Systematic review and meta-analysis of diagnosing gestational diabetes mellitus with one-step or two-step approaches and associations with adverse pregnancy outcomes

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Abstract

Background: There is an ongoing discussion about the optimal diagnostic strategy for gestational diabetes mellitus (GDM).

Objective: To assess the magnitude of the association between GDM diagnosed with the one-step (International Association of Diabetes and Pregnancy Study Groups criteria) or two-step (Carpenter and Coustan criteria) approach and selected adverse pregnancy outcomes.

Search strategy: Five electronic databases were searched up to October 2017 using Medical Subject Headings for each adverse outcome combined with the term "gestational diabetes."

Selection criteria: Observational studies assessing the one-step versus the two-step diagnostic approach in GDM.

Data collection and analysis: Relative risks were extracted and random-effects models were used to estimate pooled relative risks (RRs).

Main results: A total of 41,663 participants from nine studies were included. Gestational diabetes mellitus was significantly associated with pre-eclampsia (RR 1.68 vs RR 1.77), cesarean delivery (RR 1.28 vs RR 1.33), and large for gestational age (RR 1.44 vs RR 1.68) when diagnosed with the one-step versus the two-step approach. A one-step diagnosis also increased the risks of neonatal intensive care unit admission and gestational hypertension, whereas a two-step diagnosis increased the incidence of macrosomia.

Conclusions: Women with GDM diagnosed with either the one-step or the two-step approach were at increased risk for selected adverse pregnancy outcomes. The associations with the two-step method were slightly stronger.

Keywords
Diagnostic approach; Gestational diabetes; Meta-analysis; One-step approach; Pregnancy outcomes; Systematic review; Two-step approach

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition of glucose intolerance developed during pregnancy. Many women with GDM experience pregnancy-related complications, which primarily affect the fetus and include macrosomia, congenital malformations, prematurity, neonatal intensive care unit (NICU) admission, and respiratory distress syndrome. In addition, GDM is associated with an increased incidence of maternal complications such as pre-eclampsia, gestational hypertension, and polyhydramnios.
The delivery of health care and the design and interpretation of research into GDM have been complicated by a lack of consensus over the diagnostic criteria for GDM. Various diagnostic glucose thresholds have been proposed and are in use in different countries. A common approach to the diagnosis of GDM is the two-step process first recommended by the American Diabetes Association (ADA) in 2000. With this approach, initial screening with a 50-g, 1-hour glucose challenge test is performed for pregnant women, followed by a 100-g, 3-hour oral glucose tolerance test (OGTT) for those who have positive screening results; the criteria of Carpenter and Coustan (CC) are used to diagnosing GDM. In 2008, data from the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO) were published, in which approximately 25 000 pregnant women from several countries and with various ethnicities were examined with the aim to establish a uniform process for the diagnosis of GDM. The data indicated a linear relationship between adverse pregnancy outcomes and maternal blood glucose levels in a continuous form without an inflexion point or obvious cutoff values. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed the one-step approach to the diagnosis of GDM based on the results of the HAPO study. With the one-step approach, pregnant women should be screened with a 75-g, 2-hour OGTT, and the threshold values recommended for the diagnosis of GDM are lower than those recommended for the two-step approach. Following the release of the IADPSG criteria, the ADA endorsed the new criteria in its practice guidelines. Subsequently, in 2013, the WHO revised its diagnostic criteria in line with the IADPSG proposal. However, the American College of Obstetricians and Gynecologists and the National Institutes of Health recommend the two-step approach to screening.

With data available in support of either strategy, the debate about the optimal diagnostic strategy for GDM continues. More recently, the ADA recommended that GDM diagnosis can be accomplished with either of two strategies and acknowledged that further research is needed to establishing a uniform approach to diagnosing GDM.

The present study was a comprehensive systematic review and meta-analysis of available studies to assess the magnitude of the association between GDM diagnosed with the one-step approach using IADPSG criteria or the two-step approach using CC criteria, and clinically relevant adverse pregnancy outcomes.

2 | MATERIALS AND METHODS

The present study was a systematic review of the published literature, and ethics committee approval and additional written consent were not required. The Cochrane methodology and the recommendations for reporting proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed.

2.1 | Search strategy

PubMed, Scopus, Web of Science, the Cochrane Library, and ProQuest were searched from database inception up to October 31, 2017. No date, language, or country restrictions were applied, with the exception of limiting the ProQuest search to articles published in English. The following general search terms were used and adapted to each database: "gestational diabetes" or "gestational diabetes mellitus" or "diabetes, gestational" combined with the appropriate terms for each maternal or neonatal outcome using Medical Subject Headings. Moreover, review articles were checked for additional studies. The reference lists of articles selected were also reviewed for potentially eligible articles.

2.2 | Eligibility criteria

Observational studies (prospective or retrospective cohort, case–control, or cross-sectional studies) were considered for inclusion if the papers provided sufficient information to estimate the association of GDM diagnosed based on the IADPSG one-step screening criteria versus the CC two-step screening criteria (Table 1) with selected adverse maternal and neonatal outcomes. Studies were excluded if no relative risk (RR) data were provided and if the available data were inadequate for the calculation of these risk estimates.

To avoid selection bias, the present review included studies in which participants were universally screened for GDM. Studies were excluded if screening or diagnostic procedures had been performed in participants with certain clinical risk factors. Studies were also excluded if participants with unknown diabetes status or pre-existing diabetes were not distinguished and excluded at the beginning of the study.

2.3 | Quality assessment

The quality of eligible studies was evaluated independently by two investigators (EH and MJ) using the Newcastle–Ottawa Scale for assessing the quality of cohort and cross-sectional studies. The scale has been shown to be reliable and valid. With this tool, each study was assessed based on eight items, grouped into three categories: selection of the study groups; comparability of the groups; and ascertainment of the outcome measures. The scale uses a star scoring method where zero to four stars can be awarded in the selection category, one to two stars in the comparability category, and zero to three stars in the outcomes category. The maximum score is nine stars.

### Table 1: Oral glucose tolerance test thresholds for the diagnosis of gestational diabetes.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>CC criteria, mmol/L</th>
<th>IADPSG criteria, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>≤5.3</td>
<td>≤5.1</td>
</tr>
<tr>
<td>1-h glucose level</td>
<td>≤10.0</td>
<td>≤10.0</td>
</tr>
<tr>
<td>2-h glucose level</td>
<td>≤8.6</td>
<td>≤8.5</td>
</tr>
<tr>
<td>3-h glucose level</td>
<td>≤7.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CC, Carpenter and Coustan; IADPSG, International Association of Diabetes and Pregnancy Study Groups.

*Gestational diabetes mellitus diagnosed by at least two abnormal levels being recorded.

**Gestational diabetes mellitus diagnosed by any one abnormal level being recorded.
2.4 | Data extraction

All identified citations were imported into EndNote X (Bld 2114) (Thomson ResearchSoft, Philadelphia, PA, USA) and duplicates were deleted. Two investigators (MJ and EH) independently screened the titles and abstracts to select potentially eligible articles. When the information was not sufficient, the full-text article was obtained for further investigation. All articles selected based on agreement between the investigators were thoroughly reviewed and abstracted using a predefined standard form. Information was obtained on the publication (the first author’s last name, year and country of publication), study design, sample size, number of participants with GDM, participants’ age, participants’ prepregnancy body mass index, risk estimates of selected adverse pregnancy outcomes with their confidence intervals (CIs), pregnancy duration at delivery, GDM diagnostic method and criteria, and variables adjusted for in multivariate models. When the risk estimates were not reported, approximate values were calculated from percentages. The adverse pregnancy outcomes included were as follows: pre-eclampsia, defined as blood pressure ≥140/90 mm Hg and proteinuria; cesarean delivery, including both planned and emergency cesarean delivery combined; gestational hypertension, defined as blood pressure ≥140/90 mm Hg; fetal macrosomia, defined as birthweight ≥4000 g; and large for gestational age (LGA), defined as birthweight ≥90th percentile for gestational age.

2.5 | Statistical analysis

In the meta-analyses, the RR estimates for the associations between adverse pregnancy outcomes and GDM diagnosed according to the IADPSG versus the CC criteria were combined across studies using random-effect models. Heterogeneity between the studies was evaluated with the Cochran Q test and quantified with the $I^2$ statistic. An $I^2$ value equal to zero indicated no heterogeneity, a value equal or above 50% was considered an indication of moderate heterogeneity, and a value equal or above 75% was considered an indication of substantial heterogeneity between studies. A leave-one-out sensitivity analysis was carried out to explore the extent to which a particular study might have influenced the result (one study was removed at a time and the meta-analysis was repeated). Publication bias was assessed by visual inspection of funnel plots. Funnel plot asymmetry was evaluated using the Egger regression test. In addition, the Begg-adjusted rank correlation test was used. The statistical analyses were carried out with Stata version 11 (StataCorp, College Station, TX, USA). $P<0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study characteristics

The initial search identified 6695 references, of which 5886 remained after the removal of duplicates (Fig. 1). After the review of titles and abstracts, 5696 studies were excluded and 190 potentially relevant articles were fully reviewed. Sixteen studies met the predefined inclusion criteria. A total of nine studies met the eligibility criteria and were selected for the systematic review (Table S1). The studies included a total of 41 663 participants. The incidence of GDM varied from 5.7% to 54.1% in studies using the one-step diagnostic approach and from 4.0% to 51.3% in studies using the two-step approach.

Of the selected studies, six were retrospective cohort studies, two were prospective cohort studies, and one was a cross-sectional study (Table S1). Three studies were conducted in Europe, three in the USA, two in Asia, and one in Mexico. Seven studies examined the association of GDM with a variety of adverse maternal and neonatal outcomes, whereas two studies investigated the single outcomes of LGA and cesarean delivery.

3.2 | Maternal outcomes

Three studies provided data on pre-eclampsia, defined as a blood pressure of 140/90 mm Hg or more and proteinuria (Fig. 2). In one of the three studies, the association between GDM and pre-eclampsia was significant regardless of whether the IADPSG or the CC criteria were used for the GDM diagnosis (Fig. 2). The pooled analysis indicated a significant positive association between GDM and pre-eclampsia when the IADPSG criteria were used (RR=1.68, 95% CI 1.29–2.19; $P<0.001$), with the results consistent across studies ($I^2=0.0%$). When the CC criteria were used, the RR for the same association was slightly higher (RR=1.77, 95% CI 1.14–2.75; $P=0.011$) and the results were also consistent ($I^2=0.0%$).

Seven studies provided data on the association of GDM with cesarean delivery (Fig. 2). Five of these studies found a significant positive association between GDM and cesarean delivery when the IADPSG criteria were used, and five studies found a significant positive association when the CC criteria were used. The pooled RR was 1.28 (95% CI 1.19–1.37; $P<0.001$) when GDM was
diagnosed according to the IADPSG criteria, and 1.33 (95% CI 1.19–1.49; \( P < 0.001 \)) when the CC criteria were used. The associations with GDM diagnosed according to the IADPSG criteria were consistent across the seven studies analyzed (\( I^2 = 0.0\% \)), but there was moderate heterogeneity between the studies for GDM diagnosed according to the CC criteria (\( I^2 = 57.0\%; \ P = 0.03 \)).

Sensitivity analysis consistently revealed a significant positive association between GDM diagnosed using the CC criteria and cesarean delivery (range of RRs [95% CI], 1.29 (1.15–1.45) to 1.38 (1.22–1.55)). The studies by Ethridge et al.\(^{33}\) and Hosseini and Janghorbani\(^{30}\) contributed most to the heterogeneity. In an analysis excluding these studies, the overall pooled estimate of the association between GDM diagnosed using the CC criteria and cesarean delivery was 1.28 (95% CI 1.16–1.41; \( P < 0.001 \)) and the heterogeneity was not significant (\( I^2 = 36.6\%; \ P = 0.177 \)).

Six studies provided sufficient information to evaluate the diagnostic criteria as predictors for gestational hypertension.
Eight studies assessed the association between GDM and LGA, defined as a birthweight at or above the 90th percentile for gestational age (Fig. 3). Two of these studies found a significant positive association between GDM and LGA when the IADPSG criteria were used, and six found such an association when the CC criteria were used. The pooled RR was 1.44 (95% CI 1.11–1.87; P=0.006) for the IADPSG criteria but there was heterogeneity between the studies (I²=74.1%; P=0.001). Sensitivity analysis consistently revealed a significant positive association between GDM diagnosed with the IADPSG criteria and LGA (range of RRs [95% CI], 1.32 [1.03–1.69] to 1.60 [1.28–1.98], except when excluding the study by Waters et al. The studies by Ethridge et al. and Waters et al. contributed most to the heterogeneity. In an analysis excluding these studies, the association between GDM diagnosed using the IADPSG criteria and LGA was no longer significant (RR=1.14, 95% CI 0.95–1.36; P=0.155) and the test for heterogeneity was not significant (I²=0.0%; P=0.596).

In the pooled analysis for the CC criteria, a similar association between GDM and LGA was noticed (RR=1.68, 95% CI 1.32–2.13; P=0.001) but the heterogeneity between the studies was moderate (I²=69.4%; P=0.002). The sensitivity analysis consistently showed a significant positive association between GDM diagnosed with the CC criteria and LGA (range of RRs [95% CI], 1.54 (1.24–1.92) to 1.79 (1.39–2.31)). The studies by Hosseini and Janghorbani, Lapolla et al., and Waters et al. contributed most to the heterogeneity. In an analysis excluding these studies, the association between GDM diagnosed using the CC criteria and LGA was 1.62 (95% CI 1.36–1.93; P<0.001) and the test for heterogeneity was not significant (I²=0.0%; P=0.421).

With regard to NICU admission, one of six studies found a significant positive association with GDM diagnosed using the IADPSG criteria and only five studies found such an association for the CC criteria (Fig. 3). The pooled RR for the IADPSG criteria was 1.22 (95% CI 1.02–1.46, P=0.027) and the results were consistent (I²=0.0%). For the CC criteria, the magnitude of the association was clinically relevant but not statistically significant (RR=1.35, 95% CI 0.98–1.87; P=0.071) and there was moderate heterogeneity between the studies (I²=61.6%, P=0.034). The sensitivity analysis consistently demonstrated no significant association between GDM and NICU admission when the CC criteria were used (range of RRs [95% CI], 1.18 (0.91–1.54) to 1.54 (1.20–1.97)], except when excluding the study by Ethridge et al. The studies by Ethridge et al. and Liao et al. contributed most to the heterogeneity. In an analysis excluding these studies, a significant positive association between GDM diagnosed using the CC criteria and NICU admission was found (RR=1.34, 95% CI 1.04–1.72; P=0.022) and there was no significant heterogeneity (I²=0.0%; P=0.951).

3.4 | Publication bias

A funnel plot analysis revealed no evidence of publication bias. The Begg-adjusted rank correlation test and the Egger regression test also indicated a low probability of publication bias (P=0.805 and P=0.333, respectively).

4 | DISCUSSION

The findings from the present meta-analysis indicated that a GDM diagnosis based on either the one-step or the two-step approach was associated with LGA, pre-eclampsia, and cesarean delivery. In addition, GDM diagnosed with the one-step method increased the risks of NICU admission and gestational hypertension, whereas GDM diagnosed with the two-step method increased the risk for macrosomia. For LGA (RR=1.68 vs RR=1.44), pre-eclampsia (RR=1.77 vs RR=1.68),
and cesarean delivery (RR=1.33 vs RR=1.28), the magnitudes of the effects were slightly stronger with the two-step method than with the one-step method.

Gestational diabetes mellitus has been associated with adverse pregnancy outcomes regardless of whether it is diagnosed with the one-step or the two-step approach.32,34 The observed discrepancies between some of the studies included in the present meta-analysis may be attributable to small sample sizes, which may have resulted in insufficient statistical power to detect some relationships in individual studies.

In all but four28,30–32 of the studies included in the present analysis, patients who underwent two-step screening with the CC criteria were later reclassified using the IADPSG criteria, including women...
not diagnosed with GDM based on the CC criteria—some of whom were identified as having GDM when reclassified using the IADPSG criteria. The patients who were reclassified with GDM received no treatment in any of the studies, whereas all women diagnosed with the CC criteria were intensively treated. This observation indicates that the IADPSG criteria identify a milder degree of hyperglycemia, compared with other diagnostic approaches, and this milder degree of hyperglycemia may slightly increase the risk of adverse pregnancy outcomes; nevertheless, these women received no treatment. The identification of milder hyperglycemia may explain the similarities in adverse pregnancy outcomes associated with GDM in both approaches. Moreover, use of the diagnostic criteria and thresholds for the 75-g, 2-hour OGTT in women who have undergone a 100-g, 3-hour OGTT leads to an overestimation of the prevalence of GDM because the plasma glucose responses during a 100-g, 3-hour OGTT are greater than those during a 75-g, 2-hour OGTT. Therefore, some women who were classified as having GDM with the IADPSG criteria may not actually have been at an increased risk for developing adverse pregnancy outcomes.

Whereas untreated GDM diagnosed with the IADPSG criteria is associated with poor pregnancy outcomes compared with no GDM, more patients being treated in the one-step method was not associated with a decrease in adverse pregnancy outcomes. These findings provide a rationale for further research to investigate whether the risk of adverse pregnancy outcomes among women with GDM diagnosed with the IADPSG criteria but not with the CC criteria might be reduced by treatment. The present study also found a small increased risk for adverse pregnancy outcomes among women with GDM diagnosed using the CC criteria after treatment; these patients would benefit from treatment. This finding is consistent with previous reports in which improved pregnancy outcomes were noticed for women with hyperglycemia below the threshold for overt diabetes after treatment.

The present findings must be interpreted in the context of the limitations in the original data. Six (67%) of the studies did not calculate the RRs of selected adverse pregnancy outcomes and control for confounding variables. Thus, the stronger association with adverse pregnancy outcomes observed with the two-step method might be attributable to confounding by such uncontrolled risk factors. Besides, differences in the way women with GDM were managed might also have influenced the adverse pregnancy outcomes in the studies included. Therefore, the magnitudes of the associations between GDM and adverse pregnancy outcomes should be interpreted with caution. It is also important to consider the heterogeneity between studies, which was mostly seen with findings for the two-step method. Potential reasons for this heterogeneity include differences in the population characteristics, the study design, and the diagnostic criteria (this was mostly the case for the CC criteria). The removal of individual studies in the sensitivity analyses did not substantially alter the findings indicating the robustness of the pooled estimates. Moreover, only a few studies were available that compared the pregnancy outcomes with the one-step versus the two-step method and the sample sizes were small. Finally, as with any meta-analysis, the findings might have been affected by publication bias. The funnel plot analysis and the formal statistical tests did not provide any evidence for the presence of such bias, but publication bias cannot be ruled out completely because of the small number of studies included.

The present results have important implications for GDM testing. The prevalence of GDM is high and will continue to increase as a result of the increasing incidences of both obesity and advanced maternal age. The one-step method identifies more women with GDM. However, the increased number of patients with GDM when diagnosed with the one-step IADPSG criteria does not present an excess risk of maternal and neonatal adverse pregnancy outcomes compared with women diagnosed using the two-step CC criteria. Therefore, the present data seem to confirm concerns expressed in the literature that the one-step approach may classify lower-risk women as having GDM, which will increase women's anxiety and healthcare costs with more visits, more ultrasonography examinations, additional laboratory tests, and no clear indication of benefit in the short term.

In conclusion, it seems reasonable to adopt the higher cutoff values of the two-step method to determine GDM. However, further studies are required to adequately estimate the magnitudes of the associations of GDM diagnosed with the one-step and two-step approaches with selected adverse pregnancy outcomes.

AUTHOR CONTRIBUTIONS

EH contributed to data collection and analysis, and writing the manuscript. MJ contributed to the conception and design of the study, data interpretation, and revising the manuscript. Both authors approved the final version submitted for publication.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES


**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Selected characteristics of the included studies.