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Antenatal risk factors associated with neonatal morbidity in large for gestational age infants: an international prospective cohort study

Running Head: Risk factors for LGA related morbidity.

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Conflict of Interests Statement

LCK has a consultancy relationship with Alere. PNB and LCK are minority shareholders in Metabolomic Diagnostics, an SME who have licensed IP pertaining to the prediction of preeclampsia from UCC. In addition, PNB and LCK declare a US patent PCT/EP2010/070446. All other authors report no conflict of interest.

Abstract

Introduction: Large for gestational age (LGA) infants are associated with increased risk of neonatal morbidity and mortality, however most of them will not have adverse outcomes. Our aim was to identify antenatal clinical factors associated with neonatal morbidity in LGA infants. *Material and methods:* Nulliparous women from the Screening for Pregnancy Endpoints (SCOPE) study were included. We compared maternal and fetal factors between LGA infants (birthweight >90th customized centile) with and without neonatal morbidity, defined as admission to neonatal intensive care unit or severe neonatal morbidity. Factors were selected based on *a-priori* hypotheses of association and included maternal demography, anthropometric measures and self-reported physical activity (15 and 20 weeks), fetal biometry (20 weeks), and clinical information. Multivariable logistic regression was used to identify risk factors. Stratified analyses were performed by maternal obesity and physical activity. *Results:* Amongst term pregnancies, prevalence of LGA infants was 9.3% (491/5,255), with 11.8% (58/491) prevalence of neonatal morbidity. Random glucose at 20 weeks (OR 1.52; 95% CI1.17 to 1.97, per 1mmol/L increase) and no regular physical activity at 20

weeks (3.93; 1.75 to 8.83) were associated with increased risk of neonatal morbidity after adjustment for birthweight, gestational age at delivery and gestational diabetes. The increased risk associated with higher glucose levels was not evident in women with regular physical activity or without obesity. *Conclusions:* Regular physical activity in mid-pregnancy is associated with lower risk for neonatal morbidity in LGA infants and seems to offer protection against the increased risk associated with higher maternal glucose levels.

Key words

Large for gestational age, macrosomia, risk factors, adverse outcome, neonatal morbidity.

Abbreviations

AC	abdominal circumference
BMI	body mass index
FL	femur length
GDM	gestational diabetes mellitus
HC	head circumference
LGA	large for gestational age
NICU	neonatal intensive care unit
SGA	small for gestational age
SNM	severe neonatal morbidity

Key message

Factors associated with neonatal morbidity in large for gestational age infants are present as early as 20 weeks. Regular physical activity is a modifiable factor related to reduced risk and seems to protect against the deleterious effect of higher maternal glucose.

Introduction

The population prevalence of risk factors associated with delivery of a large for gestational age (LGA) infant, particularly maternal obesity, is increasing (1). LGA, most often defined as a birthweight above the 90th centile, is associated with significant maternal and neonatal morbidity and mortality (2, 3); LGA increases the risk of neonatal Apgar score below seven at five minutes, shoulder dystocia and neonatal intensive care unit (NICU) admission (4, 5) and maternal risks include higher cesarean section rates, postpartum hemorrhage and 3rd and 4th degree tear (4, 5).

The majority of LGA infants at term, although at higher risk, will not experience any short-term adverse perinatal outcomes. The incidence of neonatal morbidity, as assessed through NICU admission, is approximately 5-12% (4, 6). Improved antenatal detection of LGA infants and appropriate management of delivery in suspected LGA infants has the potential to prevent delivery related neonatal morbidity (7), but interventions in pregnancy aimed to prevent LGA in high-risk groups, have, to date, not reduced either incidence or related morbidity (8, 9). We recently reported a prediction model in early pregnancy for LGA infants with modest performance at 20 weeks' gestation but with the potential to inform which women might benefit from a third trimester ultrasound (10). We hypothesized that improved identification of maternal factors linked to neonatal morbidities in LGA infants will better define a selected group of mothers in whom early interventions are more likely to be effective in prevention of LGA related morbidities. In addition, the identification of antenatal risk factors would allow for better risk stratification so that clinician can better anticipate adverse neonatal outcomes in LGA infants.

Our aim was to determine the incidence of severe neonatal morbidity (SNM) and NICU admission in LGA infants by customized centiles at term and to identify antenatal clinical factors associated with these adverse outcomes amongst LGA infants.

Material and methods

Participants were healthy nulliparous women recruited to the SCOPE (Screening for Pregnancy Endpoints) study in Auckland, New Zealand; Adelaide, Australia; London, Leeds and Manchester, UK; and Cork, Ireland. This is a multicenter cohort, the primary aim of which was to develop screening tests for prediction of preeclampsia, preterm birth and small for gestational age babies (SGA) (11). Eligible nulliparous women with singleton pregnancies were recruited between 14-16 weeks' gestation between 2004 and 2011 (consecutive recruitment of women). Women were excluded if they had chronic hypertension requiring antihypertensive drugs, pre-gestational diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease, HIV, previous cervical knife cone biopsy, three or more previous miscarriages or terminations of pregnancy, current ruptured of membranes, known major fetal anomaly or abnormal karyotype, and those who received interventions that may modify pregnancy outcomes.

At study entry, extensive participant assessment recorded demographic characteristics, clinical and behavioral information, physical and laboratorial examinations, and an ultrasound scan. At 19-21 weeks, women returned for clinical assessment and an anatomy ultrasound was also performed. Blood samples were taken at both visits. Women were followed until 30 days postpartum and data was recorded for any event during pregnancy, at delivery or during the neonatal period.

For the present study, only women whose infants were born at term (delivered at or after 37 completed weeks) were included. Additional exclusion criteria for this analysis were infants SGA or appropriate for gestational age infants according to customized centiles ($\leq 90^{th}$ percentile). Birthweight customized centiles were calculated adjusting for maternal height and weight, ethnicity, parity, fetal sex, and gestational age (12).

The primary outcome was a composite of neonatal morbidity, which included SNM or NICU admission. SNM was defined as stillbirth, neonatal death or other severe neonatal morbidities, which included one or more of the following: grade II or III hypoxic ischemic encephalopathy, Apgar score of less than four at five minutes, arterial cord pH < 7.0 and/or base excess less than -15,

neonatal seizures, neonatal ventilation for longer than 24 hours or admission to the NICU for longer than four days.

Factors were selected for analysis based on *a-priori* hypotheses of association and were composed of maternal age and birthweight, ethnicity, educational level, job situation, family history of diabetes or gestational diabetes mellitus (GDM), maternal anthropometry (weight, height and body mass index (BMI)), systolic blood pressure, random glucose (15 and 20 weeks), weight change between 15 and 20 weeks, physical activity during pregnancy (15 and 20 weeks), fetal biometry at 20 weeks scan (head circumference (HC), abdominal circumference (AC), femur length (FL) and head circumference to abdominal circumference (HC/AC) ratio), GDM and hypertensive disorders in current pregnancy.

Ethnicity was grouped as European, Asian, Maori or other. Educational level was assessed by total number of schooling years and job situation was divided in the following categories: full time work, part time work or other. Physical activity was assessed using a questionnaire developed specifically for this study and was categorized into three levels of intensity: vigorous (physical activities that made the woman breathe harder), moderate (physical activities that did not make the women breathe harder), light (walking for recreation of exercise). Participants were categorized by the highest intensity level of physical activity they regularly performed (at least once a week). No regular physical activity was defined as absence of any kind of regular (at least once a week) self-reported physical activity (vigorous moderate and light). Women were defined as having GDM according to local policies. Women without a 75g Oral Glucose Tolerance Test (OGTT) were considered as unknown GDM status; these were women without risk factors according to local policy. Preeclampsia was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions four hours apart after 20 weeks of gestation but before the onset of labor, or postpartum, with either proteinuria (24 hour urine protein ≥300 mg or spot urine protein to creatinine ratio ≥ 30 mg/mmol or urine dipstick protein ≥ 2+) or any multi-system complication of preeclampsia.

Statistical analyses

All women with known outcomes were included in the analysis. Missing data was minimal (<3%) for the exposures; except for maternal birthweight (n=32; 6.5%). Missing data were imputed for analyses using expected maximization, or for variables unrelated to other data points that had <1% missing data, single imputation was performed using the median (continuous variables) or mode (binary/categorical variables) as previously described.(6) Factors were summarized as mean and standard deviation (SD), median and interquartile range (IQR) or by frequency (proportion), as appropriate. Comparison between groups was by t-test, Mann-Whitney test or chi square/exact test, as appropriate. Factors with $p<0.05$ were combined in a multivariable model. Logistic regression was used to identify risk factors for neonatal morbidity. A pre-defined adjustment for GDM status, birthweight, and gestation at delivery was performed. Risk factors were identified by a significant association in a multivariable model ($p<0.05$). Potential use of factors for risk stratification was assessed based on antenatal risk factors identified. In addition, we explored obesity as a factor for risk stratification due to known association with adverse outcomes.(13) Formal interaction test between variables assessed for risk stratification was performed using likelihood ratio tests. All analyses were performed in Stata software, version 14.1 (StataCorp LP, College Station, Texas). This study has been reported in line with STROBE recommendations (14).

Ethical approval

Ethical approval was obtained in each participant local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London, Leeds and Manchester 06/MRE01/98, and Cork ECM5 (10) 05/02/08) and all participants provided written informed consent.

Results

Amongst the 5628 women recruited in SCOPE, data from those with preterm birth (n=351), miscarriage (n=18) and with missing information on birthweight centile (n=4) were excluded. In term pregnancies, 80.4% (4225/5255) were appropriate for gestational age infants and 10.3% (538/5255) were SGA pregnancies at term (Figure 1). The present analysis was restricted to the remaining 9.3% (491/5255) women with LGA at term. The prevalence of LGA related morbidity in this group was 11.8% (58/491) using a composite fetal outcome of either SNM or NICU admission. This comprised

4.5% (22/491) SNM and 11.0% (54/491) NICU admission. Four SNM infants were not admitted to NICU (3 stillbirths at term and one infant (Apgar 10 at 5 minutes) with a low cord blood pH and a fractured clavicle).

Comparisons between LGA infants with and without morbidity are described in Table 1. There was a higher prevalence of maternal obesity in the neonatal morbidity group (24.1% vs. 11.8%, p=0.01). Other demographic and clinical characteristics in early pregnancy (15 weeks) were not different between groups. At 20 weeks, the mean random glucose concentration was higher in women whose LGA infant had morbidity after birth compared to women with LGA infants without morbidity (6.1 ±1.1 mmol/L vs. 5.5 ±1.0 mmol/L, p<0.001). Also, mothers of infants with morbidity were more likely not to routinely engage in physical activity at 20 weeks (20.7% vs. 5.8%, p<0.001). In women who reported physical activity during mid-pregnancy, the intensity of self-reported physical activity was not different between those with infant morbidity and those without. Fetal biometry measures at anatomy scan were not different but the HC/AC ratio was lower in babies that later developed morbidity (p=0.03).

Maternal pregnancy complications were similar in morbidity and no morbidity groups, with no significant difference in preeclampsia, gestational hypertension and mode of delivery (Table 2). However, induction of labor was more frequent (37.9% vs. 22.6%, p=0.006) and birthweight higher (4300 ±440 g vs. 4183 ±347 g, p=0.02) in LGA infants with morbidity.

In multivariable analysis, random glucose at 20 weeks (adjusted odds ratio 1.52; 95% confidence interval 1.17 to 1.97, per 1 mmol/L increase) and no regular physical activity at 20 weeks (3.93; 1.75 to 8.83) were associated with increased risk of neonatal morbidity after adjustment for birthweight, gestation at delivery and GDM status (Table 3).

Maternal risk factors were used to stratify the risk at mid pregnancy of morbidity in LGA infants. Random glucose was categorized into three groups using approximates of the interquartile range (<25th, 25th–75th, >75th) and plotted according to physical activity status (Figure 2a). Women not undertaking regular physical activity had an increased risk of morbidity when random glucose was between 5.0 and 6.0 mmol/l or higher than 6.0 mmol/l (p<0.001 and p<0.001, respectively).

However, in women undertaking regular physical activity, there was no association between glucose category and risk of morbidity. Stratification according to obesity was also assessed (Figure 2b and 2c). In obese women, random glucose > 6.0 mmol/l was associated with increased risk of neonatal morbidity (p=0.03), but this was not observed in women without obesity. No regular physical activity was associated with neonatal morbidity in women with or without obesity (p=0.001 and p=0.04, respectively) and the combination of no regular physical activity and being obese identified women with highest rate of neonatal morbidity. Interaction tests between glucose and physical activity, glucose and obesity, and physical activity and obesity showed no evidence for interaction (p=0.19, p=0.16, and p=0.18, respectively) although limitations of sample size may have compromised statistical power.

Discussion

Delivery of a LGA baby is associated with increased risk of adverse perinatal outcomes (4-6, 15). In this analysis of a large low risk primiparous cohort, we have identified differences in maternal characteristics during pregnancy between LGA infants with and without neonatal morbidity as early as mid-pregnancy. Plasma glucose concentration and no regular self-reported physical activity in mid-pregnancy were independently associated with increased risk of SNM or NICU admission. These findings may provide insight into metabolic pathways involved in LGA and related morbidity. Amongst pregnancies with LGA infants, induction of labor and birthweight were also associated with adverse outcome, which reflects the challenge in managing delivery of these overgrown infants.

The metabolic pathways leading to LGA are incompletely understood (16). Maternal GDM, obesity and excessive gestational weight gain are strong risk factors; for example, LGA increases from 5.7% in normal BMI women to 8.6-13.9% when BMI is >30 kg/m^2 (17). We found that the prevalence of maternal obesity is also different between LGA infants with and without morbidity but that this association was attenuated following adjustment for other factors including maternal random glucose at 20 weeks. In agreement with others we found a pivotal role for maternal dysglycemia in the pathway between maternal metabolic dysfunction and LGA-related neonatal morbidity, with an approximately 1.5-fold increase in the odds of neonatal morbidity in LGA infants for each unit increase in random glucose levels at 20 weeks. This association is not specific to fetal overgrowth; the HAPO study described higher glycemic levels (in a pre-diabetic range) during the OGTT to be associated with adverse perinatal outcomes, such as shoulder dystocia or birth injury,

hyperbilirubinemia, NICU admission as well as giving birth to an LGA infant (18). These data reinforce the recommendations for adoption of healthy lifestyle behaviors in pregnancy which are likely to improve glucose homeostasis. This advice seems to be applicable to all women since our findings are derived from a low risk population.

Another potential modifiable factor identified was physical activity during mid-pregnancy. Physical activity is safe during pregnancy and the American College of Obstetricians and Gynecologists guidelines recommends 30 minutes of moderate physical activity in most, if not all days of the week (19). The UK Chief Medical Officers have reinforced this by recently recommending 150 minutes of moderate physical activity per week for pregnant women (20). Physical activity has been associated with improved insulin sensitivity in both non-pregnant (21) and pregnant women (22). Insulin sensitivity during pregnancy seems to be associated with favorable fat distribution in the offspring and physical activity is likely to mediate this relation (23). Furthermore, physical activity during pregnancy improves gestational weight gain control, reduces symptoms of depression, and prevents urinary incontinence and low back pain whilst not influencing birthweight (24). Watson and McDonald, assessing physical activity during pregnancy in 197 unselected women, described that a lower level of maternal physical activity was associated with a greater probability of admission to NICU and premature delivery (25). Focusing on LGA infants, we observed a three-fold increase in the chance of neonatal morbidity in women who did not take physical activity regularly during mid-pregnancy. As this was unaffected after adjustment for the maternal glucose concentration, this implies that physical activity has benefits other than through improved glucose homeostasis. This finding adds support to the recommendation of physical activity in pregnancy.

These risk factors associated with LGA-related morbidity may be useful in stratification of a high-risk group for targeted intervention or increased surveillance. We recently reported early pregnancy predictors of LGA including maternal birthweight, random glucose at 14-16 weeks, weight gain between (between 14-16 and 19-21 weeks) and ultrasound parameters at the anatomy scan (10). Random glucose was also associated with neonatal morbidity in the present study, whereas the other factors were not. LGA infants whose mother had a random glucose above 5.0 mmol/L and did not undertake regular physical activity at 20 weeks had a rate of admission to NICU or SNM of above 30% (Figure 2a). The combination of a random glucose above 6.0 mmol/L or no regular physical activity at 20 weeks with an early pregnancy BMI above 30 kg/m^2 were also associated with a rate of

neonatal morbidity above 30%. This is much higher than the expected 5.4-11.7% rate of admission to NICU for LGA infants (4, 6).

Most lifestyle interventions involving physical activity during pregnancy have been shown to reduce gestational weight gain during pregnancy but have not reduced the risk of GDM, LGA or neonatal morbidity; the latter is often a secondary outcome in these trials (26, 27). We recognize that the causes of neonatal morbidity relates to fetal growth (SGA or LGA) (28). Our findings suggest that lifestyle interventions based on physical activity are more likely to improve neonatal outcomes in LGA infants either born to obese women or women with high glucose concentration in mid pregnancy. Our findings of associations from the present observational study should be tested for evidence of causation through randomized controlled trials. Future trials should consider these higher risk subgroups and focus on more clinically relevant outcomes such as LGA related morbidity. The ability to design a targeted intervention based on the identified risk factors is limited by the definition of LGA used, which is only available after birth. Our findings should be validated by ultrasound detection of LGA before planning any intervention. Nonetheless, the risk factors identified here may assist neonatologists in deciding the level of post-natal surveillance for LGA infants.

The strength of this study includes a large prospective cohort and a very low loss of follow up. Although neonatal morbidity at term was not restricted to LGA infants, it is likely that the causes varied according to the growth status. Therefore, our approach of assessing LGA infants separately provides a clearer insight on the mechanisms related to morbidity in this group. As SCOPE's primary aim was prediction of preeclampsia, SGA and preterm birth, data on shoulder dystocia and brachial plexus injury was not routinely collected. Systematic recording of these outcomes might reveal a mechanical pathway to neonatal morbidity related to birth trauma (29). Assessment of physical activity is widely discussed in the literature and there is considerable variation on the accuracy of self-report compared to direct measurement both in adults (30, 31) and in pregnant women (32, 33). Our physical activity questionnaire was developed by a combination of existing resources at the start of the study and has not been previously validated which is a limitation of our study; our findings need to be replicated using existing validated questionnaires however the strength of association observed with no regular physical activity has biological possibility and will likely be replicated. The absence of indication for NICU admission also limited our analysis. Hypoglycemia, possibly followed

by hyperbilirubinemia, was likely to be the major reason on the basis of the sample characteristics and risk factors identified. We observed a higher rate of induction of labor in the LGA group with morbidity but, in the absence of data for reasons for induction, interpretation is limited. The differing protocols for GDM screening between centers was also a limitation but amongst those untested for GDM, the LGA rates and LGA related morbidities were lower, indicating a lower risk status.

In summary, a combination of risk factors identified a group of LGA with considerable prevalence of neonatal morbidity. Regular physical activity in mid-pregnancy is associated with lower risk for neonatal morbidity in LGA infants and seems to offer protection against the increased risk associated with higher maternal glucose levels. Our findings add to the evidence advocating physical activity throughout pregnancy.

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Figure legends

Figure 1. Study population.

Figure 2. Rate of neonatal morbidity stratified by random glucose and physical activity at 19-21 weeks and maternal obesity.

Table 1. Characteristics of pregnancies of large for gestational age infants with and without neonatal morbidity.

	LGA no morbidity (n=433; 88%) Mean ±SD or n (%)	**LGA and morbidity (n=58; 12%) Mean ±SD or n (%)**	**p value**
Age	29.1 ±5.4	28.5 ±5.7	0.40
Maternal birthweight	3420 ±590	3472 ±571	0.52
Ethnicity			
European	375 (86.6)	55 (94.8)	
Asian	34 (7.9)	1 (1.7)	0.32
Maori	12 (2.8)	1 (1.7)	
Other	12 (2.8)	1 (1.7)	
FH Diabetes or GDM	72 (16.6)	10 (17.2)	0.91
Educational level (<12 years)	151 (34.9)	20 (34.5)	0.95
Full- or part-time job	378 (87.3)	50 (86.2)	0.82
BMI Category			
Underweight	5 (1.2)	1 (1.7)	
Normal	248 (57.3)	32 (55.2)	0.04
Overweight	129 (29.8)	11 (19.0)	
Obese	51 (11.8)	14 (24.1)	0.01[a]
Height	165 ±7	166 ±7	0.09
Weight [b]	65 (59-74)	69 (58-86)	0.35
Systolic BP	106 ±10	105 ±12	0.68
Rand. Glucose at 15w	5.4 ±1.0	5.6 ±1.0	0.12
No regular physical activity at 15w	40 (9.2)	8 (13.8)	0.27
Physical activity intensity			
Light	66 (16.8)	13 (26.0)	
Moderate	193 (49.1)	22 (44.0)	0.28
Vigorous	134 (34.1)	15 (30.0)	
Wgt change 15-20w (kg/week)	0.6 ±0.4	0.7 ±0.5	0.04
Rand. glucose at 20w	5.5 ±1.0	6.1 ±1.1	<0.001
No regular physical activity at 20w	25 (5.8)	12 (20.7)	<0.001

Physical activity intensity			
Light	63 (15.4)	6 (13)	
Moderate	195 (47.8)	22 (47.8)	0.90
Vigorous	150 (36.8)	18 (39.1)	
US HC z-score	0.5 ±1.0	0.2 ±1.2	0.09
US AC z-score	0.5 ±1.2	0.6 ±1.1	0.52
US FL z-score	0.2 ±1.1	0.2 ±0.8	0.90
US HC/AC ratio	1.14 ±0.05	1.12 ±0.05	0.03

Abbreviations: AC – abdominal circumference, BMI – body mass index, BP – blood pressure, FH – family history, FL – femur length, GDM – gestational diabetes mellitus, HC – head circumference, LGA – large for gestational age, US – ultrasound, Wgt – weight, w – weeks.

[a] post hoc test assessing BMI obese as binary.

[b] Median (IQR) shown and Mann-Whitney test used.

Table 2. Pregnancy outcomes in pregnancies of large for gestational age infants with and without neonatal morbidity.

	LGA no morbidity (n=433; 88%) Mean ±SD or n (%)	**LGA and morbidity (n=58; 12%) Mean ± SD or n (%)**	**p value**
Preeclampsia	19 (4.4)	4 (6.9)	0.40
Gestational Hypertension	32 (7.4)	4 (6.9)	0.89
Gestational diabetes			
No	271 (62.6)	40 (69.0)	
Yes	16 (3.7)	5 (8.6)	0.07
Unknown	146 (33.7)	13 (22.4)	
Induction of labor	125 (28.9)	27 (46.6)	0.006
Mode of delivery			
Spontaneous Vaginal	121 (27.9)	10 (17.2)	
Assisted Vaginal	112 (25.9)	20 (34.5)	0.21
Emergency c-section	132 (30.5)	21 (36.2)	
Elective c-section	68 (15.7)	7 (12.1)	
Gestation at delivery	39.9 ±1.2	39.8 ±1.3	0.62
Birthweight	4183 ±347	4300 ±440	0.02
Birthweight centiles [a]	96 (93-98)	96 (93-99)	0.24

[a] Median (IQR) shown and Mann-Whitney test used.

Table 3. Risk factors for neonatal morbidity in large for gestational age infants.

	Univariate		Multivariable [a]	
	OR	95% CI	OR	95% CI
Obesity (BMI >30 kg/m^2)	2.38	1.22 - 4.65	1.11	0.51 - 2.41
No regular physical activity 20w	4.26	2.00 - 9.04	3.93	1.75 - 8.83
Rand glucose 20w (mmol/L)	1.57	1.23 - 2.00	1.52	1.17 - 1.97
US HC/AC ratio [b]	1.34	1.02 - 1.75	1.24	0.93 - 1.67

Abbreviations: AC – abdominal circumference, BMI – body mass index, HC – head circumference, US – ultrasound, w – weeks.

[a] Adjusted for all factors listed in addition to birthweight, GA at delivery and GDM.

[b] HC/AC ratio was inversed and standardized (unit of one standard deviation)