Annals of Internal Medicine | Review

Benefits and Harms of Treating Gestational Diabetes Mellitus: A Systematic Review and Meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research

Lisa Hartling, PhD; Donna M. Dryden, PhD; Alyssa Guthrie, MSSc; Melanie Muise, MA; Ben Vandermeer, MSc; and Lois Donovan, MD

Background: Outcomes of treating gestational diabetes mellitus (GDM) are not well-established.

Purpose: To summarize evidence about the maternal and neonatal benefits and harms of treating GDM.

Data Sources: 15 electronic databases from 1995 to May 2012, gray literature, Web sites of relevant organizations, trial registries, and reference lists.

Study Selection: English-language randomized, controlled trials ($n = 5$) and cohort studies ($n = 6$) of women without known preexisting diabetes.

Data Extraction: One reviewer extracted data, and a second reviewer verified them. Two reviewers independently assessed methodological quality and evaluated strength of evidence for primary outcomes by using a Grading of Recommendations Assessment, Development and Evaluation approach.

Data Synthesis: All studies compared diet modification, glucose monitoring, and insulin as needed with no treatment. Women who were treated had more prenatal visits than those in control groups. Moderate evidence showed fewer cases of preeclampsia, shoulder dystocia, and macrosomia in the treated group. Evidence was insufficient for maternal weight gain and birth injury. Low evidence showed no difference between groups for neonatal hypoglycemia. Evidence was insufficient for long-term metabolic outcomes among offspring. No difference was found for cesarean delivery (low evidence), induction of labor (insufficient evidence), small-for-gestational-age neonates (moderate evidence), or admission to a neonatal intensive care unit (low evidence).

Limitations: Evidence is low or insufficient for many outcomes of greatest clinical importance. The strongest evidence supports reductions in intermediate outcomes; however, other factors (for example, maternal weight and gestational weight gain) may impart greater risk than GDM, particularly when glucose levels are modestly elevated.

Conclusion: Treating GDM results in less preeclampsia, shoulder dystocia, and macrosomia; however, current evidence does not show an effect on neonatal hypoglycemia or future poor metabolic outcomes. There is little evidence of short-term harm of treating GDM other than an increased demand for services.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2013;159:123-129. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 28 May 2013.

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first discovered in pregnancy. It predicts risk for overt diabetes in women. The more immediate risk for adverse outcomes of GDM in the mother and child is less well-established.

The prevalence of GDM ranges from 1.1% to 25.5% of pregnancies in the United States (1–3) and is influenced by diagnostic criteria and population characteristics, such as ethnicity. The incidence of this condition has increased over the past decades in parallel with the increase in rates of obesity and type 2 diabetes mellitus, and this trend is expected to continue.

Initial treatment of GDM involves diet modification, glucose monitoring, and moderate exercise. When dietary management does not achieve desired glucose control, insulin or oral antidiabetic medications may be used (4). Increased prenatal surveillance and changes in delivery management may also occur.

A report commissioned by the U.S. Preventive Services Task Force in 2008 found that treatment of women with mild GDM diagnosed after 24 weeks' gestation improved maternal and neonatal health outcomes (5). Specifically, on the basis of 1 study, the report found a reduction in "any serious perinatal complication," which included death, shoulder dystocia, bone fracture, and nerve palsy (6). The number of events for many of the individual outcomes was extremely small, which did not provide adequate evidence to make conclusions for individual outcomes. The same study also found less depression and a trend to better quality of life 3 months after parturition and reduced maternal hypertension in the treated group (6).

Potential harms of GDM treatment may include small-for-gestational-age neonates; maternal stress; and additional costs, including those associated with laboratory testing as well as patient and clinician time (7). Anxiety of health care providers over the diagnosis could result in unnecessary or overly aggressive fetal and neonatal surveil-

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lance and delivery management. The purpose of this review is to evaluate whether treatment of GDM modifies outcomes of mothers and their offspring and whether it is associated with any harms.

METHODS

An a priori protocol was followed. Questions were developed by the Office of Medical Applications of Research and the U.S. Preventive Services Task Force. A technical expert panel that included representatives from both organizations provided content and methodological expertise. The full technical report is available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1295&pageaction=displayproduct.

Data Sources and Searches

We searched for trials and cohort studies published in English from 1995 to May 2012 in MEDLINE (Ovid interface) (**Appendix Table 1**, available at www.annals.org), Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Global Health, EMBASE, Pascal CINAHL Plus with Full Text (EBSCOhost), BIOSIS Previews (Web of Knowledge), Science Citation Index Expanded and Conference Proceedings Citation Index (both via Web of Science), PubMed, Latin American and Caribbean Health Science Literature, National Library of Medicine Gateway, and OCLC ProceedingsFirst and PapersFirst. We also searched trial registries and the Web sites of relevant professional associations and research groups for conference abstracts and proceedings between 2010 and 2012. We evaluated the reference lists of relevant reviews and included studies.

Study Selection

Two reviewers independently screened titles, keywords, and abstracts. We retrieved the full text for any study that was considered potentially relevant by at least 1 reviewer. Two reviewers independently assessed each full-text article by using a detailed form. We resolved disagreements through discussion. We included studies if they were randomized, controlled trials (RCTs) or non-RCTs or cohort studies; involved pregnant women with no known preexisting diabetes; compared any treatment of GDM with no treatment; and reported short- and long-term maternal, fetal, neonatal, and child outcomes that the technical panel deemed important.

Data Extraction and Quality Assessment

One reviewer extracted data by using a structured, electronic form, and a second reviewer checked the data for accuracy and completeness. Discrepancies were resolved through consensus. We extracted information on study characteristics, populations, interventions, outcomes, and results.

Two reviewers independently assessed the methodological quality of included studies and resolved disagreements through discussion. We used the Cochrane risk-of-bias tool to assess RCTs (8) and the Newcastle-Ottawa Scale to assess cohort studies (9).

Data Synthesis and Analysis

Two independent reviewers graded the strength of evidence by using the Evidence-based Practice Center Grading of Recommendations Assessment, Development and Evaluation approach (10). We resolved discrepancies by discussion. We assessed 4 major domains (risk of bias, consistency, directness, and precision) and summarized the overall strength of evidence for each outcome as high, moderate, or low. When no studies were available for an outcome or the evidence did not permit estimation of an effect, we rated strength of evidence as insufficient.

We described the results of studies qualitatively and in evidence tables. We performed meta-analyses when studies were sufficiently similar in terms of statistical homogeneity (that is, $I^2 \leq 75\%$). We used the Mantel–Haenszel method for relative risks and the inverse variance method for pooling mean differences.

We combined results by using the random-effects model (11). For dichotomous outcomes, we computed relative risk to estimate between-group differences. If no event was reported in 1 treatment group, a correction factor of 0.5 was added to each cell of the 2×2 table to obtain estimates of the relative risk.

For continuous variables, we calculated mean differences for individual studies. We reported all results with 95% CIs and used Review Manager, Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark), to perform meta-analyses.

Role of the Funding Source

The Agency for Healthcare Research and Quality (AHRQ) approved copyright assertion for this manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS

Of 14 428 citations, 5 RCTs (6, 12–15) and 6 retrospective cohort studies (16–21) met inclusion criteria (**Appendix Figure 1**, available at www.annals.org). All studies compared diet modification, glucose monitoring, and insulin as needed with standard care. Two studies had 2 associated publications reporting initial (6, 15) and longer-term (22, 23) outcomes. Diagnostic testing in all studies occurred at or after 24 weeks' gestation (when reported).

Numerous glucose inclusion criteria were used, varying from screening positive on the 50-g glucose challenge with nondiagnostic oral glucose tolerance tests to meeting National Diabetes Data Group criteria for a diagnosis of GDM. The 2 largest RCTs used different glucose thresholds for entry in their trials: World Health Organization (6) and Carpenter–Coustan criteria with a fasting glucose

Table. **Strength of Evidence for Benefits and Harms of Treating GDM**

Outcome	Source	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Summary
Preeclampsia	3 RCTs	Low	Consistent	Direct	Imprecise	Moderate (favors treatment)	Difference in favor of treatment for RCTs (RR, 0.62 [95% CI, 0.43 to 0.89]); no difference observed for cohort study
	1 cohort study	High	Unknown	Direct	Imprecise	Insufficient	
Maternal weight gain	4 RCTs	Medium	Inconsistent	Direct	Imprecise	Insufficient	Results not pooled for RCTs because of substantial heterogeneity; no difference for cohort studies (MD, −1.04 [CI, −2.89 to 0.81])
	2 cohort studies	High	Consistent	Direct	Imprecise	Insufficient	
Birth injury	2 RCTs	Medium	Consistent	Direct	Imprecise	Low	No difference for RCTs (RR, 0.48 [CI, 0.12 to 1.90]); difference favoring treatment for cohort study (RR, 0.02 [CI, 0.00 to 0.22])
	1 cohort study	High	Unknown	Direct	Imprecise	Insufficient (favors treatment)	
Shoulder dystocia	3 RCTs	Medium	Consistent	Direct	Precise	Moderate (favors treatment)	Difference in favor of treatment for RCTs (RR, 0.42 [CI, 0.22 to 0.77]) and cohort studies (RR, 0.38 [CI, 0.19 to 0.78])
	4 cohort studies	High	Consistent	Direct	Precise	Low (favors treatment)	
Neonatal hypoglycemia	4 RCTs	Medium	Consistent	Direct	Imprecise	Low (no difference)	No difference for RCTs (RR, 1.18 [CI, 0.92 to 1.52]) or cohort studies (RR, 0.55 [CI, 0.10 to 2.97])
	2 cohort studies	High	Inconsistent	Direct	Imprecise	Insufficient	
Macrosomia (birthweight >4000 g)	5 RCTs	Medium	Consistent	Direct	Precise	Moderate (favors treatment)	Difference in favor of treatment for RCTs (RR, 0.50 [CI, 0.35 to 0.71]); results not pooled for cohort studies because of substantial heterogeneity
	6 cohort studies	High	Inconsistent	Direct	Precise	Low (favors treatment)	
Long-term metabolic outcomes							
Impaired glucose tolerance	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient	No difference between groups (RR, 5.63 [CI, 0.31 to 101.32])
Type 2 DM	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient	No difference between groups (RR, 1.88 [CI, 0.08 to 44.76])
BMI (assessed as >85th and >95th percentiles)	2 RCTs	Medium	Consistent	Direct	Imprecise	Low (no difference)	No difference between groups (RR, 1.26 [CI, 0.86 to 1.84])

BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; MD = mean difference; RCT = randomized, controlled trial; RR = risk ratio.

level less than 5.3 mmol/L (95 mg/dL) (12); however, the mean glucose levels of women at study entry were similar between these 2 studies. Risk of bias was low for 1 trial (6), unclear for 3 trials (12–14), and high for 1 trial (15). All cohort studies were considered high quality, with overall scores of 7 to 9 on a 9-point scale.

Benefits of Treating GDM

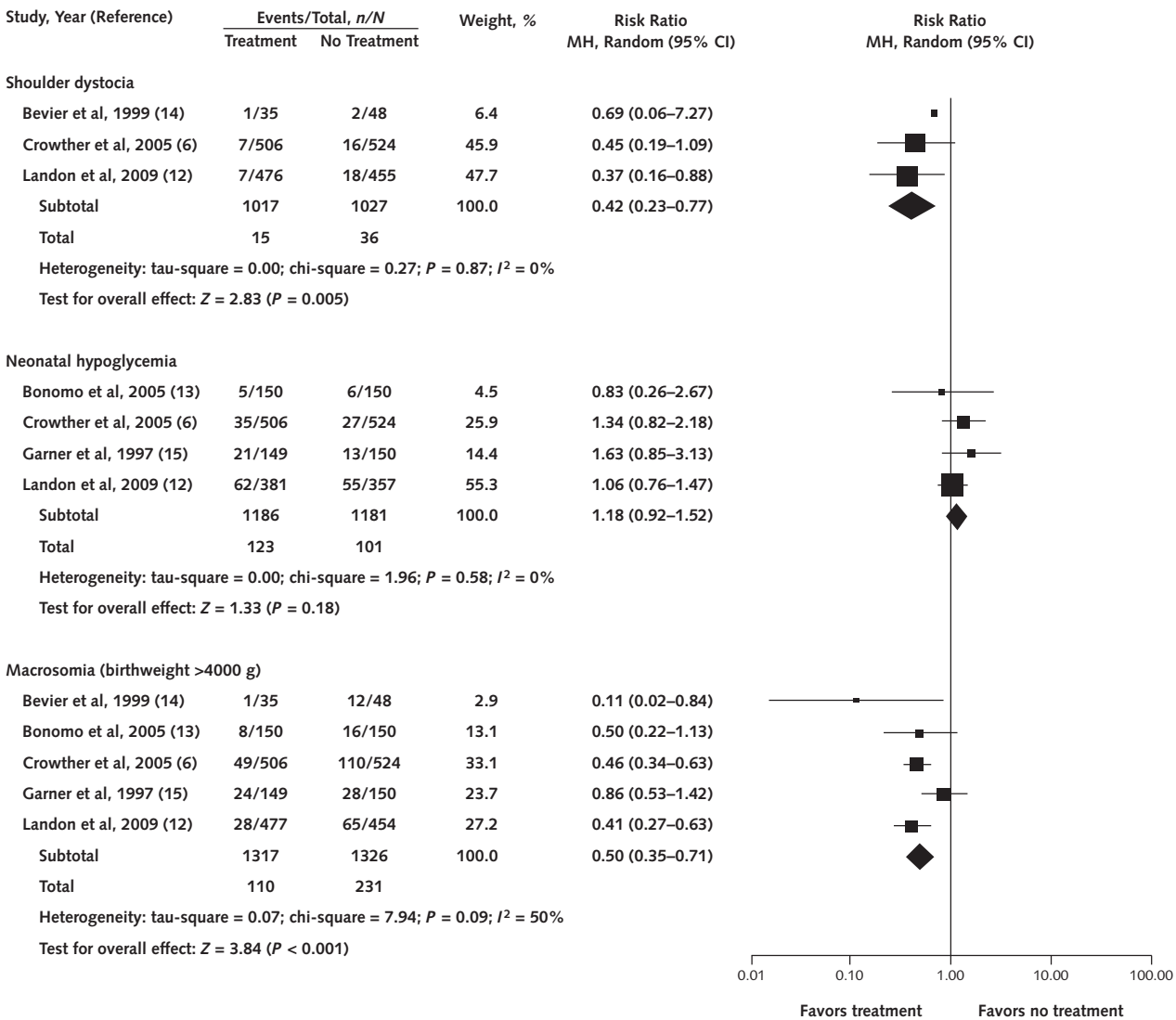
The **Table** and **Appendix Table 2** (available at www.annals.org) show results for maternal outcomes. Moderate evidence from 3 RCTs showed less preeclampsia with treatment (**Appendix Figure 2**, available at www.annals.org). In 2 of these trials, there was no difference between groups in gestational age at delivery. The strength of evidence for maternal weight gain was insufficient because of inconsistency across studies and imprecise effect estimates (**Appendix Figure 3**, available at www.annals.org). Two RCTs showed no difference (13, 15), whereas 2 large RCTs showed less weight gain with treatment (6, 12). Given the high body mass index (BMI) of the women studied, less gestational weight gain in the treatment group would be beneficial.

One RCT reported on BMI at delivery and showed lower BMI with treatment; however, this evidence was considered insufficient. There was no evidence from the included studies for long-term maternal outcomes, such as type 2 diabetes mellitus, obesity, and hypertension.

The **Table** and **Appendix Table 3** (available at www.annals.org) show the findings for fetal, neonatal, or child outcomes. Evidence was insufficient for birth injury due to imprecision (low number of events and participants across studies) and inconsistency (2 RCTs showed no difference [12, 15], and 1 cohort study showed fewer cases with treatment [18]). Moderate evidence showed fewer cases of shoulder dystocia with treatment (**Figure 1**). For other injury outcomes (that is, brachial plexus injury and clavicular fractures), results were inconsistent across study designs, with the RCTs showing no differences and the cohort study showing fewer cases with treatment.

For outcomes related to birthweight (including birthweight >4000 g, actual birthweight, and large-for-gestational-age neonates), lower weights or fewer cases were observed with treatment. The strength of evidence was moderate for birthweight >4000 g (**Figure 1**). There was no difference in hyperbilirubinemia for RCTs (low strength of evidence), whereas the cohort study showed significantly less hyperbilirubinemia in the treated group.

Figure 1. **Effect of treatment for shoulder dystocia, neonatal hypoglycemia, and macrosomia (birthweight >4000 g) based on data from randomized, controlled trials.**



MH = Mantel–Haenszel.

There were no differences in perinatal death, although the number of events was extremely low (<0.5%). Randomized, controlled trials showed no difference between groups for the respiratory distress syndrome, whereas 1 cohort study found fewer "respiratory complications" (17) in the treated group; overall, the respiratory distress syndrome was rare (4.3% across all studies). Several studies assessed Apgar scores; although differences were found for the Apgar score at 1 minute, no differences were observed at 5 minutes.

One RCT followed a subset of the offspring for 7 to 11 years and found no differences for impaired glucose tolerance or type 2 diabetes mellitus (insufficient strength of evidence). No differences were observed in single studies that assessed offspring with BMIs greater than the 95th percentile (7- to 11-year follow-up) and the 85th percentile (4- to 5-year follow-up). Overall, pooled results showed no difference in BMI (low strength of evidence).

Harms of Treating GDM

One RCT assessed maternal depression and anxiety at 6 weeks after study entry and 3 months after parturition (6). There was no difference between groups in anxiety at either time point. Depression rates were lower in the treatment group 3 months after parturition (**Appendix Table 2**).

Moderate evidence from 4 RCTs showed no difference in small-for-gestational-age neonates. Pooled results from 4 RCTs showed no difference between groups in neonatal hypoglycemia and no statistical heterogeneity (**Figure 1**).

Two cohort studies showed inconsistent results, which may be partly due to different definitions of hypoglycemia used across the studies and different protocols for screening neonates for hypoglycemia. Overall, the strength of evidence was low, suggesting that further study may change the results of our findings (**Table**).

Low evidence showed no difference overall in admission to the neonatal intensive care unit (**Appendix Figure 4**, available at www.annals.org). One trial was an outlier, with significantly more admissions to the neonatal intensive care unit in the treated group. Two RCTs reported on the number of prenatal visits and found more visits among the treatment groups. The strength of evidence for induction of labor was insufficient because of lack of precision and inconsistency across studies, with no difference found for the RCTs overall. There was low evidence of no differences between groups for cesarean delivery (**Figure 2**) or unplanned cesarean delivery.

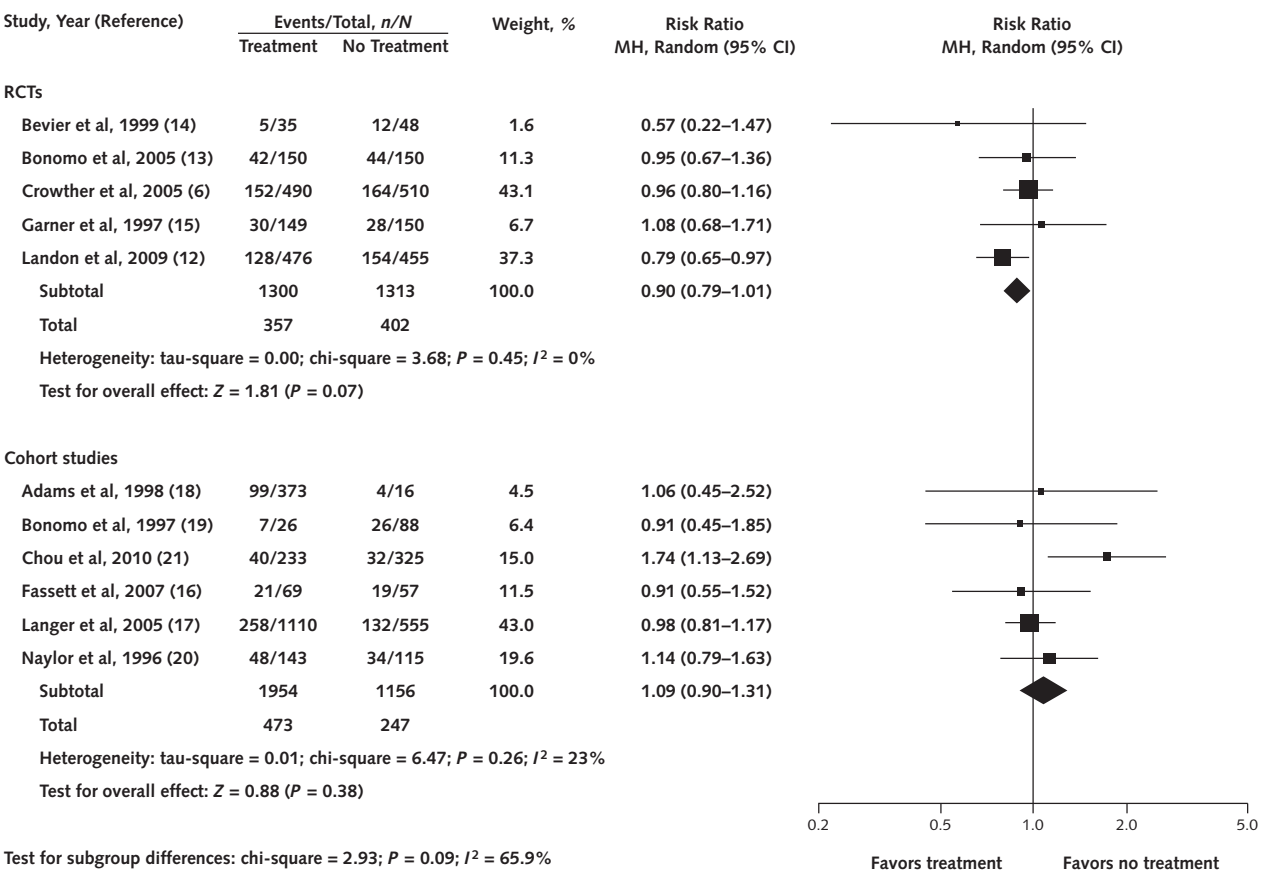
Discussion

Moderate evidence showed that treatment of GDM reduced preeclampsia, shoulder dystocia, and macrosomia (birthweight >4000 g). These outcomes, specified a priori to be of interest to our stakeholders, may be intermediate to outcomes of greater clinical importance, such as prematurity or brachial plexus injury. Evidence showing differences between groups for other benefits to mother or infant was lacking or weak.

In terms of harms, there was no evidence for some of the outcomes stipulated in the protocol, including costs and resource allocation, although there were more prenatal visits in the treatment groups. No difference was found in small-for-gestational-age neonates, which may be due to inadequate power to detect differences because of the small number of events. No differences were found for admission to the neonatal intensive care unit or rate of induction of labor. However, there was heterogeneity in these outcomes that may be attributable to different site-specific policies and procedures, study protocols, and practice patterns. Low-strength evidence showed no difference in rates of cesarean delivery.

Our results are consistent with other recent systematic reviews showing some evidence of benefit of treating GDM for select maternal and infant outcomes yet little evidence

Figure 2. **Effect of treatment on outcomes of women with GDM who have cesarean delivery.**



GDM = gestational diabetes mellitus; MH = Mantel–Haenszel; RCT = randomized, controlled trial.

of an effect on patient-important outcomes (for example, perinatal or neonatal mortality). This is probably due to the infrequent occurrence of these events and a resulting lack of power across the studies to adequately assess for differences (24, 25).

Several caveats related to this body of evidence should be considered when interpreting and applying the results of this review. First, although we found differences in preeclampsia, macrosomia, and shoulder dystocia, most such events occur in pregnant women without GDM (26). Such factors as maternal weight and gestational weight gain have been shown to impart greater risk for these outcomes, particularly in women diagnosed with GDM at lower glucose thresholds (27, 28). For example, analyses adjusting for these variables show that glycemia accounted for only 1.7% of the risk for large-for-gestational-age neonates (27). Second, where reported, definitions of preeclampsia varied (for example, a blood pressure of 140/90 mm Hg on 2 occasions 4 hours apart, these criteria with laboratory measures indicative of preeclampsia, or an increase in blood pressure medications). Preeclampsia events in our pooled analysis may have included women with the much-less-serious condition of gestational hypertension; however, a study that used the more rigorous definition showed a treatment benefit (12). Preeclampsia occurs in 3% to 5% of pregnancies (29), and the risk for this condition attributable to GDM is probably small (30). Third, this review assessed the risks and benefits of treating GDM but not those of screening for this condition. Of note, our larger technical report, which addressed screening, found no randomized trials examining the effect of screening on health outcomes (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1295&pageaction=displayproduct).

Evidence was very limited for 2 outcomes of particular interest to stakeholders. The first was patient anxiety associated with a diagnosis of GDM. A single study assessed depression and anxiety in a subgroup of a larger RCT. It found no difference between groups in anxiety at 6 weeks after study entry and 3 months after parturition, although the treatment group had lower rates of depression at 3 months after parturition. Research has shown that women with GDM had a higher level of anxiety at the time of the first GDM assessment than glucose-tolerant women; however, these differences in anxiety scores did not persist before delivery (31). Further, a survey of women 3 to 5 years after diagnosis of GDM showed more concern about their own health and rated their children's health poorer than matched control participants (32). The second outcome was metabolic changes in the children born to mothers with GDM. Follow-up of offspring from participants in 2 RCTs (6, 16) did not show any treatment effect of GDM on metabolic outcomes of the children.

Further study of the long-term metabolic effect on offspring whose mothers have been treated for GDM is warranted. Well-conducted prospective cohort studies of the real-world effect of GDM treatment on health care utilization are needed. Research is also needed to help determine the glucose thresholds and treatment targets at which GDM treatment benefits outweigh the risks of treatment and no treatment.

The IDEAL (Investigation of Dietary Advice and Lifestyle for Women With Borderline Gestational Diabetes) study, an RCT to assess the effect of treating women with very mild glucose impairment in pregnancy, is under way. Randomized, controlled trials investigating the care of women diagnosed with GDM, including fetal surveillance protocols, are needed to guide obstetric investigations and management of GDM. Such work may help avoid unnecessary interventions that are driven by the apprehension of health care providers.

The review process had several limitations. We limited the search dates from 1995 onward on the basis of advice from our technical expert panel. Our results are consistent with other systematic reviews on this topic that included studies before 1995 (24, 25). We included only studies published in English. Most studies were conducted in North America or Australia. Most of the North American studies included mixed racial populations and are probably applicable to the general U.S. population. We included cohort studies because an earlier review (5) found few RCTs; results from cohort studies should be interpreted cautiously, particularly when they differ from those of the RCTs.

In summary, evidence supports benefits of treating mild GDM. Specifically, treatment of GDM results in lower incidence of preeclampsia, macrosomia, large-for-gestational-age infants, and shoulder dystocia; however, the risk for these outcomes attributable to GDM is low, particularly when glucose levels are modestly elevated. Current research does not show a treatment effect of GDM on clinical neonatal hypoglycemia or future poor metabolic outcomes of the offspring. Randomized, controlled trials of GDM treatment show limited harm related to treating GDM, other than an increased demand for services.

From the Alberta Research Centre for Health Evidence and the University of Alberta Evidence-based Practice Center, University of Alberta, Edmonton, and the University of Calgary, Calgary, Alberta, Canada.

Acknowledgment: The authors thank Tamara Durec (searching), Andrea Milne (searching, technical support), Walie Atkary (screening, data extraction), Dion Pasichnyk (data extraction), Jennifer Seida (screening, project coordination), Teodora Radisic (article retrieval), Jocelyn Shulhan (screening), Annabritt Chisholm (research support, reference management), and Dr. Alun Edwards for providing clinical input throughout the project.

Financial Support: By the AHRQ (contract 290-2007-10021-I).

Potential Conflicts of Interest: Ms. Guthrie: *Grant (money to institution); support for travel to meetings for the study or other purposes (money to institution); fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like (money to institution); payment for writing or reviewing the manuscript (money to institution):* AHRQ. Ms. Muise: *Grant (money to institution):* AHRQ. Mr. Vandermeer: *Grant (money to institution):* AHRQ. Dr. Donovan: *Other:* grants from Bridges Grant (International Diabetes Federation and Eli Lilly) outside the submitted work. All other authors have no disclosures. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0190.

Requests for Single Reprints: Lisa Hartling, PhD, ECHA 4-472, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada; e-mail, hartling@ualberta.ca.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Hartling: ECHA 4-472, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada.
Dr. Dryden: ECHA 4-474, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada.
Ms. Guthrie: Primary Care Division, Alberta Health, 18th Floor, Telus Plaza North Tower, 10025 Jasper Avenue NW, Edmonton, Alberta T5J 1S6, Canada.
Ms. Muise: ECHA 4-492C, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada.
Mr. Vandermeer: ECHA 4-496B, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada.
Dr. Donovan: Richmond Road Diagnostic and Treatment Centre, 1820 Richmond Road SW, Calgary, Alberta T2T 5C7, Canada.

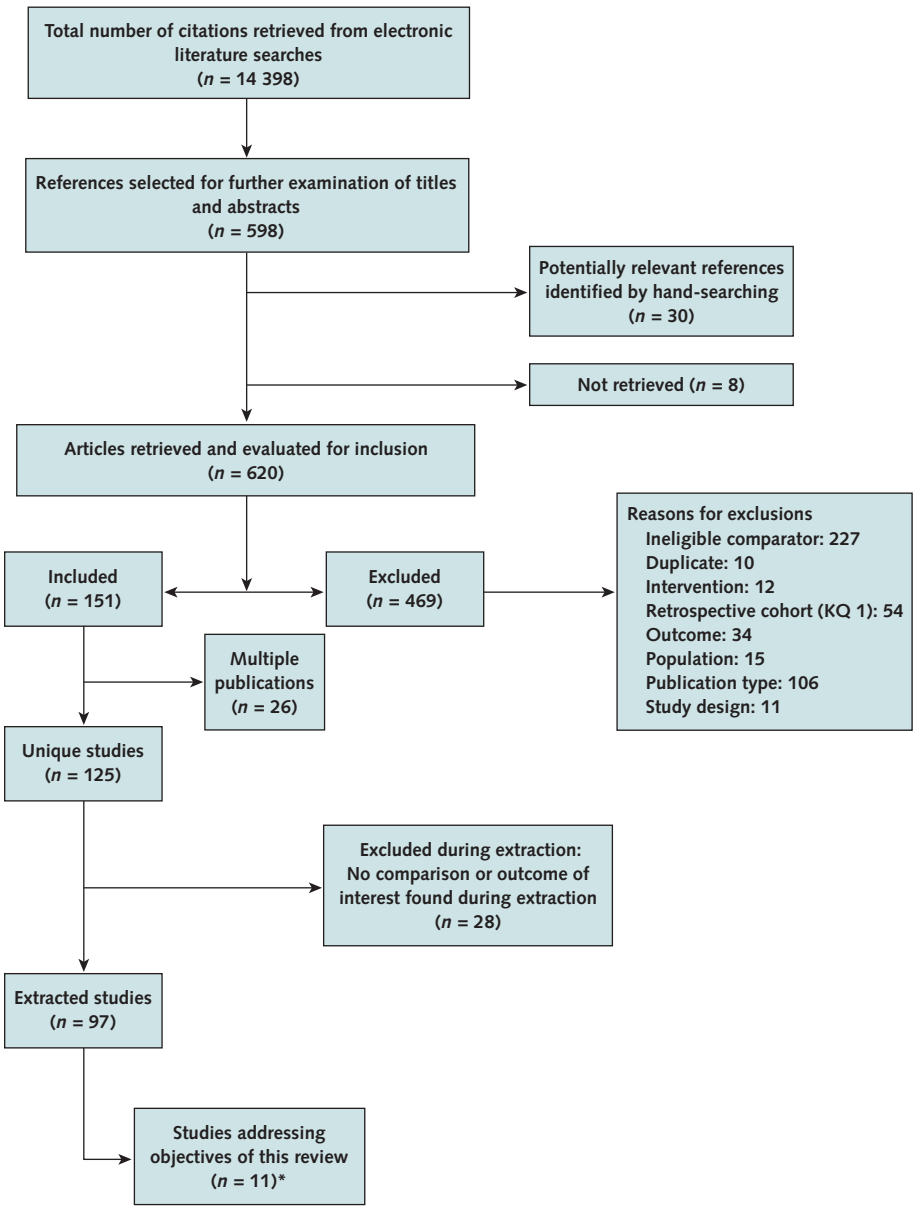
Author Contributions: Conception and design: L. Hartling, D.M. Dryden, L. Donovan.
Analysis and interpretation of the data: L. Hartling, D.M. Dryden, A. Guthrie, M. Muise, B. Vandermeer, L. Donovan.
Drafting of the article: L. Hartling, D.M. Dryden, M. Muise, B. Vandermeer, L. Donovan.
Critical revision of the article for important intellectual content: L. Hartling, D.M. Dryden, M. Muise, B. Vandermeer, L. Donovan.
Final approval of the article: L. Hartling, D.M. Dryden, M. Muise, B. Vandermeer, L. Donovan.
Statistical expertise: B. Vandermeer.
Obtaining of funding: L. Hartling, D.M. Dryden, L. Donovan.
Administrative, technical, or logistic support: L. Hartling, D.M. Dryden, L. Donovan.
Collection and assembly of data: L. Hartling, D.M. Dryden, M. Muise, A. Guthrie, L. Donovan.

Appendix Table 1. MEDLINE Search Strategy*

1. Diabetes, Gestational/
2. Fetal Macrosomia/
3. Pregnancy Complications/
4. GDM.tw.
5. (gestation$ adj2 (diabet$ or DM or glucose intoleran$ or insulin resistan$)).mp.
6. (pregnan$ adj3 (diabet$ or DM or glucose intoleran$ or insulin resistan$)).mp.
7. (maternal adj2 (diabet$ or DM or glyc?emia or hyperglyc?emia)).tw.
8. (hyperglyc?emia adj2 pregnan$).tw.
9. macrosomia.tw.
10. or/1-9
11. mass screening/
12. prenatal diagnosis/
13. screen$.tw.
14. ((prenatal or early) adj2 diagnosis).tw.
15. Glucose Tolerance Test/
16. Glucose Intolerance/
17. Blood Glucose/
18. Risk Factors/
19. (glucose adj (tolerance or intolerance or challenge)).tw.
20. OGTT.tw.
21. GCT.tw.
22. (fasting adj2 glucose).tw.
23. or/11-22
24. "Sensitivity and Specificity"/
25. "Predictive Value of Tests"/
26. ROC Curve/
27. specific$.tw.
28. sensitiv$.tw.
29. predictive value.tw.
30. accurac$.tw.
31. diagnostic errors/
32. diagnostic error?.tw.
33. false negative reactions/
34. false positive reactions/
35. (false adj (negative or positive)).tw.
36. "reproducibility of results"/
37. reference values/
38. reference standards/
39. or/24-38
40. and/10,23,39
41. intervention?.mp.
42. (treating or treatment? or therapy or therapies).mp.
43. manage$.mp.
44. monitor$.mp.
45. exp sulfonylurea compounds/
46. Gliclazide/
47. Glyburide/
48. Tolbutamide/
49. sulfonylurea?.tw.
50. gliclazid$.tw.
51. glimepirid$.tw.
52. glipizid$.tw.
53. glyburid$.tw.
54. tolbutamid$.tw.
55. (antidiabet$ or anti-diabet$).tw.
56. insulin?.mp.
57. glibenclamid$.mp.
58. acarbos$.mp.
59. exp Diet Therapy/
60. (diet adj2 (therap$ or restrict$ or advice)).tw.
61. medical nutrition$ therapy.tw.
62. MNT.tw.
63. exp Life Style/
64. (lifestyle$ or life-style$).mp.
65. Blood Glucose Self-Monitoring/
66. (blood glucose adj (self monitor$ or self-monitor$)).tw.
67. ((self monitor$ or self-monitor$) adj blood glucose).tw.
68. SMBG.tw.
69. Counseling/
70. counsel$.tw.
71. Labor, Induced/
72. (induc$ adj2 labo?r).tw.
73. exp Cesarean Section/
74. c?esarean.tw.
75. exp Pregnancy Outcome/
76. pregnanc$ outcome?.tw.
77. or/41-76
78. and/10,77
79. or/40,78
80. clinical trial.pt.
81. randomized controlled trial.pt.
82. randomi?ed.ti,ab.
83. placebo.ti,ab.
84. dt.fs.
85. randomly.ti,ab.
86. trial.ti,ab.
87. groups.ti,ab.
88. or/80-87
89. animals/
90. humans/
91. 89 not (89 and 90)
92. 88 not 91
93. cohort studies/
94. follow-up studies/
95. longitudinal studies/
96. prospective studies/
97. retrospective studies/
98. ((cohort? or follow-up or followup or longitud$ or prospectiv$ or retrospectiv$) adj (study or studies or trial?)).tw.
99. or/93-98
100. 99 not 91
101. exp Guideline/
102. Health Planning Guidelines/
103. (clinical adj2 guideline?).tw.
104. CPG?.tw.
105. ((practice or consensus or position) adj2 (guideline? or recommendation? or statement?)).tw.
106. standard?.tw.
107. protocol?.tw.
108. or/101-107
109. meta analysis.mp,pt.
110. review.pt.
111. search:.tw.
112. or/109-111 [Reviews balanced - HIRU]
113. and/79,92 [Clinical trials & RCTs]
114. and/79,100 [Observational studies]
115. and/79,108 [Guidelines]
116. and/79,112 [SRs MAs]
117. or/113-116
118. limit 117 to (english language and yr="2000 -Current")
119. limit 117 to (english language and yr="2000 -2005")
120. limit 117 to (english language and yr="2006 -Current")
121. remove duplicates from 119
122. remove duplicates from 120
123. or/121-122
124. 113 or 114 or 115
125. 113 or 114 or 115
126. limit 125 to (english language and yr="2000 -Current")
127. limit 125 to (english language and yr="2000 -2005")
128. remove duplicates from 127
129. limit 125 to (english language and yr="2006 -Current")
130. remove duplicates from 129
131. 128 or 130
132. 113 or 114
133. limit 132 to (english language and yr="2000 -Current")
134. limit 132 to (english language and yr="2000 -2005")
135. remove duplicates from 134
136. limit 132 to (english language and yr="2006 -Current")
137. remove duplicates from 136
138. 135 or 137

* Database, MEDLINE (Ovid interface); 1948 to week 4 September 2011; search date, 9 October 2011; results, 8234.

Appendix Figure 1. **Summary of evidence search and selection.**



KQ = key question.

* This systematic review was part of a larger technical report. The search was done to identify relevant studies for all objectives of the full report, which is available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1295&pageaction=displayproduct.

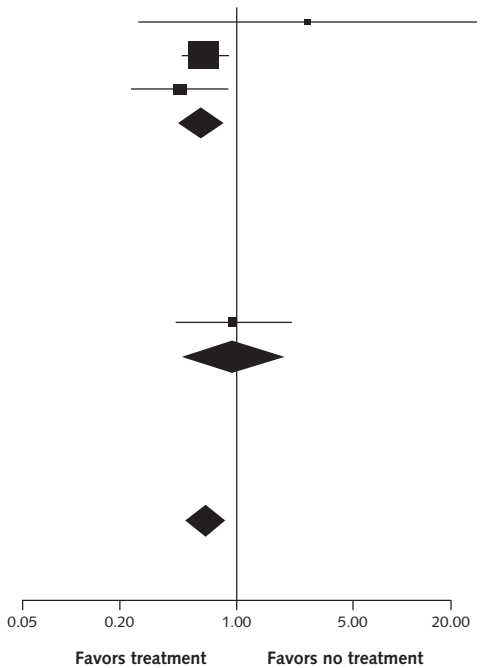
Appendix Table 2. **Evidence Summary for Benefits and Harms of Treating GDM: Maternal Outcomes**

Outcome	Studies, *n*	Participants, *n*	Effect Estimate Risk Ratio (95% CI)*	I^2, %
Benefits				
Preeclampsia				
RCT	3	2014	0.62 (0.43 to 0.89)†	16
Cohort	1	258	0.97 (0.43 to 2.15)	NA
Preeclampsia or gestational hypertension				
RCT	1	931	0.63 (0.44 to 0.92)†	NA
Cohort	1	874	0.30 (0.15 to 0.62)†	NA
Weight gain				
RCT	4	2530	Pooled estimate not reported because of heterogeneity	88
Cohort	2	515	−1.04 (−2.89 to 0.81)‡	8
Maternal birth trauma				
Cohort	1	874	0.95 (0.21 to 4.28)	NA
BMI at delivery				
RCT	1	931	−1.00 (−1.67 to −0.33)†‡	NA
Harms				
Cesarean delivery				
RCT	5	2613	0.90 (0.79 to 1.01)	0
Cohort	6	3110	1.09 (0.90 to 1.31)	23
Unplanned cesarean delivery				
RCT	1	1000	0.81 (0.62 to 1.05)	NA
Cohort	1	126	0.83 (0.33 to 2.06)	NA
Induction of labor				
RCT	2	1931	1.16 (0.91 to 1.49)	69
Cohort	1	1665	0.63 (0.55 to 0.72)§	NA
Anxiety (6 wk after study entry)				
RCT	1	682	−0.30 (−0.88 to 0.28)	NA
Anxiety (3 mo after parturition)				
RCT	1	573	−0.20 (−0.83 to 0.43)	NA
Depression (3 mo after parturition)				
RCT	1	568	0.50 (0.31 to 0.79)†	NA

BMI = body mass index; GDM = gestational diabetes mellitus; NA = not applicable; RCT = randomized, controlled trial.
* Risk ratios unless otherwise specified.
† Statistically significant, with better results for the treated group.
‡ Mean difference.
§ Statistically significant; however, all untreated women in this cohort presented at or after 37 wks' gestation, and institutional policy required that such women give birth within 1 wk of presentation.

Appendix Figure 2. Effect of treatment on outcomes of women with GDM: preeclampsia.

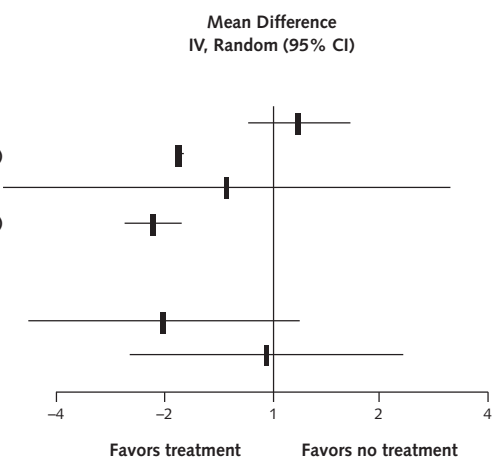
Study, Year (Reference)	Events/Total, *n/N*		Weight, %	Risk Ratio MH, Random (95% CI)
	Treatment	No Treatment		
RCTs				
Bevier et al, 1999 (14)	2/35	1/48	1.8	2.74 (0.26–29.07)
Crowther et al, 2005 (6)	58/490	93/510	65.1	0.65 (0.48–0.88)
Landon et al, 2009 (12)	12/476	25/455	19.1	0.46 (0.23–0.90)
Subtotal	1001	1013	85.9	0.62 (0.43–0.89)
Total	72	119		
Heterogeneity: tau-square = 0.02; chi-square = 2.37; $P = 0.31$; $I^2 = 16\%$				
Test for overall effect: $Z = 2.57$ ($P = 0.01$)				
Cohort studies				
Naylor et al, 1996 (20)	12/143	10/115	14.1	0.97 (0.43–2.15)
Subtotal	143	115	14.1	0.97 (0.43–2.15)
Total	12	10		
Heterogeneity: Not applicable				
Test for overall effect: $Z = 0.09$ ($P = 0.93$)				
Total (patients)	1144	1128	100.0	0.66 (0.48–0.90)
Total (events)	84	129		
Heterogeneity: tau-square = 0.02; chi-square = 3.38; $P = 0.34$; $I^2 = 11\%$				
Test for overall effect: $Z = 2.60$ ($P = 0.009$)				
Test for subgroup differences: chi-square = 0.99; $P = 0.32$; $I^2 = 0\%$				



GDM = gestational diabetes mellitus; MH = Mantel–Haenszel; RCT = randomized, controlled trial.

Appendix Figure 3. Effect of treatment on outcomes of women with GDM: maternal weight gain.

Study, Year (Reference)	Treatment		No Treatment		Mean Difference IV, Random (95% CI)
	Mean (SD), *kg*	Total, *n*	Mean (SD), *kg*	Total, *n*	
RCTs					
Bonomo et al, 2005 (13)	13.1 (4.3)	150	12.6 (3.9)	150	0.50 (–0.43 to 1.43)
Crowther et al, 2005 (6)	8.1 (0.3)	490	9.8 (0.4)	510	–1.70 (–1.74 to –1.66)
Garner et al, 1997 (15)	12.54 (16.50)	149	13.37 (19.90)	150	–0.83 (–4.97 to 3.31)
Landon et al, 2009 (12)	2.8 (4.5)	476	5.0 (3.3)	455	–2.20 (–2.71 to –1.69)
Cohort studies					
Adams et al, 1998 (18)	12.26 (7.09)	373	14.24 (4.90)	16	–1.98 (–4.49 to 0.53)
Fassett et al, 2007 (16)	10.34 (8.8)	69	10.43 (5.49)	57	–0.09 (–2.61 to 2.43)



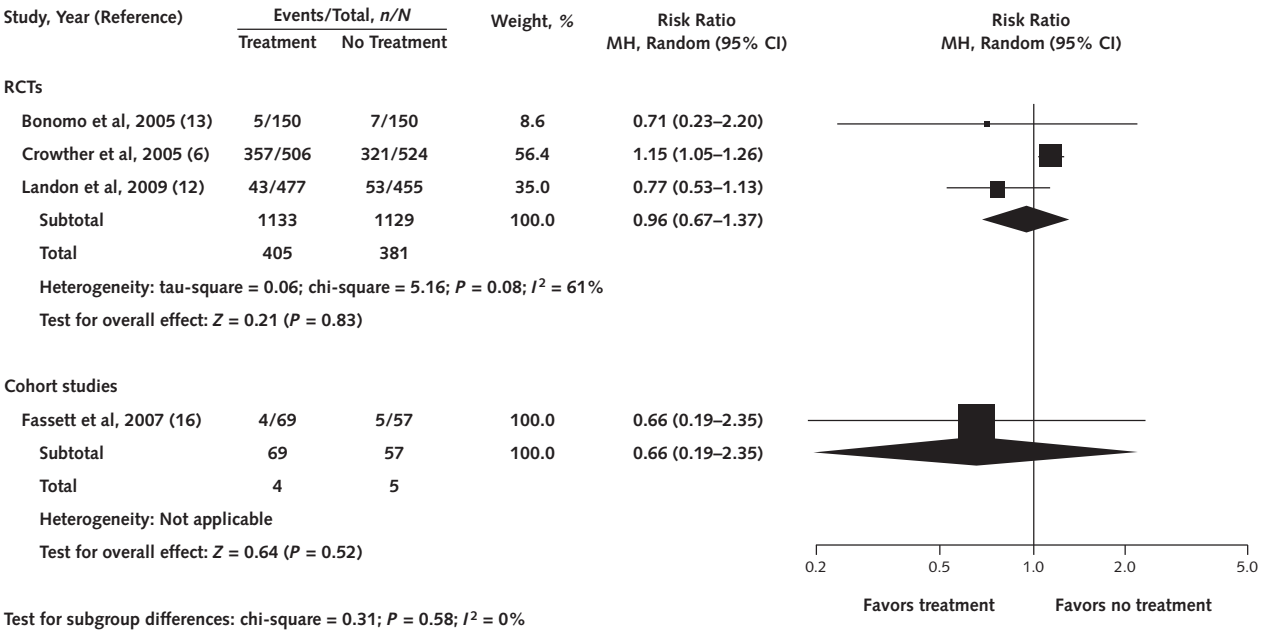
GDM = gestational diabetes mellitus; IV = inverse variance; RCT = randomized, controlled trial.

Appendix Table 3. Evidence Summary for Benefits and Harms of Treating GDM: Infant Outcomes

Outcome	Studies, *n*	Participants, *n*	Effect Estimate Risk Ratio (95% CI)*	I^2, %
Benefits				
Birthweight >4000 g				
RCT	5	2643	0.50 (0.35 to 0.71)†	50
Cohort	6	3426	Results not pooled because of substantial heterogeneity	86
Birthweight >4500 g				
RCT	1	299	1.01 (0.33 to 3.05)	NA
Cohort	2	647	0.29 (0.07 to 1.25)	69
Birthweight (actual)				
RCT	5	2670	−120.81 (−163.40 to −78.23)†‡	2
Cohort	2	515	Results not pooled because of substantial heterogeneity	77
Large-for-gestational-age neonate				
RCT	3	2261	0.56 (0.45 to 0.69)†	0
Cohort	4	2294	0.43 (0.27 to 0.70)†	58
Shoulder dystocia				
RCT	3	2044	0.42 (0.23 to 0.77)†	0
Cohort	4	3054	0.38 (0.19 to 0.78)†	20
Brachial plexus injury				
RCT	1	1000	0.15 (0.01 to 2.87)	NA
Cohort	1	389	0.04 (0.00 to 0.66)†	NA
Clavicular fracture				
RCT	1	1030	0.35 (0.01 to 8.45)	NA
Cohort	1	389	0.02 (0.00 to 0.22)†	NA
Birth trauma				
RCT	2	1230	0.48 (0.12 to 1.90)	NA
Cohort	1	389	0.02 (0.00 to 0.11)†	NA
Hyperbilirubinemia				
RCT	3	1467	0.79 (0.56 to 1.10)	0
Cohort	1	1665	0.26 (0.18 to 0.37)†	NA
Perinatal deaths				
RCT	3	2287	−0.00 (−0.01 to 0.01)§	66
Cohort	3	2928	−0.00 (−0.01 to 0.01)§	0
Respiratory complications				
RCT (RDS)	2	1962	1.05 (0.48 to 2.28)	58
Cohort (complications)	1	1665	0.16 (0.10 to 0.26)†	NA
Apgar score at 1 min				
RCT	1	83	−0.30 (−0.56 to −0.04)†‡	NA
Cohort	1	126	−1.00 (−1.54 to −0.46)†‡	NA
Apgar score at 5 min				
RCT	2	383	Results not pooled because of substantial heterogeneity	77
Cohort	1	126	0.00 (−0.27 to 0.27)‡	NA
Type 2 DM (long-term)				
RCT	1	89	1.88 (0.08 to 44.76)	NA
Impaired glucose tolerance				
RCT	1	89	5.63 (0.31 to 101.32)	44
BMI (long-term)				
>95th percentile	1	85	1.58 (0.66 to 3.79)	NA
>85th percentile	1	199	1.19 (0.78 to 1.82)	NA
Any BMI (2 studies above combined)	2	284	1.26 (0.86 to 1.84)	0
Harms				
Small-for-gestational-age neonate				
RCT	4	2345	1.10 (0.81 to 1.48)	0
Hypoglycemia				
RCT	4	2367	1.18 (0.92 to 1.52)	0
Cohort	2	2054	0.55 (0.10 to 2.97)	49
Admission to NICU				
RCT	3	2262	0.96 (0.67 to 1.37)	61
Cohort	1	126	0.66 (0.19 to 2.35)	NA

BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; NA = not applicable; NICU = neonatal intensive care unit; RCT = randomized, controlled trial; RDS = respiratory distress syndrome.
* Risk ratios unless otherwise specified.
† Statistically significant, with more benefits for the treated group.
‡ Mean difference.
§ Risk difference.

Appendix Figure 4. **Effect of treatment on outcomes of women with GDM: admission to the NICU.**



GDM = gestational diabetes mellitus; MH = Mantel–Haenszel; NICU = neonatal intensive care unit; RCT = randomized, controlled trial.