Third-trimester US performed	6415 (13.9)	951 (14.5)	0.16
GA at delivery (weeks)	39.1 (38.1–40.0)	39.4 (38.7–40.3)	< 0.01

Data are mean ± SD, median (interquartile range) or *n* (%).
BMI, body mass index; GA, gestational age; US, ultrasound.

Table 2 Incidence and risk of stillbirth in large- (birth weight > 90th centile; LGA) compared with appropriate- (birth weight 10th–90th percentile; AGA) for-gestational-age pregnancies, according to gestational age (GA) and diabetes status

	All		*Diabetes*		*No diabetes*	
GA at stillbirth	*Stillbirths/10 000 ongoing pregnancies*	*aOR (95% CI)**	*Stillbirths/10 000 ongoing pregnancies with diabetes*	*OR (95% CI)*	*Stillbirths/10 000 ongoing pregnancies without diabetes*	*OR (95% CI)*
GA ≥ 24 weeks						
AGA	21	Reference	50	Reference	19	Reference
LGA	26	1.07 (0.63–1.83)	76	1.51 (0.58–3.91)	18	0.93 (0.48–1.80)
GA ≥ 28 weeks						
AGA	15	Reference	50	Reference	12	Reference
LGA	26	1.44 (0.83–2.50)	76	1.50 (0.58–3.89)	18	1.41 (0.72–2.78)
GA ≥ 32 weeks						
AGA	12	Reference	38	Reference	11	Reference
LGA	26	1.75 (1.00–3.07)	76	2.01 (0.74–5.45)	18	1.65 (0.83–3.27)
GA ≥ 36 weeks						
AGA	7	Reference	15	Reference	7	Reference
LGA	26	3.10 (1.68–5.70)	78	5.11 (1.44–18.14)	18	2.63 (1.27–5.43)
GA ≥ 40 weeks						
AGA	5	Reference	0	Reference	6	Reference
LGA	13	2.35 (0.61–9.11)	0	NA†	13	2.38 (0.61–9.21)

*Adjusted for diabetes (pregestational or gestational). †Analysis not performed due to limited number of outcomes. aOR, adjusted odds ratio; NA, not available; OR, odds ratio.

Figure 1 Birth weight in large- (birth weight > 90th–95th (●) or > 95th (●) percentile) and appropriate- (birth weight 10th–90th percentile (○)) for-gestational-age pregnancies resulting in stillbirth, according to gestational age.

pregnancies reaching 36 weeks' gestation, the incidence of stillbirth was more than three-fold higher than that in AGA pregnancies (26/10 000 *vs* 7/10 000; aOR, 3.10; 95% CI, 1.68–5.70). All stillbirths in LGA pregnancies occurred after 36 + 5 weeks' gestation (Figure 1). Results were similar for LGA pregnancies with birth weight > 95th percentile (data not shown), with the difference in incidence of stillbirth between these pregnancies and those that were AGA also achieving statistical significance at ≥ 36 weeks (24/10 000 *vs* 6/10 000; aOR, 2.98; 95% CI, 1.45–6.15).

When results were stratified according to the presence or absence of pre-existing or gestational diabetes (Table 2), the difference in the risk of stillbirth between AGA and LGA pregnancies was significant only at ≥ 36 weeks in both groups. Among women with diabetes, those with a LGA pregnancy were more likely to have stillbirth ≥ 36 weeks (78/10 000 *vs* 15/10 000; OR, 5.11; 95% CI, 1.44–18.14). When women with diabetes were excluded, pregnancies complicated by LGA continued to be at increased risk for stillbirth ≥ 36 weeks (18/10 000 *vs* 7/10 000; OR, 2.63; 95% CI, 1.27–5.43).

DISCUSSION

In this study, we found that LGA is an independent risk factor for stillbirth at or after 36 weeks and the presence of diabetes further increases this risk. The risk of stillbirth in LGA pregnancies without diabetes is comparable to that in other common conditions for which antenatal testing is currently the standard of care, such as hypertensive diseases of pregnancy[13].

The results of this study are consistent with those of Bukowski *et al.* in a population-based, case–control study of all stillbirths and a representative sample of live births in 59 hospitals in the USA, which showed that stillbirth was associated with both growth restriction and excessive fetal growth, with a stronger association in more severe LGA (> 95th percentile)[5]. Conversely, a recent secondary analysis of a Maternal Fetal Medicine (MFMU) Network cohort of 50 374 women, in which neonatal morbidity was assessed in LGA pregnancies reaching term[7], found no difference in the rate of stillbirth between LGA and AGA pregnancies (1.5/1000 *vs* 0.9/1000; aOR, 1.64; 95% CI, 0.79–3.42). The lower overall risk of stillbirth in this cohort, inclusion of only term pregnancies and inclusion criteria defined by the primary MFMU network trials are important differences that may explain the discrepancy between their findings and those of the current study.

A major strength of our study is the use of a large, validated and well-maintained database to evaluate the risk of rare outcomes such as stillbirth. The use of certified, dedicated and experienced sonographers and

consistent guidelines for assignment of gestational age by ultrasound dating are other strengths of this study. We utilized a measure of size (LGA) that takes into account the gestational age at delivery rather than absolute macrosomia, which has been used in previous studies. The results of the current study are also generalizable to current obstetric practices, as the current standard of care in the USA involves the initiation of antenatal testing when the risk of stillbirth is deemed sufficiently high, such as that in hypertensive disorders of pregnancy. The risk of stillbirth was assessed across the full range of viable gestational ages, which suggested that the risks associated with LGA are not distributed evenly across gestational ages and seem to be negligible until 36 weeks.

The results should be considered in the context of the following limitations. Although our database is large and well-maintained, the outcome of interest (stillbirth) is rare, which may therefore have limited our ability to detect differences on stratified analyses. As this was a retrospective, secondary analysis of prospectively collected data, information on prior pregnancies complicated by LGA, placental pathology and whether the stillbirth occurred antepartum or intrapartum was not available, and the study is subject to selection bias. We were unable to identify the precise timing of fetal death so gestational age at death was assigned based on delivery date rather than fetal demise date. It is possible that this introduced error into our weight for gestational age calculations among pregnancies that experienced stillbirth. Similarly, our definitions of AGA and LGA were based on birth weight rather than fetal weight at the time of death. However, this would be expected to affect similarly AGA and LGA stillbirths and bias our results towards the null hypothesis of no difference. In addition, we do not know how many obstetrics providers suspected LGA at the time of delivery and how this information may have influenced their management. However, one would presume that clinicians suspecting LGA or impending macrosomia would be more inclined to deliver those fetuses early, especially in the period before the implications of early term birth were understood, which would have decreased the risk for stillbirth and biased our results towards the null hypothesis. Finally, the cohort was drawn from a single tertiary referral center. Therefore, our findings may not be generalizable to lower risk or community settings.

The finding of this study that LGA confers a significantly increased risk of stillbirth in pregnancies reaching 36 weeks' gestation, independent of maternal diabetes status, suggests that there may be a late-pregnancy mechanism linking stillbirth and LGA. It is biologically plausible that the metabolic demands of the LGA fetus may exceed the ability of the placenta to meet them, predisposing the fetus to stillbirth, but additional research is needed to determine the exact mechanism.

While evidence for improved perinatal outcome is derived primarily from observational studies[14,15], the American College of Obstetricians and Gynecologists suggests that antepartum fetal surveillance may be indicated when the risk of antepartum fetal demise is increased[8]. The results of this study suggest that the LGA fetus may benefit from antenatal testing starting at 36 weeks. While there are no large, randomized trials to guide testing frequency, a reasonable strategy would be to initiate weekly or twice weekly testing with a non-stress test or biophysical profile at 36 weeks. In the setting of reassuring fetal testing, a reasonable delivery target would be 39 weeks in order to balance the risk of stillbirth with the risks associated with early term birth.

In conclusion, the findings of this study suggest that the LGA fetus may benefit from antenatal testing starting at 36 weeks as a strategy to reduce the risk of stillbirth. However, additional prospective research is needed to quantify the true risk of stillbirth in LGA pregnancies and to determine whether antenatal testing has the potential to mitigate this risk.

ACKNOWLEDGMENTS

E.B.C. and A.S.T. were supported by NIH T32 Grant No. 2T32HD055172-06 (PI, G.A.M.). At the time of investigation, A.S.T. was supported by Washington University Institute of Clinical and Translational Sciences Grant No. UL1TR000448 (PI, B. Evanoff). E.B.C. is supported by a Robert Wood Johnson Grant, No. 74250. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the Robert Wood Johnson Foundation.

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