Accepted Manuscript

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Jessie V. Madden, BSc, Christopher J. Flatley, MClinEpi, Sailesh Kumar, FRCS FRCOG FRANZCOG DPhil(Oxon)

PII: S0002-9378(18)30151-0

DOI: 10.1016/j.ajog.2018.02.008

Reference: YMOB 12081

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 7 November 2017

Revised Date: 31 January 2018

Accepted Date: 8 February 2018

Please cite this article as: Madden JV, Flatley CJ, Kumar S, Term small-for-gestational-age infants from low risk women are at significantly greater risk of adverse neonatal outcomes, *American Journal of Obstetrics and Gynecology* (2018), doi: 10.1016/j.ajog.2018.02.008.

Term small-for-gestational-age infants from low risk women are at significantly greater risk of adverse neonatal outcomes

Jessie V. MADDEN, BSc[1,3], Christopher J. FLATLEY MClinEpi[1], Sailesh KUMAR FRCS FRCOG FRANZCOG DPhil(Oxon)[1,2,3]

[1]Mater Research Institute - University of Queensland, Level 3 Aubigny Place, Raymond Terrace, South Brisbane, Queensland, Australia, QLD 4101, [2]Mater Mothers' Hospital, Raymond Terrace, South Brisbane, Queensland, Australia, QLD 4101, [3]School of Medicine, The University of Queensland, Brisbane, Australia.

Abstract word count: 481

Main text word count: 2745

Disclosure of Interests: All authors report no conflict of interests.

Acknowledgement: The authors acknowledge research support by the Mater Foundation.

Table 4 to be included in the print version.

Corresponding author and individual responsible for reprint requests:

Professor Sailesh Kumar
Mater Research Institute/University of Queensland
Level 3, Aubigny Place
Raymond Terrace
South Brisbane
Queensland 4101, Australia
Tel: +617 31638844
Email: sailesh.kumar@mater.uq.edu.au

Condensation

Small-for-gestational-age infants from low-risk, term pregnancies are at increased risk of serious neonatal morbidity regardless of gestational age at birth.

Short title

Small for gestational age infants at term gestation and serious neonatal outcomes.

Implications and Contributions

- This study was conducted to ascertain the outcomes for small for gestational age (SGA) infants in a low risk maternal cohort from an Australian tertiary centre.
- SGA infants had significantly worse perinatal outcomes compared to appropriately grown cohorts particularly if birth occurred at early term.
- The results highlight the considerable risk SGA infants face even in a low risk cohort and underscore the importance of screening in pregnancy. The results also suggest that birth before 39+0 weeks should be avoided wherever possible given the increased risk of adverse outcomes.

Abstract

Background: Small-for-gestational age (SGA) infants (birthweight <10th centile) are at increased risk of perinatal complications but are frequently not identified antenatally, particularly in low risk women delivering at term (≥37 weeks gestation). This is compounded by the fact that late pregnancy ultrasound is not the norm in many jurisdictions for this cohort of women. We thus investigated the relationship between birthweight <10th centile and serious neonatal outcomes in low risk women at term.

Objective(s): We aimed to determine whether there is a difference of obstetric and perinatal outcomes for SGA infants, subdivided into 5th - <10th centile and <5th centile cohorts compared to an appropriate-for-gestational age (AGA) (birthweight 10th - 90th centile) group at term.

Study Design: This was retrospective analysis of data from the Mater Mother's Hospital in Brisbane, Australia for women who birthed between January 2000 and December 2015. Women with multiple pregnancy, diabetes mellitus, hypertension, pre-term birth, major congenital anomalies and large for gestational age infants (>90th centile for gestational age) were excluded. SGA infants were subdivided into 2 cohorts - infants with birthweights 5th - <10th centile and those <5th centile. Serious composite neonatal morbidity (SCNM) was defined as ***any*** of the following: Apgar score ≤3 at 5 minutes, respiratory distress syndrome, acidosis, admission into the Neonatal Intensive Care Unit (NICU), stillbirth or neonatal death. Univariate and multivariate analysis were performed using generalized estimating equations to compare obstetric and perinatal outcomes for SGA infants compared to AGA controls.

Results: The final study comprised 95,900 infants. 5.0% were between the 5th and <10th centiles for birthweight and 4.3% were <5th centile. The rate of SCNM was 11.1% in the

control group, 13.7% in the 5th and <10th centile and 22.6% in the <5th centile cohorts respectively. Even after controlling for confounders, both the 5th - <10th centiles and <5th centile cohorts were at significantly increased risk of SCNM compared to controls (OR 1.25, 95% CI 1.15-1.37 and OR 2.20, 95% CI 2.03-2.39 respectively). Infants with birthweights <10th centile were more likely to have severe acidosis at birth, 5 minute Apgar score ≤3 and to be admitted to NICU. The SCNM was higher in infants <5th centile compared to those in the 5th - <10th centile cohort (OR 1.71, 95% CI 1.52-1.92). The odds of perinatal death (stillbirth and neonatal death) were significantly higher in both small-for-gestational age groups than controls. After stratification for gestational age at birth, the composite outcome remained significantly higher in both small-for-gestational-age cohorts and was highest in the <5th centile group at 37+0 - 38+6 weeks (OR 3.32, 95% CI 2.87-3.85). The risk of perinatal death was highest for infants <5th centile at 37+0 - 38+6 weeks (OR 5.50, 95% CI 2.33-12.98).

Conclusion(s): SGA infants from term, low risk pregnancies are at significantly increased risk of mortality and morbidity when compared to AGA infants. Although this risk is increased at all gestational ages in infants <5th centile for birthweight, it is highest at early term gestation. Our findings highlight that early term birth does not necessarily improve outcomes and emphasize the importance of identifying this cohort of infants.

Key Words: Small for gestational age, fetal growth restriction, neonatal morbidity, neonatal mortality, stillbirth, term gestation, perinatal outcome, perinatal mortality, perinatal morbidity

Main Text

Introduction

Compared to preterm cohorts, overall perinatal complications in term small for gestational age (SGA) infants (defined as birth weight <10th centile for gestation) are lower and tend to be at the milder end of the spectrum.[1, 2] In high income countries >60% of non-anomalous SGA births occur at term with evidence that compared to appropriate for gestational age (AGA) controls reduced birthweight is associated with an increased risk of morbidity and mortality.[3, 4] The increased risk is partly due to the proportion of SGA infants that are truly growth restricted secondary to placental dysfunction. Indeed in low risk pregnancies, placental malperfusion and dysfunction accounts for a population attributable risk of 25% for SGA infants.[5] Clinical identification of SGA fetuses late in pregnancy is difficult, with physical examination and symphysis fundal height (SFH) assessment limited by a number of factors including maternal habitus and fetal lie. Furthermore, unlike women with known risk factors (hypertension, diabetes mellitus, previous fetal growth restriction etc.), routine ultrasound to assess fetal growth is generally not performed in low risk women unless there are concerns about fetal size on clinical examination.

From a healthcare burden perspective, the vast majority of SGA infants are born at term [6] often from uncomplicated, low risk pregnancies. The difficulty however, is defining what constitutes a “low risk” cohort as there are many maternal medical, demographic and psychosocial factors that are associated with an increased risk of adverse outcomes. Clearly if this population were to be defined by the absence of all possible risk factors this would result in an artificially low number of women that would be considered “normal” or “low risk”. Such an approach would be divorced from clinical reality. Notwithstanding the difficulty in defining this cohort, some investigators have suggested that excluding women with diabetes mellitus and hypertension is reasonable given their relatively high prevalence in pregnancy.[4]

124 More specifically, the objectives were to evaluate outcomes for infants with birth weight <5th
125 centile and 5th - <10th centiles stratified for gestational age at birth (≥37+0 weeks - 38+6
126 weeks, ≥39+0 weeks – 40+6 weeks and ≥41 weeks).

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Materials and Methods

This was a retrospective cohort study of women who birthed between January 2000 and December 2015 at the Mater Mother's Hospital in Brisbane, Australia using previously prospectively collected data. Maternal demographic, intrapartum and perinatal outcome information were collected from the hospital's maternity database and cross-referenced with the maternal and fetal medicine and neonatal databases to ensure robust data ascertainment. The Mater Mother's Hospital is a major tertiary center in Queensland with a birth rate of approximately 10,500 per annum, making it the largest maternity hospital in Australia. Approval for this study was granted by the institution's Human Research Ethics Committee (Reference number HREC/14/MHS/37).

We included all women with non-anomalous singleton, term pregnancies with a recorded birth weight. Gestational age was calculated using the last menstrual period or earliest ultrasound examination, or by correlation of both. Birth weight centiles were calculated with reference to previously published Australian standards.[7] AGA was defined as a birth weight of 10^{th} - 90^{th} centile. The SGA cohort was subdivided into two categories: **SGA1 (birth weight 5^{th} - $<10^{th}$ centiles)** and **SGA2 (birth weight $<5^{th}$ centile)**. Women with multiple gestations, diabetes mellitus (either pre-existing or gestational), hypertension (either pre-existing, pregnancy induced or pre-eclampsia), congenital fetal malformations and pre-term birth (<37 weeks) were excluded.

Demographic data analyzed included maternal age, ethnicity (Caucasian, Asian, Indigenous or other), parity, marital status, smoking status, alcohol consumption and body mass index (BMI). Indigenous ethnicity was defined as women who identified as being of Aboriginal or Torres Strait Islander origin. Intrapartum outcomes collected included onset of labor (induced or spontaneous) and mode of birth (spontaneous vaginal delivery (SVD), instrumental, elective cesarean, emergency cesarean for non-reassuring fetal status (NRFS), or emergency

cesarean for other indications). Univariate analysis was first performed to identify significant potential confounders.

Neonatal outcomes analyzed included gestational age at birth, birth weight, Apgar score ≤3 at 5 minutes, presence of significant respiratory distress (as defined by the attending neonatologist), perinatal death, neonatal death, stillbirth, acidosis at birth and admission to the neonatal intensive care unit (NICU). Perinatal death was defined as stillbirths and neonatal death combined. Only stillbirths confirmed to have occurred ≥37 weeks gestation were included in the analysis. Neonatal death was defined as death within 28 days of birth. Acidosis was defined as cord pH <7, lactate ≥6 mmol/L or cord base excess ≤-12mmol/L. Serious composite neonatal morbidity **(SCNM)** was defined as ***any*** of the following: Apgar score ≤3 at 5 minutes, respiratory distress syndrome, acidosis, admission into NICU, stillbirth or neonatal death.

Statistical analysis

Data integrity was assessed using a year by year analysis to identify inconsistencies of reporting between years. Where data integrity was questionable with sudden drops in outcomes that could not be accounted for by change in policy or treatment, those variables were excluded from any analysis. Efforts were made to correct missing and data entry errors through searches of individual patient records. Where data were collected with different degree of outcomes between years, these variables were collapsed into dichotomous variables to indicate whether the outcome occurred or not. Where only the outcomes were recorded, after discussion with data custodians it was determined that it was reasonable to assume that missing data indicated that the outcome had not occurred.

Descriptive analysis was performed using Mann Whitney U Tests for continuous variables and categorical variables compared using Chi-square test. All continuous variables were

tested for normality using a Shapiro-Wilk W Test and deemed to be non-normally distributed. Subsequently data are reported as median (Inter-quartile Range (IQR)) or as the number of observations with the percentage of total. Univariate and multivariate analysis was performed using Generalized Estimating Equations to adjust for the correlation between mothers who birthed more than once within the study period. Multivariate analysis was adjusted for sex, maternal age and BMI at delivery, ethnicity, parity, smoking status and mode of birth. All statistical analyses were conducted using StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

Results

Between 2000 and 2015 there were 137,398 women who birthed at the Mater Mother's Hospital. After excluding 41,498 women the final cohort (Figure 1) comprised of 95,900 women and infant dyads. Infants with birthweights 5^{th} - $<10^{th}$ centiles (SGA1) and $<5^{th}$ centile SGA2) constituted 5.0% (4,748/95,900) and 4.3% (4,135/95,900) of the total cohort respectively.

Both the SGA1 and SGA2 cohorts were found to significantly differ from the AGA cohort with respect to maternal age, ethnicity, parity, marital status, smoking status and maternal BMI. They were more likely to be young (maternal age <20 years), of Asian, Indigenous and other ethnicity, nulliparous and smoke, and less likely to be married and obese. When the SGA1 and SGA2 cohorts were compared, the odds of maternal age <20 years, Asian and Indigenous ethnicity, nulliparity and smoking status were higher in the SGA2 cohort. (Table 1)

For intrapartum outcomes, both the SGA1 and SGA2 cohorts were significantly more likely than the AGA cohort to have an instrumental or emergency cesarean for non-reassuring fetal status ("fetal distress"). The odds of requiring induction of labor (IOL) was higher in the SGA2 compared to the AGA cohort and higher in the SGA2 compared to the SGA1 group. The odds of spontaneous vaginal delivery (SVD) were, however, lower in the SGA2 cohort when compared to both the AGA and the SGA1 cohorts. (Table 2)

There was no difference in median gestation at birth for either of the SGA sub-cohorts compared to AGA controls. The odds of severe acidosis at birth, very low ($\leq$3) 5 minute Apgar score and NICU admission were significantly higher in the SGA1 and SGA2 cohorts even after controlling for confounders (sex, maternal age and BMI, parity, ethnicity, smoking and mode of birth). The odds of stillbirth or neonatal death were however not different

between the SGA1 and SGA2 cohorts. The odds of serious composite neonatal morbidity (SCNM) was highest in the SGA2 cohort (OR 2.20, 95% CI 2.03-2.39) compared to the AGA controls. The odds of the SCNM was also higher in the SGA2 compared to the SGA1 cohort (OR 1.71, 95% CI 1.52-1.92). (Table 3)

The risk of perinatal death (stillbirth and neonatal death) was substantially higher in both SGA cohorts compared to the control group. The SGA1 cohort had an almost 3-fold increased odds of perinatal death (OR 2.62, 95% CI 1.45-4.72), more than 4-fold increased odds of neonatal demise (OR 4.34, 95% CI 1.46-12.95) and more than 2-fold increased risk of stillbirth (OR 2.22, 95% CI 1.10-4.49) compared to the AGA cohort whilst the SGA2 cohort had even greater odds for the same outcomes [perinatal death (OR 3.91, 95% CI 2.27-6.73), neonatal death (OR 5.70, 95% CI 2.03-16.01) and stillbirth (OR 3.45, 95% CI 1.82-6.53)] respectively. (Table 3)

Following stratification of neonatal outcomes by gestational age, the odds of SCNM remained significantly increased in both SGA groups compared to controls. The SGA2 cohort had higher odds of SCNM than the SGA1 cohort at 37+0 - 38+6 weeks (OR 2.48, 95% CI 2.02-3.04) and at 39+0 - 40+6 weeks (OR 1.54, 95% CI 1.30-1.83). For both cohorts, the odds of NICU admission was highest at early term (37+0 - 38+6 weeks) and subsequently decreased with rising gestation. The odds of stillbirth (OR 5.40, 95% CI 1.96-14.83), and overall perinatal death (OR 5.50, 95% CI 2.33-12.98) was highest in the SGA2 cohort at 37+0 - 38+6 weeks. (Table 4)

Comment

Principal findings

The results from this large Australian study demonstrates that in low risk pregnancies, outcomes for SGA infants born at term are significantly worse compared to an AGA cohort. Specifically, newborns with birthweight <5th centile (SGA2) had a doubling of the SCNM (22.6% vs. 11.1%) while infants with birthweight 5th – 10th centile (SGA1) had 23% (13.7% vs. 11.1%) increase in adverse outcomes. Regression analyses to control for confounders showed that the SCNM was >2 fold higher in the SGA2 cohort. We also found, that although the risk of SCNM was greatest at early term gestation regardless of SGA sub-cohort, this risk remained elevated even at term and post term gestation. Importantly our results indicate that the risk of stillbirth was >5-fold and >3-fold at early term and term respectively and that the odds of neonatal death in the SGA2 cohort increased from 37+0 - 38+6 weeks (OR 5.94, 95% CI 1.20-29.34) to ≥41 weeks (OR 12.97, 95% CI, 1.53-109.80) albeit with wide confidence intervals.

Our findings also show that the odds of emergency cesarean for non-reassuring fetal status was significantly greater in both the SGA1 and SGA2 cohorts with the highest odds in the SGA2 cohort. This is an important finding given that there is significant neonatal morbidity (neonatal encephalopathy, respiratory distress, acidosis, admission to the neonatal intensive care unit) associated with intrapartum hypoxia. Furthermore, rapid delivery by emergency cesarean for non-reassuring fetal status is associated with poorer neonatal outcomes compared to uncomplicated vaginal birth.[8] In Australia, emergency cesarean rates for “fetal distress” range from 11-16% [9] reflecting trends seen in other high income countries. Alongside the increased risk of perinatal death, the possibility of hypoxia related brain injured individuals requiring a lifetime of care, intra-partum fetal compromise continues to

represent a major burden for healthcare providers around the world, with SGA infants a particularly vulnerable cohort for this specific complication.

Our study represents the largest cohort study published to date investigating serious neonatal outcomes in a population without major risk factors (hypertension and diabetes mellitus) for aberrant fetal growth. Collectively, our findings and that two another recent large publications from North America,[4 10] including one published in an earlier issue of this Journal [4] provide robust evidence of the perinatal risks that pregnancies with SGA infants face, even at term. Furthermore, when identification of SGA infants is made on the basis of ultrasound measurements, the odds of perinatal morbidity is more than doubled in infants with an estimated fetal weight <5th centile, regardless of whether the SGA diagnosis is made in early third trimester or within 28 days of the delivery, findings that concur with the results of our study.[11] Given that such women make up the majority of pregnancies in most jurisdictions [6] the imperative for prenatal identification of SGA fetuses is obvious, as it is now clear that regardless of gestation, overall perinatal outcomes for SGA infants are worse compared to their appropriately grown counterparts and this dichotomy is even more pronounced if fetal growth restriction is present.[12, 13] Additionally, the risk of term perinatal death is substantially increased with low birth weight [3] further underlining the critical importance of prenatal identification given that early term delivery could be one potential strategy of mitigating this risk, notwithstanding the potential neonatal morbidity associated with this option.

The evidence regarding ultrasound detection of SGA fetuses is confusing and conflicting with some studies showing a lack of benefit[14 15] whilst others demonstrating detection rates >50%.[16 17 18] Furthermore, Cochrane reviews do not demonstrate an advantage with the use of either routine late pregnancy ultrasound or umbilical artery Doppler assessment in low-risk populations.[19, 20] Moreover, it is also unclear whether a single late pregnancy measurement of

fetal biometry or assessment of growth velocity is superior for the identification of an SGA fetus. A recent study from North America found that there was no difference in SGA detection rates when single biometry was compared with serial measurements with only modest impact on screening performance when maternal risk factors including diabetes mellitus and hypertension were accounted for.[21] This study also demonstrated that fetal biometry measured within 2 weeks of pre-determined gestational age cut-offs (<32 weeks and <36 weeks) did not improve detection rates for SGA fetuses. Conversely, another study showed that although third trimester biometry provided poor to moderate detection of SGA fetuses, a shorter compared to a longer ultrasound to delivery interval provided better prediction.[22] Others ultrasound studies have suggested that the fetal cerebroplacental ratio (CPR) is a promising marker for identification of fetuses that have suboptimal growth.[23 24 25, 26 27]A low CPR particularly in SGA fetuses is associated with an increased risk of stillbirth[28] and other adverse perinatal outcomes.[29] It also appears to be an independent predictor of intrapartum fetal compromise, acidosis at birth and neonatal unit admission in term infants.[30 31]

Although a recent review comparing planned early delivery with expectant management at term for suspected fetal compromise failed to show a difference in perinatal mortality, neonatal morbidity or neurodevelopment disability[32] there is emerging evidence to suggest that when accompanied by careful surveillance and planned delivery, rates of adverse outcomes in SGA infants can be reduced.[33] Currently the American Congress of Obstetricians and Gynecologists recommends delivery by 39 weeks for infants with fetal growth restriction, without other risk factors [12] whilst the Royal College of Obstetricians and Gynaecologists in the United Kingdom recommend delivery by 37 weeks.[34] This difference in recommendations for timing of delivery reflects the paucity of good data to guide

management. The results from our study however would support a policy of deferring delivery of SGA infants in a low risk cohort of women until 39+0 weeks.

The main limitations of this study relate to its retrospective nature and its single institution focus. We also used population charts rather than customized ones when defining our cohorts. In our view this approach was however resonable given the data from the Intergrowth-21st [35] and other studies[36] suggesting that customized charts were not superior in identifying infants at-risk of adverse outcomes. We however acknowledge that although some investigators[37] suggest that the use of customized charts better identifies SGA infants, others urge caution[38] noting that detection rates are no different whatever charts are used. Furthermore, whilst it is clear that the risk of adverse outcomes is maximum at extremes of size,[2] the incremental risk appears to commence at higher birth weight centiles than the cut-offs we have chosen.[39] We were also not able to ascertain the number of women in whom there were antenatal concerns and had increased surveillance of wellbeing. As a consequence of this, we were unable to establish the proportion of women who had planned birth (IOL or cesarean) because of either clinical concerns regarding fetal size or an ultrasound confirmed SGA fetus. Additionally, data regarding socioeconomic status, prenatal education, specific intrapartum (chorioamnionitis, abruption etc.) and neonatal complications (necrotising enterocolitis etc.) were not consistently or reliably recorded and hence not reported in this study. The strengths of our study include the very large sample size from a tertiary institution with clear evidence based protocols guiding management providing a “real world” view of outcomes. Furthermore, it is unlikely that our results were influenced by a Hawthorne effect given that all patient data were collected contemperaneously in the absence of enrollment of participants in any clinical studies. We also chose components of the composite morbidity to reflect not only very poor condition at birth (Apgar $\leq$3 and severe acidosis, severe respiratory distress and admission to the NICU) but also mortality (stillbirth and neonatal death).

Conclusions and implications for clinical practice

In conclusion, the results presented in this paper provide further evidence that SGA infants from term uncomplicated pregnancies have significantly increased morbidity and mortality rates when compared to AGA infants, with the greatest risk seen in infants $<5^{th}$ centile regardless of gestation at birth. The evidence for increased morbidity and mortality seen in SGA infants both in this and other studies, in our view highlights the importance of prenatal identification of this group. Although the optimum management algorithm post detection is yet to be determined, identification of a vulnerable cohort such as this allows potentially closer surveillance as well a comprehensive discussion with women regarding ongoing risks and all management options including early term birth, induction of labour or planned cesarean. Our findings also support the need for large randomized controlled studies to ascertain firstly, the optimum screening gestation and technique for SGA fetuses (single late pregnancy ultrasound, serial biometry measurements and/or incorporating the fetal CPR, placental biomarkers etc.), and secondly the optimum gestation for delivery to mitigate this risk.

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Table 1: Maternal Demographics

Maternal Characteristic	AGA, n=87017	SGA, n=8883		SGA1 vs. AGA	SGA2 vs. AGA	SGA2 vs. SGA1
		SGA1, n=4748	SGA2, n=4135			
Maternal age, years						
<20	2117/87006 (2.4%)	184/4748 (3.9%)	209/4134 (5.1%)	**1.60 (1.37-1.87)[c]**	**2.07 (1.79-2.40)[c]**	**1.32 (1.07-1.62)[b]**
20-34	63127/87006 (72.6%)	3471/4748 (73.1%)	3035/4134 (73.4%)	1.03 (0.97-1.10)	1.06 (0.98-1.13)	1.02 (0.93-1.12)
≥35	21762/87006 (25.0%)	1093/4748 (23.0%)	890/4134 (21.5%)	**0.89 (0.83-0.96)[b]**	**0.82 (0.76-0.88)[c]**	0.92 (0.83-1.01)
Ethnicity						
Caucasian	67713/86959 (77.9%)	3141/4744 (66.2%)	2547/4130 (61.7%)	**0.56 (0.53-0.60)[c]**	**0.46 (0.43-0.50)[c]**	**0.82 (0.75-0.90)[c]**
Asian	10430/86959 (12.0%)	957/4744 (20.2%)	934/4130 (22.6%)	**1.84 (1.71-1.99)[c]**	**2.12 (1.96-2.29)[c]**	**1.16 (1.05-1.29)[b]**
Indigenous	1395/86959 (1.6%)	111/4744 (2.3%)	136/4130 (3.3%)	**1.46 (1.20-1.79)[c]**	**2.03 (1.69-2.45)[c]**	**1.41 (1.09-1.82)[b]**
Other	7421/86959 (8.5%)	535/4744 (11.3%)	513/4130 (12.4%)	**1.35 (1.23-1.49)[c]**	**1.49 (1.35-1.64)[c]**	**1.11 (0.97-1.26)**
Nulliparous	40915/87006 (47.0%)	2734/4748 (57.6%)	2595/4133 (62.8%)	**1.54 (1.45-1.63)[c]**	**1.91 (1.80-2.03)[c]**	**1.26 (1.15-1.37)[c]**
Married	77170/85861 (89.9%)	4033/4678 (86.2%)	3444/4056 (84.9%)	**0.71 (0.65-0.78)[c]**	**0.65 (0.60-0.71)[c]**	0.90 (0.80-1.02)
Smoker	12570/87017 (14.5%)	940/4748 (19.8%)	1023/4135 (24.7%)	**1.45 (1.35-1.56)[c]**	**1.90 (1.76-2.05)[c]**	**1.33 (1.20-1.47)[c]**
Alcohol	7865/87017 (9.0%)	399/4748 (8.4%)	347/4135 (8.4%)	0.93 (0.83-1.03)	0.93 (0.84-1.04)	1.01 (0.87-1.17)
BMI (kg/m^2) ≥30	8234/84095 (7.8%)	298/4566 (6.5%)	270/3917 (6.9%)	**0.64 (0.57-0.72)[c]**	**0.69 (0.60-0.78)[c]**	1.06 (0.89-1.26)

Data is presented as n (%); Univariate Odds Ratio (95% Confidence Interval). [a]p-value < 0.05; [b]p-value <0.01; [c]p-value <0.001

AGA: appropriate for gestational age (birthweight 10^{th}-90^{th} centile); *BMI:* body mass index; *SGA:* small for gestational age (birthweight $<10^{th}$ centile for gestational age); *SGA1*: birthweight 5^{th} - $<10^{th}$ centiles for gestational age; *SGA2*: birthweight $<5^{th}$ centile for gestational age.

Table 2: Intrapartum Outcomes

Intrapartum Outcome	AGA, n= 87017	SGA, n=8883		SGA1 vs AGA[d]	SGA2 vs. AGA[d]	SGA2 vs. SGA1[d]
		SGA1, n=4748	SGA2, n= 4135			
Gestational Age (weeks)						
37+0 – 38+6	25029/87017 (28.8%)	1308/4748 (27.6%)	1081/4135 (26.1%)	**0.94 (0.88-1.00)[a]**	**0.86 (0.80-0.93)[c]**	0.92 (0.84-1.02)
39+0 – 40+6	49175/87017 (56.5%)	2660/4748 (56.0%)	2353/4135 (56.9%)	0.98 (0.92-1.04)	1.02 (0.96-1.09)	1.04 (0.96-1.14)
≥41	12813/87017 (14.7%)	780/4748 (16.4%)	701/4135 (17.0%)	**1.15 (1.06-1.24)[b]**	**1.20 (1.10-1.30)[c]**	1.04 (0.93-1.16)
IOL	22770/68698 (33.2%)	1240/3964 (31.3%)	1202/3509 (34.3%)	0.95 (0.89 – 1.02)	**1.09 (1.01 – 1.17)[a]**	**1.15 (1.04-1.26)[b]**
Method of Birth						
SVD	46679/86990 (53.7%)	2672/4745 (56.3%)	2214/4134 (53.6%)	1.04 (0.98-1.09)	**0.92 (0.87-0.98)[b]**	**0.89 (0.82-0.96)[b]**
Instrumental	11484/86990 (13.2%)	725/4745 (15.3%)	657/4134 (15.9%)	**1.19 (1.10-1.29)[c]**	**1.25 (1.15-1.36)[c]**	1.05 (0.94-1.18)
Elective Cesarean	17642/86990 (20.3%)	717/4745 (15.1%)	527/4134 (12.8%)	**0.75 (0.70-0.81)[c]**	**0.57 (0.52-0.62)[c]**	**0.81 (0.72-0.91)[c]**
Emergency Cesarean	11184/86990 (12.9%)	631/4745 (13.3%)	736/4134 (17.8%)	1.04 (0.95-1.13)	**1.47 (1.36-1.60)[c]**	**1.42 (1.27-1.59)[c]**
Emergency Cesarean – NRFS	3657/86990 (4.2%)	336/4745 (7.1%)	450/4134 (10.9%)	**1.74 (1.55-1.95)[c]**	**2.78 (2.51 -3.09)[c]**	**1.60 (1.38 – 1.86)[c]**
Emergency Cesarean - Other	7527/86990 (8.7%)	295/4745 (6.2%)	286/4134 (6.9%)	**0.70 (0.62-0.79)[c]**	**0.78 (0.70-0.88)[c]**	1.12 (0.95-1.33)

Data is presented as n (%); [d]Univariate Odds Ratio (95% Confidence Interval). [a]p-value < 0.05; [b]p-value <0.01; [c]p-value <0.001

AGA: appropriate for gestational age (birthweight 10^{th}-90^{th} centile); *IOL*: Induction of Labor; *NRFS:* non-reassuring fetal status; *SGA*: small for gestational age (birthweight <10^{th} centile for gestational age); *SGA1*: birthweight 5^{th} - <10^{th} centiles for gestational age; *SGA2*: birthweight <5^{th} centile for gestational age; *SVD:* spontaneous vaginal delivery.

528 **Table 3: Neonatal outcomes**

Neonatal Outcome	AGA, n=87017	SGA, n=8883		SGA1 vs. AGA[d]	SGA2 vs. AGA[d]	SGA2 vs. SGA1[d]
		SGA1, n=4748	SGA2, n=4135			
Gestational Age (Weeks)	39 (38-40)	39 (38-40)	39 (38-40)	NA	NA	NA
Birth Weight (g)	3450 (3210-3690)	2870 (2730-2980)	2630 (2470-2785)	NA	NA	NA
Apgar Score ≤3 @ 5 min	142/86865 (0.2%)	16/4734 (0.3%)	19/4124 (0.5%)	**1.93 (1.12-3.33)[a]**	**2.22 (1.29-3.81)[b]**	1.24 (0.60-2.57)
Respiratory Distress	6301/87017 (7.2%)	345/4748 (7.3%)	405/4135 (9.8%)	1.04 (0.93-1.17)	**1.41 (1.26 - 1.58)[c]**	**1.32 (1.12-1.54)[b]**
Perinatal Death	94/87017 (0.1%)	15/4748 (0.3%)	20/4135 (0.5%)	**2.62 (1.45-4.72)[b]**	**3.91 (2.27-6.73)[c]**	1.46 (0.69-3.09)
Neonatal Death	19/86942 (0.02%)	5/4738 (0.1%)	6/4121 (0.2%)	**4.34 (1.46-12.95)[b]**	**5.70 (2.03-16.01)[b]**	1.22 (0.32-4.63)
Stillbirth	75/87017 (0.1%)	10/4748 (0.2%)	14/4135 (0.3%)	**2.22 (1.10-4.49)[a]**	**3.45 (1.82 - 6.53)[c]**	1.56 (0.64-3.80)
Acidosis	2442/87017 (2.8%)	225/4748 (4.7%)	257/4135 (6.2%)	**1.48 (1.28-1.72)[c]**	**1.80 (1.56-2.07)[c]**	1.21 (0.99-1.47)
NICU	3740/87017 (4.3%)	285/4748 (6.0%)	562/4135 (13.6%)	**1.41 (1.24-1.61)[c]**	**3.25 (2.94-3.61)[c]**	**2.22 (1.90-2.60)[c]**
SCNM	9660/87017 (11.1%)	650/4748 (13.7%)	933/4135 (22.6%)	**1.25 (1.15-1.37)[c]**	**2.20 (2.03 - 2.39)[c]**	**1.71 (1.52-1.92)[c]**

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530 Data is presented as n (%) or Median (Interquartile Range); [d]Adjusted Odds Ratio (95%
531 Confidence Intervals) - Adjusted for sex, maternal age and BMI, ethnicity, parity, smoking
532 status and mode of birth. [a]p-value < 0.05; [b]p-value <0.01; [c]p-value <0.001
533
534 *AGA*: appropriate for gestational age (birthweight 10^{th}-90^{th} centile); *SGA*: small for
535 gestational age (birthweight <10^{th} centile for gestational age); *SGA1*: birthweight 5^{th} - <10^{th}
536 centiles for gestational age; *SGA2*: birthweight <5^{th} centile for gestational age; *NICU:*
537 Neonatal Intensive Care Unit; *SCNM*: Serious Composite Neonatal Morbidity
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Table 4: Neonatal Morbidity Stratified by Gestational Age

Neonatal Outcome	Gestational Age 37+0 – 38 +6 Weeks			Gestational Age 39+0 – 40 +6 Weeks			Gestational Age ≥41 Weeks		
	SGA1 vs. AGA[d]	**SGA2 vs. AGA**[d]	**SGA2 vs. SGA1**[d]	**SGA1 vs. AGA**[d]	**SGA2 vs. AGA**[d]	**SGA2 vs. SGA1**[d]	**SGA1 vs. AGA**[d]	**SGA2 vs. AGA**[d]	**SGA2 vs. SGA1**[d]
Apgar Score ≤3 @ 5 min	**2.77 (1.21-6.34)**[a]	**5.57 (2.65-11.70)**[c]	1.92 (0.71-5.20)	1.95 (0.88-4.31)	1.42 (0.57-3.55)	0.83 (0.26-2.59)	0.58 (0.08-4.41)	NA	NA
Respiratory Distress	0.92 (0.75-1.13)	**1.61 (1.32-1.96)**[c]	**1.73 (1.32-2.28)**[c]	1.12 (0.94 - 1.32)	**1.35 (1.15-1.59)**[c]	1.17 (0.94-1.47)	1.08 (0.83-1.42)	1.23 (0.95-1.61)	1.17 (0.80-1.70)
Perinatal Death	2.61 (1.00-6.84)	**5.50 (2.33-12.98)**[c]	1.91 (0.60-6.07)	**3.39 (1.58-7.27)**[b]	**3.16 (1.45-6.88)**[b]	0.90 (0.33-2.46)	NA	2.56 (0.52-12.66)	NA
Neonatal Death	2.67 (0.33 - 21.86)	**5.94 (1.20-29.34)**[a]	2.08 (0.18-24.41)	**7.69 (1.93-30.58)**[b]	2.19 (0.31-15.54)	0.26 (0.03-2.29)	NA	**12.97 (1.53-109.80)**[a]	NA
Stillbirth	2.58 (0.87 - 7.65)	**5.40 (1.96-14.83)**[b]	1.88 (0.49-7.16)	2.56 (1.00-6.58)	**3.40 (1.46-7.94)**[b]	1.36 (0.42-4.40)	NA	NA	NA
Acidosis	**1.61 (1.14-2.26)**[b]	**2.50 (1.81 - 3.45)**[c]	1.46 (0.94-2.26)	**1.41 (1.15-1.72)**[b]	**1.71 (1.41-2.08)**[c]	1.23 (0.94 - 1.62)	**1.55 (1.18-2.03)**[b]	**1.57 (1.19-2.06)**[b]	1.04 (0.72-1.51)
NICU	**1.55 (1.26-1.91)**[c]	**5.13 (4.35 - 6.04)**[c]	**3.20 (2.48-4.13)**[c]	**1.32 (1.08-1.61)**[b]	**2.82 (2.41-3.30)**[c]	**2.08 (1.62-2.66)**[c]	1.30 (0.97-1.75)	**1.87 (1.43-2.43)**[c]	1.44 (0.98-2.11)
SCNM	**1.29 (1.10 - 1.51)**[b]	**3.32 (2.87-3.85)**[c]	**2.48 (2.02-3.04)**[c]	**1.21 (1.06-1.38)**[b]	**1.92 (1.71 - 2.16)**[c]	**1.54 (1.30-1.83)**[c]	**1.26 (1.03-1.55)**[a]	**1.58 (1.30-1.92)**[c]	1.28 (0.97-1.70)

Data is presented as [d]Adjusted Odds Ratio (95% Confidence Interval) - Adjusted for: sex, maternal age and BMI, ethnicity, parity, smoking status, and mode of birth. [a]p-value < 0.05; [b]p-value <0.01; [c]p-value <0.001

AGA: appropriate for gestational age (birthweight 10^{th}-90^{th} centile); *NA*, not applicable; *NICU*: neonatal intensive care unit; *SGA*: small for gestational age (birthweight <10^{th} centile for gestational age); *SGA1*: birthweight 5^{th} - <10^{th} centiles for gender and gestational age; *SGA2*: birthweight <5^{th} centile for gestational age; *NICU:* Neonatal Intensive Care Unit; SCNM: Serious Composite Neonatal Morbidity

554 **Figure 1: Participant flow diagram**

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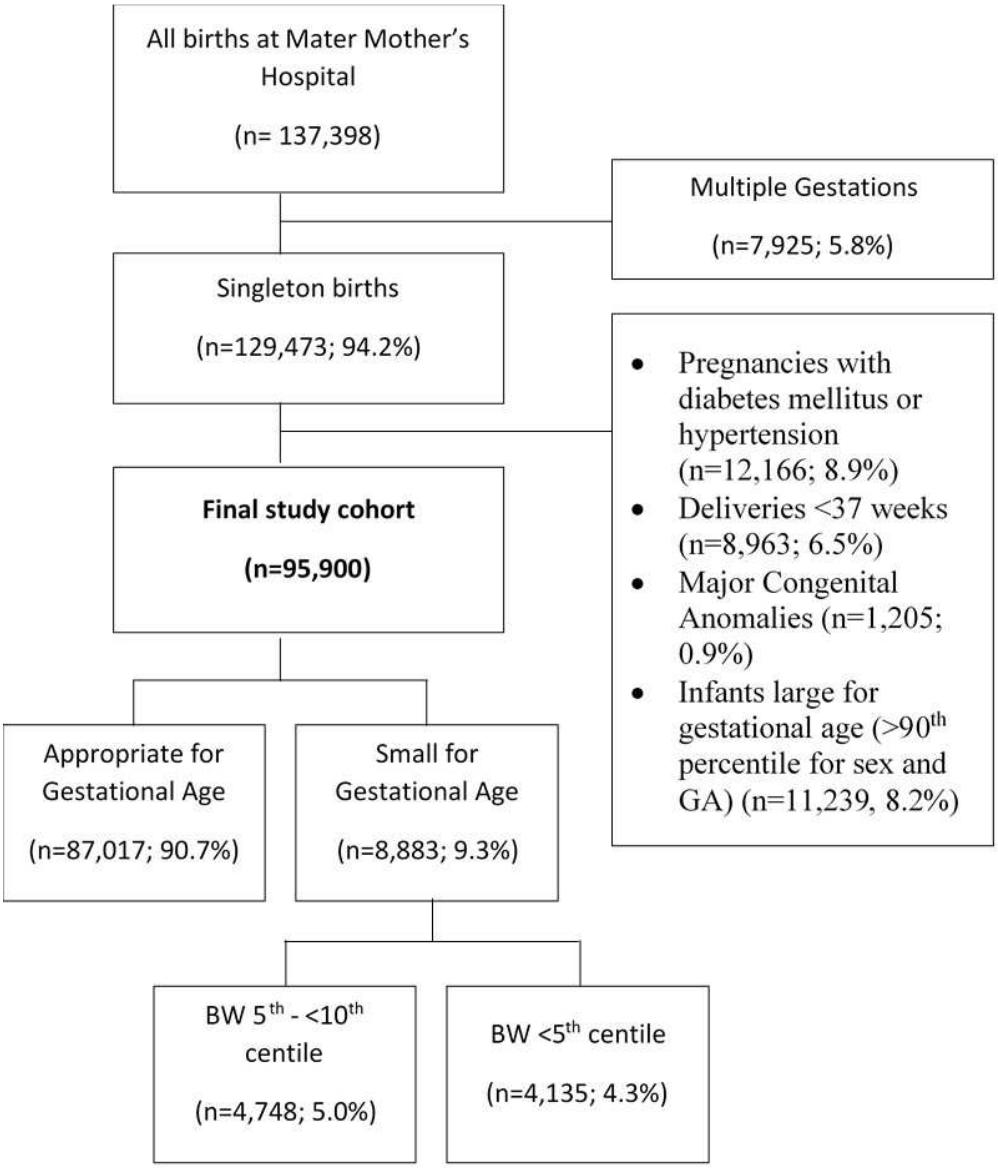
All births at Mater Mother's Hospital
(n= 137,398)
Multiple Gestations
(n=7,925; 5.8%)
Singleton births
(n=129,473; 94.2%)
Pregnancies with diabetes mellitus or hypertension (n=12,166; 8.9%)
Deliveries <37 weeks (n=8,963; 6.5%)
Major Congenital Anomalies (n=1,205; 0.9%)
Infants large for gestational age (>90th percentile for sex and GA) (n=11,239, 8.2%)
Final study cohort
(n=95,900)
Appropriate for Gestational Age
(n=87,017; 90.7%)
Small for Gestational Age
(n=8,883; 9.3%)
BW 5th - <10th centile
(n=4,748; 5.0%)
BW <5th centile
(n=4,135; 4.3%)