

Evidence Brief: Risk Factors for Large for Gestational Age (LGA) Infants in Ontario



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Issue and Research Question

Large for gestational age (LGA) is a term used to categorize a particular class of birth weight that considers the baby's gestational age. *Perinatal Health Indicators for Canada 2013* defines the indicator LGA as "the number of singleton live births whose birth weight is above the 90th percentile of the sex-specific birth weight for gestational age reference, expressed as a proportion of all singleton live births".¹ The birth of an LGA infant can pose both immediate and long-term health risks for mother and child. Immediate adverse health outcomes include: prolonged labour, caesarean delivery, shoulder dystocia (i.e., a complication that often requires emergency obstetric surgery), birth trauma,

fetal hypoxia (i.e., fetus is deprived of oxygen) and intrauterine death.² Longer-term, children who were born LGA have an increased risk of developing diabetes, obesity, metabolic syndrome, asthma and cancer, compared to peers born at an appropriate weight for gestational age.²

This report presents the results of a literature review undertaken to identify factors associated with the development and delivery of LGA infants. Provincial surveillance data related to pregnancy and birth outcomes obtained from the Better Outcomes Registry and Network (BORN) are used to explore the relationships among these factors in Ontario. BORN is a provincial program founded in 2009 to collect

and interpret data about pregnancy, birth and childhood.³ Its purpose is to amass accurate data to monitor and ultimately improve health outcomes for mothers and their children.³ BORN Information System (BIS) is a web-based platform into which healthcare organizations routinely submit data. In this report, aggregate level BIS data are used to describe associations between LGA births and risk factors identified by the literature review.

Understanding these risk factors in an Ontario context is an important step in identifying mothers who are at risk for having an LGA infant and ultimately, developing strategies to reduce the number of negative health consequences associated with LGA births.

This evidence brief asks: *What are risk factors associated with the development of LGA infants and what do the Ontario-specific data indicate about these risks?*

Methods

Literature Search:

Three databases (MEDLINE, EMBASE and CINAHL) were searched between August 6, 2014 and August 12, 2014 to identify articles published within the last ten years (2004-2014). The following search terms were used in combination: gestational age, large for gestational age, LGA, fetal development, fetal body weight, fetal birth weight, fetal macrosomia, fetal weight change, fetal weight gain, fetal weight, fetal body constitution, fetal body mass, maternal characteristics, infant, newborn and fetus. Articles retrieved by this search were assessed for eligibility by one reviewer. The search was expanded to include primary studies because there were no review articles that adequately addressed the research question. English language studies with cohorts of singleton live-births in a defined region were eligible if they reported on risk factors that may be associated with the development of LGA infants. Only studies that defined LGA using the parameters outlined by *Perinatal Health*

Indicators for Canada 2013 were included. Studies that examined LGA in relation to screening, medical procedures, or medication use, were excluded. Data were extracted from each article by one reviewer.

BIS Analysis of LGA Risk Factors in Ontario:

The second component of this project used data from BIS to examine the association between risk factors identified by the literature search and LGA birth. BIS data captures information relating to all Ontario births that occur in hospital or are attended by midwives.³ In particular, BIS offers aggregate provincial-level information that is organized into analytic cubes that can be manipulated to answer specific queries. Relevant data were extracted for analysis on August 6, 2014. Analyses utilized data corresponding to all singleton live-births occurring in Ontario between April 2012 and December 2013. This time frame was used because data prior to April 2012 were not available in BIS and data after December 2013 were incomplete. BORN uses the current Canadian reference percentile table to calculate weight for gestational age cutoffs.⁴

Births were analyzed across a range of maternal factors including: gestational diabetes, pre-existing diabetes, parity, age and body mass index (BMI). BMI was classified using the World Health Organization (WHO) standard definitions (i.e., underweight: $<18.5 \text{ kg/m}^2$, normal weight: $18.5\text{--}24.9 \text{ kg/m}^2$, overweight: $25\text{--}29.9 \text{ kg/m}^2$, obesity: $\geq 30 \text{ kg/m}^2$ age).² In this analysis, missing data were removed and the proportions of missing data are reported alongside the corresponding table (Appendix 1). Chi-squared statistics were computed to determine whether there was a significant association between LGA births and each of the identified risk factors. Unadjusted odds ratios with 95% confidence intervals were used to estimate the strength of the association between each risk factor and LGA birth.

Main Findings

Literature Search:

The literature search identified 638 articles, from which 12 single studies met inclusion criteria. Seven unique risk factors were associated with the development of LGA infants. These were all maternal factors related to: gestational weight gain (GWG)⁵⁻⁹, pre-pregnancy BMI^{7,8,10-14}, gestational diabetes¹¹, pre-existing diabetes^{11,15}, maternal age¹¹, parity^{7,11,16}, and history of previous LGA birth.¹¹

Pre-pregnancy BMI and gestational weight gain:

A woman's weight prior to pregnancy and the weight she gains during pregnancy are independently associated with the risk of giving birth to an LGA infant. Seven studies found a significant relationship between LGA infants and maternal pre-pregnancy BMI.^{7,8,10-14} A meta-analysis of the studies that used WHO standards to classify BMI^{7,8,10,14} showed that, when compared to mothers with normal BMI, overweight and obese mothers have a significantly greater risk of bearing an LGA infant (odd ratios (ORs): 1.59 and 2.31, respectively). All studies demonstrated that women with higher BMIs were more likely to have LGA infants. One study found that super-obese (BMI $\geq 50\text{kg/m}^2$) mothers were 2.7 times more likely to deliver an LGA infant.¹³

Five studies found significant associations between increased GWG and bearing an LGA infant.⁵⁻⁹ Health Canada recommends use of the United States Institute of Medicine (IOM) 2009 recommendations for GWG.¹⁷ These guidelines are stratified by pre-pregnancy BMI categories. For example, it is recommended that a woman who was obese prior to pregnancy should gain less weight (recommended weight gain: 5-7 kg) during pregnancy, than a woman classified with a normal BMI (recommended weight gain: 11.5-16 kg) (Appendix 2). The majority of the reviewed studies compared mothers who gained weight within pre-set GWG guidelines to those who exceeded those guidelines. For example, a study of 4,321 mother-infant pairs

from Ottawa and Kingston found that the odds of bearing an LGA infant increased almost three fold (OR: 2.86 (95% CI 2.09-3.92)) among mothers who exceeded the IOM GWG recommendations for total weight gain during pregnancy.⁷

Diabetes:

In mothers, gestational diabetes and pre-existing diabetes mellitus are both positively associated with LGA births. It is important to note that gestational diabetes and pre-existing diabetes mellitus are conditions that are more common among overweight and obese women.⁸ Despite this comorbidity, diabetes independently increases the risk of having an LGA infant.¹¹

Age, Parity and History of LGA Birth:

The literature search also identified maternal age, parity, and history of prior LGA birth as risk factors for LGA birth. The only study to examine the independent effects of maternal age found that mothers 17 and younger had significantly higher rates of LGA births (OR: 1.39 (95% CI 1.22- 1.58)) compared to mothers between 20-29 years old.¹¹ In terms of parity, an Ontario-based study used multivariate logistic regression to determine that as parity increased, odds of having an LGA infant increased (gestational and maternal age, pre-pregnancy weight, and smoking were controlled for in this analysis).⁷ This dose-response relationship was observed in all studies that examined parity; however the likelihood of LGA delivery decreased slightly in women with ≥ 15 previous live births (a relationship which may have been impacted by a smaller sample of women with ≥ 15 previous live births).¹⁶ Lastly, a study examining the impact of a woman's history of LGA births found that women who had previously delivered an LGA infant were approximately 4.5 times more likely (OR: 4.57 (95% CI 4.08- 5.12) to deliver another LGA infant.¹¹

BIS Analysis of LGA Risk Factors in Ontario:

In Ontario, there were 236,527 singleton live-births between April 2012 and December 2013, and LGA was present in slightly greater than ten per cent of these (n=24,228). Of the seven unique risk factors identified by the literature search, six factors were available in BIS (gestational diabetes, pre-existing diabetes, BMI prior to pregnancy, gestational weight gain, age, and parity). The indicator for gestational weight gain was not used for this analysis for several reasons, including the inability to control for other important covariates (e.g., BMI, gestational diabetes, gestational week of delivery), and high missingness (over 35%). The prevalence of each of the other five risk factors within the overall BIS cohort, and within LGA births is presented in Table 1. Tables A.1- A.5 appended to this brief present the bivariate analysis of LGA births by each of the identified maternal risk factors (Appendix 1). Chi-squared analyses were used to determine the significance of associations between LGA births and gestational diabetes, pre-existing diabetes, pre-pregnancy BMI category, maternal age, and parity.

Diabetes:

Five per cent of women in this BIS cohort had recorded cases of gestational diabetes and <1% had pre-existing diabetes. The likelihood of having an LGA infant is significantly increased for women with gestational diabetes (unadjusted OR 1.59, 95% CI 1.51- 1.67) (Table A.1). Women with pre-existing diabetes were more than four times as likely to deliver an LGA infant (unadjusted OR 4.75, 95% CI 4.33- 5.21) compared to those with no history of the disease (Table A.2). Overall, gestational diabetes and pre-existing diabetes were associated with 7.9% and 3.0% of all LGA births in the study period, respectively (Table 1).

Table 1: Prevalence of Risk Factors in the Ontario BIS cohort, and among LGA births in the BIS cohort

Risk Factor	Prevalence in the overall BIS cohort	Prevalence among LGA Births
Gestational Diabetes	5.4%	7.9%
Pre-existing Diabetes	0.9%	3.0%
Pre-pregnancy Overweight	25.0%	29.1%
Pre-pregnancy Obesity	19.0%	30.9%
Maternal Age ≤ 17	0.8%	0.6%
Parity 0	43.5%	32.5%

Pre-pregnancy BMI:

Pre-pregnancy BMI data available in BIS are categorized into underweight, normal, overweight and obese strata using the WHO standards discussed above. In Ontario, prior to pregnancy, approximately 4.2% of women were classified as underweight, 41.7% were normal weight, 18.5% were overweight, 14.1% were obese and 21.0% of had missing information for this indicator. In this analysis both overweight and obese women were compared to women with normal BMIs. Overweight women were almost twice as likely to deliver an LGA infant (unadjusted OR 1.72, 95% CI 1.66- 1.78) when compared to women with normal BMIs. This risk was even higher among obese women (unadjusted OR 2.58, 95% CI 2.49- 2.68) (Table A.3). Overall, in mothers with indicators of BMI, (n=19,142) pre-existing overweight and obesity were associated with 60.0% of all LGA births (n=11,484) in the study period.

Maternal Age:

BIS data were stratified into the following age categories: ≤ 17 , 18-29, 30-39 and ≥ 40 years. Women under the age of 17 were used as a reference category, and represented less than 1% of total births. Analysis indicated that older women were significantly more likely to deliver an LGA infant when compared to women 17 years and younger (unadjusted OR 1.25 – 1.52) (Table A.4).

Parity:

Lastly, BIS data categorized parity into five strata: no previous births (parity 0), one previous birth (parity 1), two previous births (parity 2), three to four previous births (parity 3-4), and five or more previous births (parity ≥ 5). Overall, women with parity greater than or equal to one were significantly more likely to give birth to an LGA infant as compared to those with parity of zero (unadjusted OR 1.60 – 2.24) (Table A.5).

Discussion and Conclusions

Overall, the literature review suggested that the risk of bearing an LGA infant is increased by maternal factors related to gestational diabetes, pre-existing diabetes, GWG above recommended standards, overweight or obesity, increased parity, maternal age ≤ 17 years, and history of previous LGA births. Significant associations between LGA births and these seven risk factors were found consistently across 12 included studies.

Five of the seven risk factors identified by the literature search were analyzed using BIS data. All five of those factors were associated with LGA births in Ontario. This data set had a large sample size and aims to capture all Ontario births within a hospital or attended by a midwife. Unadjusted odds ratios indicated that all five of the risk factors explored in this analysis had significant associations with LGA birth.

It is important to note that while the direction of most of these associations were consistent with the published literature, the analysis related to maternal age was not. Specifically, this analysis suggests that LGA births were more likely among women older than 17 years. Inconsistency with the literature suggests interpreting this result with more caution.

Maternal pre-pregnancy BMI and GWG above recommended standards were the risk factors most frequently identified in the literature. In the analysis of Ontario births, BMI also emerged as important, along with pre-existing maternal diabetes and gestational diabetes. These latter two risk factors are known to be co-morbidities with overweight and obesity, suggesting an important role for maternal weight in the risk for LGA birth.

Implications for Practice

While some of the risk factors for LGA birth are not considered to be modifiable (i.e., maternal age, parity), public health does have a role in interventions related to modifiable risk factors (e.g., overweight and obesity, chronic disease prevention). Thus, a review of successful and potentially scalable public health interventions to help women reach healthy weights before conception, and maintain healthy weights during their reproductive years, and particularly throughout pregnancy may be warranted. Such interventions could prove valuable for reducing the incidence of LGA births in Ontario.

Specifications and Limitations of Evidence Brief

This Evidence Brief presents key findings from the scientific literature. Its purpose is to investigate a research question in a timely manner in order to help inform decision making. This report is not a comprehensive review of the literature, but rather a rapid assessment of the best available research evidence. There may be relevant pieces of

evidence that are not included and these may alter the conclusions drawn from the document.

Analysis of the BIS data has limitations as well. First, data were missing for each of the indicators that were extracted in this analysis and this may have introduced biases. For the majority of risk factors the proportion of missing data was low, however, pre-pregnancy BMI had 22% missing data. Though the association between pre-pregnancy BMI and LGA birth was generally in agreement with the findings from the literature search, it may need to be interpreted with some caution. Second, the relationships reported here are unadjusted, and confounding factors have not been accounted for. Thus, it is impossible to determine the independent relative contribution of each factor to the risk for LGA birth. This possibly explains the result related to maternal age, which conflicted with that reported in the published literature.

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Appendix 1: BIS Data for Singleton Live Births in Ontario, April 2012- December 2013

Table A.1: LGA Births by Maternal Gestational Diabetes in the Ontario BIS Cohort between April 2012 and December 2013

Gestational Diabetes	LGA	Non-LGA	Total	P-value (Chi-squared)	Unadjusted Odds Ratio (95% Confidence Interval)
Yes	1,842 (7.9%)	10,291 (5.1%)	12,133	<0.001	1.59 (1.51, 1.67)
No	21,600 (92.1%)	191,873 (94.9%)	213,473	Reference	Reference
Total	23,442	202,164	225,606		

Note: 5% of the data extracted for the following variables were classified as missing and therefore removed from the analysis. Column percentages are presented in parentheses alongside raw numbers.

Table A.2: LGA Births by Maternal Pre-Existing Diabetes in the Ontario BIS Cohort between April 2012 and December 2013

Pre-Existing Diabetes	LGA	Non-LGA	Total	P-value (Chi-squared)	Unadjusted Odds Ratio (95% Confidence Interval)
Yes	693 (3.0%)	1,287 (0.6%)	1,980	<0.001	4.75 (4.33, 5.21)
No	22,509 (97.0%)	198,534 (99.4%)	221,043	Reference	Reference
Total	23,202	199,821	223,023		

Note: 6% of the data extracted for the following variables were classified as missing and therefore removed from the analysis. Column percentages are presented in parentheses alongside raw numbers.

Table A.3: LGA Births by Pre-pregnancy Maternal BMI (Normal, Overweight and Obese) in the Ontario BIS Cohort between April 2012 and December 2013

Maternal BMI	LGA	Non-LGA	Total	P-value (Chi-squared)	Unadjusted Odds Ratio (95% Confidence Interval)
Normal (18.5-24.9 kg/m ²)	7,658 (40.0%)	90,819 (58.1%)	98,477	Reference	Reference
Overweight (25.0-29.9 kg/m ²)	5,563 (29.1%)	38,273 (24.5%)	43,836	<0.001	1.72 (1.66, 1.78)
Obese (≥30 kg/m ²)	5,921 (30.9%)	27,227 (17.4%)	33,148	<0.001	2.58 (2.49, 2.68)
Total	19,142	156,319	175,461		

Note: 22% of the data extracted for the following variables were classified as missing and therefore removed from the analysis; underweight women not shown. Column percentages are presented in parentheses alongside raw numbers.

Table A.4: LGA Births by Maternal Age in the Ontario BIS Cohort between April 2012 and December 2013

Maternal Age (years)	LGA	Non-LGA	Total	P-value (Chi-squared)	Unadjusted Odds Ratio (95% Confidence Interval)
≤17	139 (0.6%)	1,670 (0.8%)	1,809	Reference	Reference
18 - 29	9,207 (38.2%)	88,288 (42.0%)	97,495	0.011	1.25 (1.05, 1.49)
30 - 39	13,694 (56.8%)	111,875 (53.2%)	125,569	<0.001	1.47 (1.23, 1.75)
≥40	1,056 (4.4%)	8,358 (4.0%)	9,414	<0.001	1.52 (1.27, 1.82)
Total	24,096	210,191	234,287		

Note: 1% of the data extracted for the following variables were classified as missing and therefore removed from the analysis. Column percentages are presented in parentheses alongside raw numbers.

Table A.5: LGA Births by Parity in the Ontario BIS Cohort between April 2012 and December 2013

Parity	LGA > 90th percentile	Non-LGA	Total	p-value (chi squared)	Unadjusted Odds Ratio (95% Confidence Interval)
Parity 0	7,796 (44.5%)	93,446 (56.2%)	101,242	Reference	Reference
Parity 1	9,721 (55.5%)	72,778 (43.8%)	82,499	<0.001	1.60 (1.55, 1.65)
Parity 2	4,148 (23.7%)	28,150 (16.9%)	32,298	<0.001	1.77 (1.70, 1.84)
Parity 3-4	1,904 (10.9%)	11,848 (7.1%)	13,752	<0.001	1.93 (1.83, 2.04)
Parity ≥5	438 (2.5%)	2,342 (1.4%)	2,780	<0.001	2.24 (2.02, 2.49)
Total	24,007	208,564	232,571		

Note: 2% of the data extracted for the following variables were classified as missing and therefore removed from the analysis. Column percentages are presented in parentheses alongside raw numbers

Appendix 2: Health Canada Recommendations for Weight Gain during Pregnancy (Adapted from The Institute of Medicine 2009 Recommendations)

Table: Rate and Total Weight Gain Recommended for Singleton Pregnancies Based on a Woman's Pre-pregnancy BMI

Pre-Pregnancy BMI	Mean rate of weight gain in the 2nd and 3rd trimester		Recommended total weight gain	
	kg/week	lb/week	kg	lbs
BMI < 18.5	0.5	1	12.5 - 18	28 - 40
BMI 18.5 - 24.9	0.4	1	11.5 - 16	25 - 35
BMI 25.0 - 29.9	0.3	0.6	7 - 11.5	15 - 25
BMI ≥ 30.0	0.2	0.5	5 - 9	11 - 20

Note: Table and full explanation of GWG guidelines available from Health Canada (16)