The Relationship between Maternal Gestational Impaired Glucose Tolerance and Risk of Large-for-Gestational-Age Infant: A Meta-Analysis of 14 Studies

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Abstract

Objective: To explore, by conducting a meta-analysis, whether gestational impaired glucose tolerance (IGT) is an independent predictor of neonatal large for gestational age (LGA) or not.

Methods: Medline, Embase, and Cochrane Library databases were searched to identify published epidemiological studies (cohort and case-control studies) investigating the association between gestational IGT and neonatal LGA. Calculations of pooled estimates were conducted in random-effect models or fixed-effects models. Heterogeneity was tested by using chi-square test and I² statistics. Egger’s test (linear regression method) and Begg’s test (rank correlation method) were used to assess potential publication bias.

Results: Fourteen observational studies were included in the meta-analysis. The overall risk for the effect of IGT on LGA was 2.09 (1.56, 2.78). Stratified analyses showed no differences regarding different geographic regions or the analysis of overall adjusted odds ratios. No evidence of publication bias was observed in either Egger’s test or Begg’s test results.

Conclusion: Gestational IGT is an independent predictor of neonatal LGA.

Keywords: Gestational impaired glucose tolerance, large for gestational age, meta-analysis

Introduction

Gestational impaired glucose tolerance (IGT) is defined as an abnormal glucose level obtained in an oral glucose tolerance test (OGTT) during pregnancy. Gestational IGT is considered to reflect a serious defect in beta-cell function in the early and...
late-phases of insulin secretion and is regarded as a sign of pre-gestational diabetes mellitus (GDM) (1). Universally, GDM is associated with adverse pregnancy outcomes and its incidence increased in parallel to the increase in frequency of obesity worldwide. Women identified as GDM patients are treated with dietary or insulin therapy to reduce their glucose levels and hence the risk of adverse pregnancy outcomes (2). While the importance of identification and treatment of GDM and the benefit of controlled blood glucose in the prenatal period is universally confirmed, knowledge on the mechanisms responsible for the impact of gestational IGT on pregnancy outcome is inconclusive. The offspring of women with IGT, compared to those of women who had good glucose control during pregnancy, are reported to have increased birth weights, increased rates of macrosomia, and increased frequency of large for gestational age (LGA) (3). Some studies demonstrated that women with gestational IGT were at higher risk of adverse pregnancy outcomes as compared with women with normal glucose tolerance (NGT), but others have attributed these findings to differences in the criteria used to diagnose this condition (4,5). However, there is no systematic review or meta-analysis of the studies on the importance of gestational IGT as a public health problem. With this background, we attempted to conduct a meta-analysis of the studies on the association between gestational IGT and pregnancy outcome published within the last decade.

**Methods**

We performed a detailed search on Medline, Embase, and Cochrane Library to identify articles that reported the relationships between IGT during pregnancy and neonatal outcomes. We also attempted to reach the comments on these studies through review articles. The database was searched from 1999 to April 2015 and limited to human studies which were published in English.

We used the following search terms: “gestational” or “pregnant” and “impaired glucose tolerance” or “IGT” and “large for gestational age” or “LGA”. Studies were included in the analysis if they examined outcomes in pregnant women who had IGT but not GDM and women who had not received any treatment. The primary adverse outcome searched in this meta-analysis was LGA, defined as a birth weight >90th percentile for gestational age.

Quality assessment of the available studies was conducted independently by two reviewers (Hai-Qing Wang, Han-Lin Lai) using the Newcastle-Ottawa quality assessment scale for cohort studies and for case-control studies (6). The scores range from 0 to 9 and scores ≥6 were graded as of high-quality.

**Data Extraction**

Using a standardized data-collection form, the two reviewers (Hai-Qing Wang, Han-Lin Lai) extracted the data from the searched article independently, and any disagreement was resolved by discussion. The following study characteristics were recorded: first author’s name, year of publication, country of origin, study design, inclusion and exclusion criteria, sample size, diagnostic criteria for gestational IGT, potential confounding factors adjusted for. All search results were exported to Endnote 7.0 to organized references and duplications were thus eliminated.

**Statistical Analysis**

We extracted the odds ratio (OR) and the 95% confidence intervals (95% CI) to reflect the uncertainty of point estimates from each study. The crude OR for gestational IGT and LGA could be calculated from 5 studies and the other 9 studies which were stratified by some confounding factors (such as quality grade, number of confounding factors adjusted for, study population) which reported adjusted OR and the 95% CI. The chi-square test was used to analyze the heterogeneity of the results, and p<0.10 was considered as the cut-off level of heterogeneity. We also used I² to judge the heterogeneity between these studies, I² representing the percentage of the true heterogeneous (non-sampling error) in the total variability; when I² was >50%, we recognized the existence of heterogeneity (7). When substantial heterogeneity was detected, the summary estimate on the basis of the random-effects model using the method of Der Simonian and Laird (8) was presented. These two approaches yield similar results when the heterogeneity of the study is small, the random-effects model gives more weight to imprecise (or small) studies compared to a fixed-effects model (9). In addition, the pooled estimate that was based on the fixed-effects model using the inverse variance method was presented (10). In order to assess the impact on the results of a single study, we conducted a sensitivity analysis of each study by excluding each study one by one and recalculating the combined estimates on remaining studies. We used a funnel plot (11) to visualize the publication bias and used Egger’s test (linear regression method) (12) and Begg’s test (rank correlation method) (13) to assess potential publication bias. The Egger’s test is a linear regression method about standard normal deviate and precision of all the studies in meta-analysis. The Begg’s test is a rank correlation test for inspection of the correlation of effect and sample size. When the number of the studies in the meta-analysis is <20, the effects of these two methods are low, but the sensitivity of the Egger’s test is higher than the Begg’s test. Meta-analysis was performed with Stata/SE10.0 (Stata Corp, College Station, TX, USA).

**Results**

In the preliminary literature search, we identified 1377 unique citations from the electronic databases (Figure 1). No supernumerary article was found in the citations by
manual search and 145 were rejected because of duplicates. 711 were rejected because of 687 articles were on bias of titles, 6 studies were meta-analysis, and 18 were systematic reviews. The remaining 521 full-text articles were selected and inspected and then we excluded 507 articles because there were 30 reviews and 477 studies which did not meet the inclusion criteria of meta-analysis. Finally, we ended up with 14 observational studies (4,5,14,15,16,17,18,19,20,21,22,23,24,25) for our analysis.

The characteristics of these 14 observational studies are displayed in Table 1. There were 13 cohort studies and only one case–control study. Six of the studies were conducted in Europe, 4 in North America, and 4 in Asia. The effect of gestational IGT on LGA and the definition of gestational IGT in each study are also demonstrated in Table 1.

The ORs of LGA in relation to gestational IGT from each study and the overall OR are presented in Figure 2. We assembled the OR and 95% CI of the 14 studies which were related to the effect of gestational IGT on LGA, the homogeneity hypothesis was rejected by the chi-square test (p<0.10, I^2=70.2%), thus we selected the random-effects model and obtained the overall OR, and 95% CI was 2.08 (1.56, 2.78) (Figure 2).

Table 2 presents the results of subgroup analyses of the effects of gestational IGT on LGA. When stratified by geographic region, a positive association of gestational IGT and LGA was observed in the studies conducted in each region. We abstracted the ORs from the 14 studies, the analysis of the effects of gestational IGT on LGA yielded an overall adjusted OR of 2.36 (1.64, 3.37), but this apparent relationship was not observed in the analyses of the unadjusted ORs. The definitions of gestational IGT in these studies were different - some studies restricted the value of fasting plasma glucose (FPG) (4,5,14,15,23,24), the others just formulated the value of OGTT (16,17,18,19,20,21,22,25). When stratified by the unequal definition, the analysis of the effects of gestational IGT with restricted FPG value on LGA yielded an overall OR of 1.73 (1.01, 2.99). The definition of gestational IGT employed different forms of OGTT as well - for instance, some studies used the value of OGTT at 0, 60, 120, and 180 min (19,20,21,25), some used the value of 2-h 75-g OGTT (4,5,14,15,17,18,22,23,24), and one used the value of 1-h 50-g OGTT (16). When we stratified by the different forms of OGTT, a positive association of gestational IGT and LGA was obtained in the studies conducted in unequal definition.

Sensitivity analyses investigating the influence of the 14 studies individually on the overall risk estimate by excluding one study per iteration suggested that the overall risk estimates did not substantially change by any single study. The analysis of the effects of gestational IGT on LGA was with a range from a low of OR 1.7 (95% CI 1.49, 1.95) to a high of OR 2.19 (95% CI 1.66, 2.9). The results did not change substantially after sensitivity analysis.
Table 1. Characteristics of the studies included in the meta-analysis

| Publication year, Author | Number of cases/controls | Country | Study design | Effect on LGA | NOS scores | Definition of IGT |
|--------------------------|--------------------------|---------|--------------|---------------|------------|------------------|
| 2015, Graves et al (25)  | 26/2206                  | Canada  | Cohort study | Adjusted OR 2.84 (1.53, 5.27) | 6/9        | 50 g OGTT 0 time >5.2, 1 h >9.9, 2 h >8.5, 3 h >7.7 mmol/L, only one above the range |
| 2013, Disse et al (14)   | 39/20                    | France  | Cohort study | Unadjusted OR 0.25 (0.05,1.18) | 8/9        | FPG <5.1 mmol/L, 2-h 75 g OGTT >8.5 mmol/L |
| 2012, Ryan (15)          | 104/368                  | Canada  | Cohort study | All women: adjusted OR 1.36 (0.71,2.61)  White women: adjusted OR 1.34 (0.622.90) | 6/9        | FPG <6.1 mmol/L, 2-h 75 g OGTT 7.8-11.0 mmol/L |
| 2012, Melamed et al (16) | 809/12,899               | Israel  | Cohort study | Adjusted OR 1.6 (1.3,2.0) | 7/9        | 1-h 50 g OGTT > 7.7 mmol/L |
| 2010, Miyakoshi et al (4) | 174/4,512                | Japan   | Cohort study | Unadjusted OR 1.38 (0.82,3.38) | 7/9        | FPG <5.6 mmol/L, 2-h 75 g OGTT >8.3 mmol/L |
| 2010, Black et al (5)    | 474/7020                 | USA     | Cohort study | Unadjusted OR 1.38 (1.02,1.89) | 7/9        | FPG <5.1 mmol/L, 2-h 75 g OGTT >8.4 mmol/L |
| 2010, Anderberg et al (17)| 744/329                  | Sweden  | Cohort study | Adjusted OR 2.1 (1.1,3.9)  | 8/9        | 2-h 75 g OGTT 8.6-9.9 mmol/L |
| 2009, Retnakaran et al (18)| 166/33                  | England | Cohort study | Unadjusted OR 2.41 (0.87,6.65) | 7/9        | 2-h 75 g OGTT 7.8-11.0 mmol/L |
| 2007, Lapolla et al (19) | 48/334                   | Italy   | Cohort study | Adjusted OR 2.53 (0.57,11.2) | 7/9        | 100 g OGTT 0 m >5.2, 1 h >9.9, 2 h >8.5, 3 h >7.7 mmol/L, only one above the range |
| 2005, Chico et al (20)   | 59/5767                  | Spain   | Cohort study | Unadjusted OR 4.49 (1.59,12.64) | 8/9        | 50 g OGTT 0 m >5.2, 1 h >9.9, 2 h >8.5, 3 h >7.7 mmol/L, only one above the range |
| 2003, Saldana et al (21) | White women 40/1,080     | USA     | Cohort study | White women adjusted OR 1.1 (0.4,2.9) Black women adjusted OR 7.7 (2.3,26) | 7/9        | 100 g OGTT 0 m >5.2, 1 h >9.9, 2 h >8.5, 3 h >7.4 mmol/L, only one above the range |
| 2003, Ostlund et al (23) | 211/810                  | Sweden  | Cohort study | Adjusted OR 7.3 (4.1,12.7) | 7/9        | FPG <6.7 mmol/L, 2-h 75 g OGTT 9.0-11.0 mmol/L |
| 2002, Lao and Wong (24)  | 73/382                   | China   | Case-control study | Adjusted OR 2.59 (1.52,4.24) | 6/9        | FPG <5.8 mmol/L, 2-h 75 g OGTT >8.0 mmol/L |
| 2002, Yang et al (22)    | 102/302                  | China   | Cohort study | Adjusted OR 2.42 (1.07,5.46) | 7/9        | 2-h 75 g OGTT 7.8-11.1 mmol/L |

a: Study quality assessment is listed using the results of the Newcastle-Ottawa questionnaire. OR: odds ratio, OGTT: oral glucose tolerance test, FPG: fasting plasma glucose, LGA: large for gestational age, NOS: Newcastle-Ottawa Scale, IGT: impaired glucose tolerance.
Publication Bias

In the funnel plot (Figure 3), we found that the scatters are substantially symmetric. There was no evidence of potential publication bias with the association of gestational IGT with LGA, as suggested by Egger’s test (p=0.314) and Begg’s test (p=0.499).

Discussion

The aim of our meta-analysis was to explore the association between gestational IGT and LGA. The results of a total of 14 epidemiologic studies of this meta-analysis showed that gestational IGT is an independent risk factor for neonatal LGA. Egger’s test and Begg’s test revealed no significant publication bias. The overall adjusted OR indicated that gestational IGT is an independent risk factor for neonatal LGA, and the overall combined OR of the effects of IGT with restricted FPG value on LGA also reflected this conclusion. When we stratified IGT by different forms of OGTT, the consequences of analysis implied that the different forms of OGTT employed in the studies have no effect on our conclusion. When we excluded one study, there was no significant impact on the results.

| Group          | Number of studies | OR (95% CI) | \( p \) heterogeneity | \( I^2 \) (%) |
|----------------|-------------------|-------------|------------------------|---------------|
| Total          | 14                | 2.09 (1.56, 2.78) | <0.001                | 70.2          |
| By geographic area |                   |             |                        |               |
| North America  | 4                 | 1.78 (1.17, 2.70) | 0.04                   | 57.0          |
| Europe         | 6                 | 2.52 (1.16, 5.47) | <0.001                | 75.7          |
| Asia           | 4                 | 1.71 (1.42, 2.05) | 0.243                 | 28.1          |
| Adjusted OR    | 9                 | 2.36 (1.64, 3.37) | <0.001                | 71.7          |
| Unadjusted OR  | 5                 | 1.56 (0.92, 2.65) | 0.034                 | 61.5          |

Table 2. Sensitivity analysis of the effects of impaired glucose tolerance on large for gestational age

In conclusion, the results of our meta-analysis have shown that gestational IGT is an independent risk factor for neonatal LGA. Today, it is known that the monitoring of blood glucose during pregnancy is important for the control of the frequency of neonatal LGA. As the results of our meta-analysis have shown, gestational IGT is an independent risk factor for neonatal LGA. Therefore, if treatment suggestions are to be introduced to women with gestational IGT, the effects of such suggestions on pregnancy outcomes will need to be evaluated, also taking social, cultural, economic, and clinical benefits into account.

In conclusion, the results of our meta-analysis have shown that maternal gestational IGT increased the risk of LGA infants and was an independent predictor for neonatal LGA. Additional studies are needed to evaluate whether the monitoring of blood glucose and control of blood sugar by means of lifestyle programs (e.g. physical activity, diet) are beneficial in reducing the risk of neonatal LGA. The use of potentially biased evidence was the principal limitation of this study since the definition of gestational IGT showed differences among the studies. However, the consequences of the subgroup analyses implied that the different definition of gestational IGT employed in the studies had no effect on our conclusion.

Ethics

Ethics Committee Approval: Retrospective study, Informed Consent: Retrospective study.
Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: Li Li, Design: Li Li, Data Collection or Processing: Yi Li, Qi-Fei Liu, Shuang Hu, Analysis or Interpretation: Yi Li, Qi-Fei Liu, Shuang Hu, Literature Research: Hai-Qing Wang, Han-Lin Lai, Writing: Hai-Qing Wang, Han-Lin Lai.

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