OBSTETRICS

# Small-for-gestational-age infants among uncomplicated pregnancies at term: a secondary analysis of 9 Maternal-Fetal Medicine Units Network studies

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**BACKGROUND:** Most small (birthweight <10%) for-gestational-age cases occur at term, in uncomplicated pregnancies, and are not identified during prenatal visits as having fetal growth restriction. Hence, they do not benefit from antepartum surveillance and timed delivery. There is dismissive and disquieting opinion that small for gestational age among uncomplicated pregnancies is not associated with increased morbidities and, therefore, does not warrant improved detection. Our hypothesis was that among uncomplicated pregnancies at term, small for gestational age have significantly higher morbidity and mortality than appropriate (birthweight 10-89%) for gestational age.

**OBJECTIVE:** We sought to compare composite neonatal morbidity among uncomplicated term singleton pregnancies with small vs appropriate for gestational age.

**STUDY DESIGN:** We culled collected data from 9 completed Maternal-Fetal Medicine Units studies conducted from 1989 through 2004. All data were collected prospectively by trained staff. We excluded women who delivered <37 weeks and those with hypertension or diabetes, multiple gestation, known anomalies, and birthweight of ≥90% for gestational age. Using multivariable analysis, we compared composite neonatal morbidity, which included stillbirth and neonatal mortality between small and appropriate for gestational age. Random effect logistic regressions were used to account for study heterogeneity, with adjustment for potential confounders. We calculated adjusted odds ratios and 95% confidence intervals.

**RESULTS:** Of the >91,000 women enrolled in the studies, 60% (n = 50,011) met the inclusion criteria. Among the uncomplicated pregnancies, 10.8% (n = 5416) were small for gestational age. The rate of composite neonatal morbidity of 16% in small for gestational age and 10% in appropriate for gestational age persisted (adjusted odds ratio, 1.75; 95% confidence interval, 1.71—1.78). After adjustment for confounders, the following neonatal morbidities were significantly more common among term small than appropriate for gestational age: Apgar <4 at 5 minutes, respiratory distress syndrome, mechanical ventilation, necrotizing enterocolitis grade 2 or 3, and neonatal sepsis. Lastly, rate of stillbirths (3.5 vs 0.9/1000 births; adjusted odds ratio, 3.49; 95% confidence interval, 1.83—6.67) and neonatal mortality (1.1 vs 0.4/1000 births; adjusted odds ratio, 2.56; 95% confidence interval, 1.83—3.57) were significantly more common with small than appropriate for gestational age. In secondary analyses the composite neonatal morbidity among newborns at <5% and at 5-9% was significantly higher than appropriate for gestational age. Lastly, in subgroup analyses of women who delivered at 37.0-38.6 weeks or at ≥39.0 weeks, the increased rate of composite neonatal morbidity, stillbirth, and neonatal mortality among small for gestational age persisted.

**CONCLUSION:** Among uncomplicated pregnancies at term, small- compared to appropriate-for-gestational-age newborns have a significantly higher likelihood of composite neonatal morbidity, stillbirth, and neonatal mortality. A large multicenter trial is warranted to determine if improved detection of small for gestational age among uncomplicated pregnancies can mitigate morbidities and mortality, without disproportionate interventions and iatrogenic complications.

**Key words:** growth restriction, morbidity, SGA

## Introduction

Small-for-gestational-age (SGA) newborns, defined as birthweight <10%, are at increased risk of both neonatal morbidity (respiratory distress syndrome, intraventricular hemorrhage, seizure, sepsis) and mortality including risk of stillbirth and death within 28 days of birth.[1] Frequently, the publications linking SGA with morbid sequelae include all pregnancies irrespective of maternal comorbidity,[2-4] gestational age (GA) at birth,[5] presence of premature rupture of membranes,[6] hypertensive disease,[7] pregestational diabetes,[8] or multiple gestations.[9] There is, however, a paucity of publications on neonatal morbidity and mortality among SGA at term (≥37 weeks) without concomitant maternal comorbidities such as hypertension or diabetes.

The importance of focusing on SGA among uncomplicated pregnancies is that the majority of newborns with weight <10th percentile are born at term. Lee et al,[10] for example, reported that in 2010 of the 32 million SGA born in 138 developing countries, >29 million were born at term. In 2014, of the 3.98 million births in the United States,[11] about two thirds of pregnancies were uncomplicated and, among them, the likelihood of SGA is roughly 10%. Thus, we estimate that annually in the United States, there are >235,000 SGA newborns born at term from uncomplicated pregnancies and there is a significant knowledge gap about their outcomes.

The primary purpose of this secondary analysis of 9 Maternal-Fetal Medicine Unit (MFMU) Network studies was to compare the morbidity and mortality among SGA vs appropriate for GA (AGA) (birthweight between 10-89%

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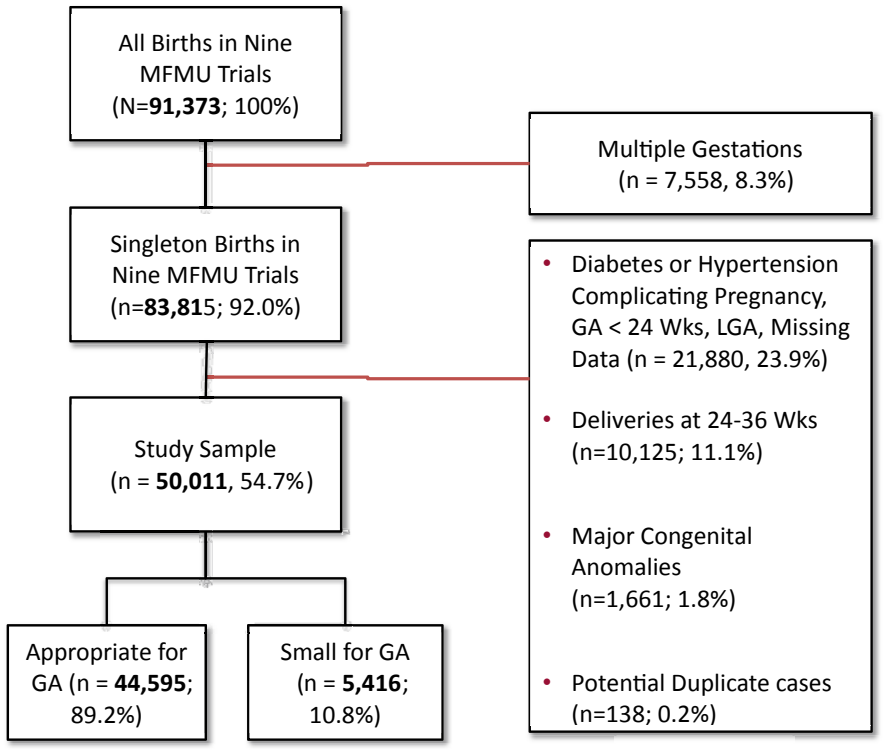
**FIGURE 1**
**Flow diagram demonstrating the exclusion of subjects from all analyzed databases**




Sample size for analysis.

*GA*, gestational age; *LGA*, large for gestational age; *MFMU*, Maternal-Fetal Medicine Unit.

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for GA) among term pregnancies without known comorbidities. The secondary purpose was to compare: (1) the adverse outcomes among infants with birthweight <5% and 5-9% to AGA newborns; and (2) the morbidity and mortality for the subgroups of deliveries occurring at 37.0-38.6 weeks (early term) and at ≥39.0 weeks (term).

## Materials and Methods

All MFMU databases available to us as member of the network were considered for this study. These included: (1) a randomized trial of low-dose aspirin to prevent preeclampsia[12]; (2) a preterm prediction study[13]; (3) a clinical trial of low-dose aspirin to prevent preeclampsia in high-risk women[14]; (4) a randomized trial of 17-alpha hydroxyprogesterone caproate for the prevention of preterm birth in high-risk women[15]; (5) an observational study of cesarean delivery and vaginal birth after cesarean delivery[16]; (6) a randomized clinical trial of the beneficial effects of antenatal magnesium sulfate[17]; (7) a randomized placebo-controlled trial of antenatal corticosteroids regimens[18]; (8) a prospective observational study of effects of factor V Leiden mutation on maternal and perinatal outcomes[19]; and (9) midtrimester endovaginal sonography in women at high-risk for spontaneous preterm birth.[20] The obstetrical determinant of neonatal survival database was not included due to the limited number of eligible participants and obstetrical variables collected.[21] Full details of these studies have been previously reported.

All variables and data from these studies were collected prospectively by trained research nurses following strict and specific protocols outlined in the manual of operations. All eligible databases were combined, all variables of interest were aligned, and definitions standardized using the original designations within each study's protocol. We used uniform coding for all study variables.

The inclusion criteria for our study were nonanomalous singleton pregnancies, with a documented estimated GA (EGA) and birthweight, a GA ≥37.0 weeks at birth, and birthweight <90% for GA. Methodology utilized to determine GA for each trial included was previously reported.[12-20] For this analysis, birthweight percentiles were calculated using the data reported by Alexander et al.[22] This reference curve was used as it was determined to be the most robust and most contemporary of the growth curves available. SGA included all birthweights <10th percentile while AGA was birthweights between 10th-89th percentile.

We excluded women who had a multiple gestation, anomalies, EGA <37 weeks, medical or obstetrical complications like pregestational or gestational diabetes, hypertensive disease of pregnancy, chronic hypertension, missing EGA or birthweight, and potential duplicates, ie, women who may have potentially participated in >1 study during the same pregnancy. A mother was considered a duplicate if she matched all of the following variables across ≥2 studies: maternal age, parity, GA at delivery, route of delivery, neonatal gender, birthweight, and Apgar score at both 1 and 5 minutes.

Composite neonatal morbidity (CNM) was defined as any of the following: Apgar score <4 at 5 minutes, respiratory distress syndrome, need for mechanical ventilation, intraventricular hemorrhage grade III or IV, necrotizing enterocolitis stage 2 or 3, neonatal sepsis—suspected or proven, confirmed seizure, and stillbirth or neonatal death. Each parameter of CNM was previously defined in the parent publications of the 9 trials.[12-20] Stillbirth was defined as any fetal death occurring prior to or during labor and neonatal mortality as death occurring after delivery up to 28 days after birth.

The sample size for this analysis was determined by the size of all databases included. Descriptive statistics were used

to report all variables of interest. Crude odds ratios (OR) and 95% confidence intervals (CI) from random effect logistic regression models were utilized. We fit separate models to each component of CNM and to the composite primary outcome. Mixed effect logistic regressions with a random intercept for study (to account for study heterogeneity) were adjusted for maternal age (<20, 20-34, ≥35 years), race/ethnicity (Caucasian, Afro-American, Hispanic, other), marital status (yes, no), education level (≤12 or >12 years of education), nulliparity (yes, no), pre-pregnancy body mass index (BMI) (<30, ≥30 kg/m$^2$), maternal smoking (yes, no), maternal alcohol use (yes, no), neonatal gender (male, female), and diagnosis of chorioamnionitis (yes, no). In cases where the logistic mixed effects model did not converge, we used logistic regression with robust SE accounting for the cluster study effect and adjusted for the same covariates. Secondary analyses used similar models to compare neonatal outcomes in infants with birthweight <5% and those at 5-9% to AGA newborns.

We imputed missing data in BMI and education variables (24% and 27% missing, respectively) using the method of multivariate imputation by chained equation.[23] Variables included in the imputation model were the same as those included in the analyses models. We generated 10 imputed data sets and combined coefficient estimates across these using Rubin rules.[24] Adjusted OR (aOR) and 95% CI from multiple imputation estimates are presented. A *P* value <.05 was considered statistically significant.

To assess the influence of GA and morbidity, we ran subgroup analyses on all outcomes of interest for infants delivered at 37.0-38.6 weeks (early term pregnancy) and those delivered at ≥39 weeks (full-term pregnancy). All analyses were performed in software (Stata v13; StataCorp LP, College Station, TX). The STrengthening the Reporting of OBservational studies in Epidemiology guidelines for reporting observational studies were followed. This analysis qualified for exempt status from the institutional review board at the University of Texas Health Science Center at Houston because it involved the study of publically available deidentified data.

**TABLE 1**
**Maternal demographics**

| | SGA, N = 5416 | AGA, N = 44,595 | OR[a] (95% CI) |
|---|---|---|---|
| Maternal age, y | | | |
| <20 | 3952 (73.0) | 33,530 (75.2) | 1 |
| 20–34 | 750 (13.8) | 4537 (10.2) | 1.30 (1.19–1.42)[b] |
| ≥35 | 714 (13.2) | 6526 (14.6) | 0.95 (0.87–1.03) |
| Ethnicity | | | |
| Caucasian | 1463 (27.0) | 16,842 (37.7) | 1 |
| Afro-American | 2569 (47.5) | 13,626 (30.6) | 2.11 (1.97–2.26)[b] |
| Hispanic | 1167 (21.5) | 12,138 (27.2) | 1.11 (1.03–1.20)[b] |
| Other | 217 (4.0) | 1989 (4.5) | 1.28 (1.10–1.48)[b] |
| Nulliparous | 1401 (26.0) | 10,225 (23.0) | 1.14 (1.06–1.22)[b] |
| High school education | 1041 (26.2) | 11,639 (35.5) | 0.67 (0.62–0.72)[c] |
| Married | 2384 (44.0) | 25,917 (58.1) | 0.55 (0.52–0.58)[c] |
| Smoker | 1496 (27.7) | 6101 (13.7) | 2.38 (2.22–2.54)[b] |
| Alcohol | 478 (9.6) | 2494 (6.0) | 1.54 (1.36–1.74)[b] |
| Drugs | 465 (10.0) | 1526 (3.9) | 2.59 (2.31–2.90)[b] |
| BMI at delivery, km/m$^2$ | | | |
| <30 | 3086 (80.1) | 26,025 (76.3) | 1[c] |
| ≥30 | 764 (19.9) | 8054 (23.7) | 0.82 (0.75–0.89)[c] |

Data presented as N (%).

*AGA*, appropriate for gestational age (birthweight between 10–89% for gestational age); *BMI*, body mass index; *CI*, confidence interval; *OR*, odds ratio; *SGA*, small for gestational age (birthweight <10% for gestational age).

[a] Unadjusted OR from logistic regression with random effect of study; [b] Significantly more common among SGA than AGA; [c] Significantly less common among SGA than AGA.

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## Results

From 1989 through 2004, in the 9 MFMU studies, 91,373 women were enrolled of whom 83,815 (92%) had singleton pregnancies. Among these women, we excluded 33,804 (40.3%) for the following reasons: 32,005 were less than 37 weeks at birth, were missing birth weight or gestational age at birth or were labeled as large for gestational age (LGA); 1661 were anomalous, and 138 patients were excluded as suspected duplicates. For our analyses, 50,011 (54.7%) singletons met the inclusion criteria and are the focus of our report. The prevalence of SGA in our cohort was 10.8% (Figure 1).

Baseline characteristics differed significantly between SGA and AGA groups for maternal age; ethnicity; nulliparity; education; marital status; self-reported cigarette, alcohol, or drug use; and BMI at delivery. The 3 variables associated with significantly lower likelihood of SGA were having at least high school education, being married, and at delivery having BMI of ≥30 kg/m$^2$ (Table 1).

Compared to AGA, women with SGA were significantly less likely to be induced, have chorioamnionitis, deliver at ≥39.0 weeks, and have cesarean delivery. SGA pregnancies, however, were significantly more likely than AGA to have cesarean delivery for nonreassuring fetal heart rate and have abruption (Table 2).

SGA infants were significantly more likely than AGA to be female. After adjustments for confounding variables,

**TABLE 2**
**Intrapartum outcomes**

| | SGA, N = 5416 | AGA, N = 44,595 | OR[a] (95% CI) |
|---|---|---|---|
| Abruption | 62 (1.2) | 270 (0.6) | 1.92 (1.46–2.54)[b] |
| Antenatal corticosteroids | 101 (2.3) | 342 (0.9) | 2.16 (1.63–2.87)[b] |
| Labor | | | |
| Spontaneous | 1659 (47.3) | 11,767 (42.9) | 1 |
| Induced or augmented | 1785 (51.2) | 15,217 (55.6) | 0.85 (0.79–0.92)[c] |
| Chorioamnionitis | 124 (2.5) | 2027 (4.8) | 0.52 (0.43–0.62)[c] |
| Gestational age, wk | | | |
| 37.0–38.6 | 2187 (40.4) | 14,147 (31.8) | 1 |
| 39.0–40.6 | 2787 (51.4) | 24,521 (55.0) | 0.73 (0.69–0.78)[c] |
| ≥41 | 442 (8.2) | 5927 (13.3) | 0.48 (0.43–0.53)[c] |
| Route of delivery | | | |
| Vaginal | 2068 (38.3) | 14,716 (33.1) | 1 |
| Cesarean | 3346 (61.8) | 29,874 (67.0) | 0.87 (0.82–0.93)[c] |
| Reason for cesarean[d] | | | |
| CPD | 400 (11.1) | 6427 (20.1) | 0.50 (0.45–0.56)[c] |
| Repeat | 1427 (39.9) | 15,108 (47.4) | 0.74 (0.69–0.80)[c] |
| Failed trial of labor | 47 (1.5) | 338 (1.3) | 0.98 (0.70–1.36) |
| Nonreassuring FHR | 762 (21.1) | 3327 (10.4) | 2.35 (2.15–2.57)[b] |
| Others | 673 (96.3) | 4495 (97.5) | 0.65 (0.43–1.02) |

Data presented as N (%).

*AGA*, appropriate for gestational age (birthweight between 10–89% for gestational age); *CI*, confidence interval; *CPD*, cephalopelvic disproportion; *FHR*, fetal heart rate; *OR*, odds ratio; *SGA*, small for gestational age (birthweight <10% for gestational age).

[a] Unadjusted OR from logistic regression with random effect of study; [b] Significantly more common among SGA than AGA; [c] Significantly less common among SGA than AGA; [d] Not all indications included in table and since woman could have >1 indication, total percentage is >100%.

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the CNM was significantly higher among SGA (16.3%) than AGA (10.3%): aOR, 1.75; 95% CI, 1.71–1.78. Compared to AGA, morbidity was more common with SGA including an Apgar score <4 at 5 minutes, rate of respiratory distress syndrome, need for mechanical ventilation, and diagnosis of neonatal sepsis. The likelihood of neonatal death was 2.5-fold more common with SGA than AGA: 11 vs 4.0/1000 births, respectively (aOR, 2.56; 95% CI, 1.83–3.57) (Table 3).

Compared to AGA, the CNM was significantly higher for newborns at 5-9% for GA and for those <5%. The association of adverse outcomes was consistently stronger for those <5% than at 5-9% for GA. The significantly increased risk of stillbirth and of neonatal mortality, however, was limited to newborns <5% and not those at 5-9% (Table 4).

When the neonatal outcomes were stratified according to GA at delivery (37.0-38.6 weeks vs ≥39.0 weeks), the CNM was significantly higher among SGA when compared to AGA at both early term (18.4% vs 10.5%) and full term (15.0% vs 10.1%) pregnancies. Compared to AGA, the likelihood of neonatal death was 2.3-fold higher with SGA whether they were delivered 37.0-38.6 or ≥39.0 weeks.

## Comment

Among women at term and without known comorbidities, SGA newborns, compared to AGA, had 60% higher CNM (16.3% vs 10.3%, respectively). After adjustments for confounders, CNM was 75% more likely in SGA than AGA (aOR, 1.75). The likelihood of stillbirth and neonatal mortality were 3-fold and 2-fold higher, respectively, among term SGA. Secondary analyses indicated that compared to AGA, the significantly increased CNM is present among newborns <5% and for those at 5-9% GA. Additionally, at ≥39.0 weeks, SGA newborns, compared to AGA, still have significantly higher CNM, including stillbirth and neonatal mortality.

Our study has 2 main advantages that help to strengthen the evidence of poor outcomes in SGA infants. First, our analysis, though secondary, is multicentered and prospectively collected. Several of the publications on the topic have been retrospective, originating from a single center[3,5] or based on birth and death certificates.[2,4] Thus, our data alleviate the potential bias, lack of generalizability, and unreliability of neonatal diagnoses that have been cited as limitations in previous studies. Second, this may be the first study that has focused completely on uncomplicated pregnancies at term and the likelihood of differential CNM in SGA compared to AGA. With concomitant maternal comorbidity and SGA, it is difficult to discern if poor outcomes are secondary to the underlying disease (eg, hypertension or diabetes), suboptimal growth, or both. It is noteworthy that of the 5 national guidelines on this topic, none of them specify if the adverse outcomes linked with SGA are pertinent to the women who were the primary aim of this analysis.[1,25-28]

This current investigation was designed to focus on uncomplicated term pregnancies; an important subgroup of patients who constitute the majority of cases affected by fetal growth abnormalities. Thus, from a clinical standpoint, the data generated from the current analysis have the potential to have a much broader impact than prior analyses linking SGA with adverse perinatal outcomes. The additional stratification by GA at delivery may also allow for better planning with regards to timing of delivery.

**TABLE 3**
**Neonatal outcomes**

| | AGA, N = 44,595 | SGA—BW <10th percentile, N = 5,416 | BW <5%, N = 2,530 | BW <10% vs AGA, OR[a] (95% CI) | BW <5% vs AGA, OR[a] (95% CI) |
|---|---|---|---|---|---|
| Female | 21,819 (48.9) | 3134 (57.9) | 1459 (57.7) | 1.44 (1.36—1.52)[b] | 1.42 (1.31—1.54)[b] |
| Apgar score <4 at 5 min | 92 (0.2) | 31 (0.6) | 20 (0.8) | 2.57 (1.63—4.07)[b] | 3.62 (2.10—6.22)[b] |
| Respiratory distress syndrome | 720 (1.7) | 143 (2.8) | 89 (3.7) | 1.76 (1.45—2.14)[b] | 2.34 (1.83—2.98)[b] |
| Mechanical ventilation | 477 (1.1) | 112 (2.1) | 68 (2.7) | 2.00 (1.60—2.50)[b] | 2.64 (2.00—3.47)[b] |
| IVH grade III or IV | 2 (0) | 0 (0) | 0 (0) | 1.99 (0.92—4.31)[c] | — |
| NEC stage 2/3 | 2 (0.01) | 2 (0.05) | 1 (0.06) | 9.19 (1.29—65.26)[b,c] | — |
| Neonatal sepsis | 3645 (8.7) | 654 (13.1) | 256 (9.7) | 1.70 (1.54—1.88)[b] | 2.37 (2.10—2.68)[b] |
| Periventricular leukomalacia | 0 (0) | 0 (0) | 0 (0) | — | — |
| Confirmed seizures | 53 (0.1) | 11 (0.3) | 6 (0.3) | 1.80 (0.90—3.63) | 2.00 (0.78—5.13) |
| Stillbirth/1000 | 41 (0.9) | 19 (3.5) | 14 (5.5) | 3.49 (1.83—6.67)[b] | 6.02 (2.95—12.28)[b] |
| Neonatal death/1000 | 17 (0.4) | 6 (1.1) | 4 (1.6) | 2.56 (1.83—3.57)[b,d] | 4.37 (3.05—6.25)[b,d] |
| Composite neonatal morbidity[e] | N = 37,094<br>3798 (10.3) | N = 4277<br>699 (16.3) | N = 2006<br>428 (21.3) | 1.75 (1.71—1.78)[b] | 2.44 (2.41—2.47)[b,d] |

Data presented as N (%) unless otherwise noted.

Analysis adjusted for: maternal age, nulliparity, race, study inclusion, body mass index (<30 or ≥30 kg/m$^2$), smoking, education level, alcohol use, marital status, chorioamnionitis, and neonatal gender.

Composite neonatal morbidity consisted of any of following: Apgar score <4 at 5 min, respiratory distress syndrome, mechanical ventilation, IVH grade III or IV, NEC stage 2/3, neonatal sepsis, periventricular leukomalacia, confirmed seizures, stillbirth, or neonatal death.

*AGA*, appropriate for gestational age (BW between 10—89% for gestational age; referent group); *BW*, birthweight; *CI*, confidence interval; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *OR*, odds ratio; *SGA*, small for gestational age (BW <10% for gestational age).

[a] Adjusted OR from logistic regression with random effect of study; [b] Significantly more common among SGA than AGA; [c] Unadjusted OR from logistic regression with random effect of study; [d] Adjusted OR from robust logistic regression; [e] Excludes infants with missing composite neonatal morbidity outcome.

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Our findings of increased CNM at term are supportive of the consensus statement and American Congress of Obstetricians and Gynecologists (ACOG) guideline that state that fetal growth restriction (estimated birthweight <10th percentile for GA) without other risk factors should be delivered by 39.0 weeks.[1] In our cohort, 10% of women at 39.0-40.6 weeks were SGA and 7% were SGA at ≥41.0 weeks (Table 2). The possible explanations for SGA >39.0 weeks are that the data originate from trials preceding the publication of the ACOG practice bulletin, published in 2013, since our data range from 1989 through 2004. Additionally, it is possible that the SGA newborns were not identified as being growth restricted before birth,[29] and thus did not warrant intervention. Regardless of the reasons for SGA at ≥39 weeks, it is noteworthy that the adjusted risk of stillbirth is 4 times higher with SGA than AGA, and 2 times higher for neonatal death.

The shortcomings of our study should be acknowledged. This is an unplanned secondary analysis albeit of prospectively collected data from multiple centers. Thus, our findings should be hypothesis generating and an impetus for interventional trial. The management of the parturient and newborn was in centers participating in trials and thus our findings may not be applicable to institutions with limited resources. We categorized the newborns as SGA vs AGA based on a population curve[22] and did not utilize customized growth curve,[30] which may be better at identifying those that will have morbidity or mortality.[31] Our reasons for not utilizing customized growth curve was that it has not been consistently shown to identify pregnancies with adverse outcomes[32] and, more importantly, ACOG does not recommend using individualized growth standards.[1] The variables collected for the trials did not provide information on what proportion of SGA had estimated fetal weight <10% for GA or had antepartum surveillance. But since 70-90% of SGA are not identified as having estimate of fetal weight <10%, we assume that the majority of pregnancies with abnormal growth did not have surveillance with umbilical artery Doppler.[29,33] The potential reasons for why the majority of SGA are undetected include that ACOG does not recommend routine third-trimester sonographic exams among uncomplicated pregnancies,[1] clinical estimate is not as reliable in detection of SGA as it is for macrosomia,[34] vagaries of sonographic estimate of fetal weight, and that prediction of birthweight is optimally done within a week of delivery.[35] A major portion (82%) of our participants originated from the cesarean registry[16] and this may limit the generalizability of our results. Since the data were collected prospectively, clinicians were aware of the ongoing study and this fact may lead to a Hawthorne effect. Despite these

**TABLE 4**
**Neonatal morbidity stratified by gestational age**

| | Gestational age 37.0–38.6 wk | | | Gestational age ≥39.0 wk | | |
|---|---|---|---|---|---|---|
| | SGA, N = 2187 | AGA, N = 14,147 | OR[a] (95% CI) | SGA, N = 3230 | AGA, N = 30,503 | OR[a] (95% CI) |
| Apgar score <4 at 5 min | 18 (0.8) | 39 (0.3) | 2.10 (1.12–3.94)[b] | 13 (0.4) | 53 (0.2) | 2.65 (1.34–5.24)[b] |
| Respiratory distress syndrome | 66 (3.1) | 277 (2.0) | 1.80 (1.34–2.43)[b] | 77 (2.5) | 443 (1.5) | 1.69 (1.30–2.19)[b] |
| Mechanical ventilation | 41 (1.9) | 19 (1.2) | 1.80 (1.24–2.61)[b] | 71 (2.2) | 311 (1.0) | 2.11 (1.60–2.79)[b] |
| IVH grade III or IV | 0 (0) | 1 (0.01) | 2.19 (0.89–5.43)[c] | 0 (0) | 1 (0) | 1.27 (0.31–5.16)[c] |
| NEC stage 2/3 | 2 (0.14) | 1 (0.01) | 14.95 (1.36–165.03)[c] | 0 (0) | 1 (0) | – |
| Neonatal sepsis | 300 (14.8) | 1202 (8.9) | 1.84 (1.58–2.14)[b] | 354 (12.0) | 2443 (8.6) | 1.56 (1.37–1.77)[b,d] |
| Periventricular leukomalacia | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Seizure proven | 5 (0.3) | 16 (0.1) | 1.33 (0.85–2.08) | 6 (0.23) | 37 (0.14) | 1.97 (0.81–4.77)[d] |
| Stillbirth/1000 births | 5.0 | 1.6 | 2.42 (1.64–3.58)[b,d] | 2.5 | 0.7 | 4.51 (2.74–7.41)[b,d] |
| Neonatal death/1000 live births | 1.4 | 0.6 | 2.32 (1.26–4.29)[b,d] | 0.9 | 0.3 | 2.31 (2.16–2.47)[b,d] |
| Composite neonatal morbidity[e] | N = 1721<br>317 (18.4) | N = 11,941<br>1249 (10.5) | 1.87 (1.61–2.17)[b] | N = 2556<br>382 (15.0) | N = 25,153<br>2549 (10.1) | 1.58 (1.39–1.80)[b] |

Data presented as N (%) unless otherwise noted.

Analysis adjusted for: maternal age, nulliparity, race, study inclusion, body mass index (<30 or ≥30 kg/m$^2$), smoking, education level, alcohol use, marital status, chorioamnionitis, and neonatal gender.

Composite neonatal morbidity consisted of any of following: Apgar score <4 at 5 min, respiratory distress syndrome, mechanical ventilation, IVH grade III or IV, NEC stage 2/3, neonatal sepsis, periventricular leukomalacia, confirmed seizures, stillbirth, or neonatal death.

*AGA*, appropriate for gestational age (birthweight between 10–89% for gestational age); *CI*, confidence interval; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *OR*, odds ratio; *SGA*, small for gestational age (birthweight < 10% for gestational age).

[a] Adjusted OR from logistic regression with random effect of study; [b] Significantly more common among SGA than AGA; [c] Unadjusted OR from logistic regression with random effect of study; [d] Adjusted OR from robust logistic regression; [e] Excludes infants with missing composite neonatal morbidity outcome.

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limitations, it should be noted that this is one of the few publications on CNM among uncomplicated pregnancies at term. One of the few publications on SGA among uncomplicated pregnancies at term (n = 67) reported that the likelihood of admission to neonatal intensive care unit, respiratory distress, hypoglycemia, and thrombocytopenia were significantly higher than in controls.[36] We confirm the finding of respiratory distress in our analysis and highlight other morbidities that are significantly more common with SGA.

In conclusion, when compared to AGA, newborns with birthweight <10% for GA are at significantly greater risk of morbidity and mortality among term uncomplicated pregnancies. Randomized trials are warranted to determine the optimum manner to identify SGA at term and identify strategies that could mitigate the associated increased CNM without disproportionate interventions and iatrogenic complications. ■

## References


1. American College of Obstetricians and Gynecologists. Fetal growth restriction. ACOG Practice bulletin no. 134. Obstet Gynecol 2013;121:1122-33.
2. Bukowski R, Hansen NI, Willinger M, et al. Fetal growth and risk of stillbirth: a population-based case-control study. PLoS Med 2014;11:e1001633.
3. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234-8.
4. Chen HY, Chauhan SP, Ward TC, Mori N, Gass ET, Cisler RA. Aberrant fetal growth and early, late, and postneonatal mortality: an analysis of Milwaukee births, 1996-2007. Am J Obstet Gynecol 2011;204:261.e1-10.
5. Odibo AO, Goetzinger KR, Cahill AG, Odibo L, Macones GA. Combined sonographic testing index and prediction of adverse outcome in preterm fetal growth restriction. Am J Perinatol 2014;31:139-44.
6. Burstein E, Sheiner E, Mazor M, Carmel E, Levy A, Hershkovitz R. Identifying risk factors for premature rupture of membranes in small for gestational age neonates: a population-based study. J Matern Fetal Neonatal Med 2008;21:816-20.
7. Ankumah NA, Cantu J, Jauk V, et al. Risk of adverse pregnancy outcomes in women with mild chronic hypertension before 20 weeks of gestation. Obstet Gynecol 2014;123:966-72.
8. Bennett SN, Tita A, Owen J, Biggio JR, Harper LM. Assessing White's classification of pregestational diabetes in a contemporary diabetic population. Obstet Gynecol 2015;125:1217-23.
9. Blickstein I, Keith LG. Neonatal mortality rates among growth-discordant twins, classified according to the birth weight of the smaller twin. Am J Obstet Gynecol 2004;190:170-4.
10. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health 2013;1:e26-36.
11. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2014. Natl Vital Stat Rep 2015;64:1-64.

**12.** Sibai BM, Caritis SN, Thom E, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1993;329:1213-8.
**13.** Goldenberg RL, Mercer BM, Meis PJ, Copper RL, Das A, McNellis D. The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth. NICHD Maternal Fetal Medicine Units Network. Obstet Gynecol 1996;87:643-8.
**14.** Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1998;338:701-5.
**15.** Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.
**16.** Landon MB, Hauth JC, Leveno KJ, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N Engl J Med 2004;351:2581-9.
**17.** Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med 2008;359:895-905.
**18.** Wapner RJ, Sorokin Y, Thom EA, et al. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol 2006;195:633-42.
**19.** Dizon-Townson D, Miller C, Sibai B, et al. The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol 2005;106:517-24.
**20.** Owen J, Yost N, Berghella V, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA 2001;286:1340-8.
**21.** Bottoms SF, Paul RH, Iams JD, et al. Obstetric determinants of neonatal survival: influence of willingness to perform cesarean delivery on survival of extremely low-birth-weight infants. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 1997;176:960-6.
**22.** Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163-8.
**23.** Raghunathan TW, Lepkowksi JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey Methodology 2001;27:85-95.
**24.** Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585-98.
**25.** Society for Maternal-Fetal Medicine Publications Committee; Berkley E, Chauhan SP, Abuhamad A. Doppler assessment of the fetus with intrauterine growth restriction. Am J Obstet Gynecol 2012;206:300-8.
**26.** Royal College of Obstetricians and Gynecologists. The investigation and management of the small-for-gestational-age fetus. Green-Top Guidelines 2013;31. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf. Accessed August 5, 2016.
**27.** Lausman A, Kingdom J, Maternal Fetal Medicine Committee, et al. Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can 2013;35:741-57.
**28.** Royal College of Physicians of Ireland. Fetal growth restriction—recognition, diagnosis and management. RCPI clinical practice guideline 2014;28. Available at: https://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/29-_Fetal_Growth_Restriction-IUGR_CPG_final_.pdf. Accessed August 5, 2016.
**29.** Chauhan SP, Beydoun H, Chang E, et al. Prenatal detection of fetal growth restriction in newborns classified as small for gestational age: correlates and risk of neonatal morbidity. Am J Perinatol 2014;31:187-94.
**30.** Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. Am J Obstet Gynecol 2009;201:28.e1-8.
**31.** McCowan LM, Harding JE, Stewart AW. Customized birthweight centiles predict SGA pregnancies with perinatal morbidity. BJOG 2005;112:1026-33.
**32.** Larkin JC, Hill LM, Speer PD, Simhan HN. Risk of morbid perinatal outcomes in small-for-gestational-age pregnancies: customized compared with conventional standards of fetal growth. Obstet Gynecol 2012;119:21-7.
**33.** Hammad IA, Chauhan SP, Mlynarczyk M, et al. Uncomplicated pregnancies and ultrasounds for fetal growth restriction: a pilot randomized clinical trial. AJP Rep 2016;6:e83-90.
**34.** Chauhan SP, Hendrix NW, Magann EF, Morrison JC, Kenney SP, Devoe LD. Limitations of clinical and sonographic estimates of birth weight: experience with 1034 parturients. Obstet Gynecol 1998;91:72-7.
**35.** Chauhan SP, Hendrix NW, Magann EF, Morrison JC, Scardo JA, Berghella V. A review of sonographic estimate of fetal weight: vagaries of accuracy. J Matern Fetal Neonatal Med 2005;18:211-20.
**36.** Minior VK, Divon MY. Fetal growth restriction at term: myth or reality? Obstet Gynecol 1998;92:57-60.

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