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Very tight vs. tight control: what should be the criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy? Evidence from randomized controlled trials

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Key words
Diabetes, pregnancy, diabetes mellitus, gestational diabetes mellitus, insulin, metformin

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Abstract

Introduction. There is inconclusive evidence from randomized controlled trials (RCTs) to support any specific criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy. Our objective was to analyze the criteria for dose adjustment of pharmacologic treatment for diabetes mellitus (DM) in pregnancy. *Material and methods.* Data sources: MEDLINE, OVID and Cochrane Library were searched from their inception to September 2017. Selection criteria included all trials of DM in pregnancy managed by oral hypoglycemic agents or insulin reporting criteria for pharmacologic therapy dose adjustment. RCTs in women with pregestational DM and gestational DM (GDM) were included. For each trial, data regarding glucose values used for pharmacologic therapy dose adjustment were extracted and carefully reviewed. *Results.* Of 51 RCTs on therapy for GDM or pregestational DM, 17 (4230 women) were included as they reported criteria for pharmacologic therapy dose adjustment. Most of them (88%, 15/17) included women with GDM only. For RCTs including women with GDM, 12/16 (75%) used the two-step approach, three (19%) the one-step approach and one (6%) either the one- or two-step approach. Regarding the type of initial therapy, 13 (77%) RCTs used different types and doses of insulin; nine (53%) used metformin; five (30%) used glyburide; and one (6%) used placebo. In most RCTs, glucose monitoring was assessed four times daily, i.e. fasting (all RCTs) and two hours (15 RCTs, 88%) after each of the three main meals – breakfast, lunch, and dinner. For fasting glucose target, all used a value <105 mg/dL; nine (53%) used 95 mg/dL as target. Of the 15 RCTs using a two-hour postprandial value as target, 11 (73%) had 120 mg/dL as cutoff. Regarding the criteria for pharmacologic therapy dose adjustment, we found six different criteria. The majority of RCTs (9/17, 53%) used either one or two values per week higher than the target values, of which two-thirds used only one value (35% of total), and one-third (18% of total) two values. Five RCTs (29%) used >50%, one (6%) >30%, and one (6%) >20% of the values higher than the target value; one (6%) used the appearance of glycosuria. *Conclusions.* When evaluating RCTs which included criteria for pharmacologic GDM therapy dose adjustment, the most common criterion for diagnosis was the two-step test, and the most common used therapies were insulin and metformin. Regarding glucose monitoring, the most common frequency was four times per day, fasting and two hours after each

main meal, using as target glucose values 95 and 120 mg/dL, respectively. Importantly, we found six different criteria for pharmacologic GDM therapy dose adjustment, with the majority using very tight criteria of either one or two values per week higher than the target values, of which two-thirds used only one value, and one-third used two values.

Abbreviations: DM, diabetes mellitus; GMD, gestational diabetes mellitus; NPH, neutral protamine Hagedorn; RCT, randomized controlled trial.

Introduction

Carbohydrate disorders in pregnancy, including gestational diabetes mellitus (GMD) and pregestational diabetes mellitus (DM), are the most common morbidities complicating pregnancy, with short- and long-term consequences to mothers, fetuses, and newborns. It has been estimated that up to 6–7% or more of all pregnancies are complicated by DM in pregnancy (1–52). The latest reports from the International Diabetes Federation estimate that, worldwide, approximately one in seven births in 2015 were complicated by some form of hyperglycemia during pregnancy (53).

Management for women with carbohydrate disorders in pregnancy includes diet, physical activity, oral hypoglycemic agents or insulin as needed. The management of those women aims to achieve the best possible glycemic control, with normal or near normal glucose values while avoiding hypoglycemia. This management is effective in reducing maternal and neonatal morbidity and mortality (3,9,24,31,38).

Nevertheless, the optimal schedule, frequency and timing of glucose monitoring remains disputable, as are the glycemic metabolic goals. Moreover, there is no evidence from randomized controlled trials (RCTs) to support any specific criteria for pharmacologic therapy dose adjustment.

Thus, the aim of this review was to analyze the criteria for dose adjustment of pharmacologic treatment for DM in pregnancy through a systematic review of RCTs.

Material and methods

Search strategy

This review was performed according to a protocol recommended for systematic review (54). The review protocol was designed *a priori* to define methods for collecting, extracting, and analyzing data. The research was conducted with the use of MEDLINE, OVID, and Cochrane Library as electronic databases. The trials were identified with the use of a combination of the following text words: "gestational diabetes", "GDM", "diabetes in pregnancy", "therapy", "treatment", "insulin", "oral hypoglycemic", "metformin", "trial" and "randomized" from the inception of each database to September 2017. Review of articles also included the abstracts of all references that were retrieved from the search. No restrictions on language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (C.C., G.S.). Differences were discussed with a third reviewer (V.B.).

Study selection

Selection criteria included all RCTs of diabetes in pregnancy managed by oral hypoglycemic agents or insulin. Trials in women with pregestational DM and trials in women with GDM were included. Trials in women treated only with exercise or diet at the time of randomization were excluded. Trials in women with impaired glucose tolerance and trials not reporting criteria for dose adjustment of pharmacologic treatment were also excluded. We analyzed retrospective and prospective studies.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Seven domains related to risk of bias were assessed in each included trial since

Key message

The majority of trials used very tight criteria of either one or two values per week higher than the target values for pharmacologic diabetes therapy dose adjustment.

there is evidence that these issues are associated with biased estimates of treatment effect: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias (54).

Outcomes and data extraction

For each trial, data regarding glucose values used for pharmacologic therapy dose modification were extracted and carefully reviewed. We also planned to review the type of screening, type of initial therapy (for example insulin vs. oral hypoglycemic agent), frequency of glucose monitoring, and target glucose values. The types of DM screening were defined as one step, i.e. 75 g two-hour glucose load, and two-step, i.e. 50 g one-hour glucose load, followed if abnormal by a 100 g three-hour glucose load test.

The primary outcome was the incidence of macrosomia, as defined by the original trials (13 RCTs defined macrosomia as a birthweight >4000 g, the other four RCTs used a birthweight >90th percentile).

The secondary outcomes were cesarean delivery, maternal hypoglycemia and neonatal hypoglycemia. Primary and secondary outcomes were assessed for each criteria used by the original trials, for example one or two values higher than the target values, a cutoff based on percentage of abnormal glucose values, ultrasound criteria, or symptoms.

Primary and secondary outcomes were also assessed in sensitivity analyses according to type of therapy, i.e. oral hypoglycemic agent or insulin.

We also aimed to compare a policy of very tight (i.e. more restrictive) vs. tight (i.e. less restrictive) control for diabetes in pregnancy to assess the best criteria for pharmacologic therapy dose adjustment, using indirect meta-analysis.

We considered a policy of very tight control to use the following criteria:

- one or two values higher than the target values (i.e. intervention group)

We considered a policy of tight control to use the following criteria:

- >50% higher than the target values (i.e. comparison group)

Other criteria (for example >20% or >30% higher, ultrasound criteria, symptoms) were not included in the indirect meta-analysis.

Statistical analyses

To show robustness of our review, we aimed to perform a meta-analysis for the primary outcome (i.e. incidence of macrosomia) (54,55). To complete such analyses, we performed an adjusted indirect meta-analysis to compare a policy of very tight control with a policy of tight control for diabetes in pregnancy, as previously described (56). The adjusted indirect comparison meta-analysis was performed according to the most widely applied indirect comparison method by Bucher et al. In this method, the randomization of each trial is maintained, and the direct comparison is used to yield an indirect comparison (55,56). In the indirect comparison, meta-analysis, data were combined in a two-stage approach in which outcomes were analyzed in their original study and then summary statistics combined using standard summary data meta-analysis techniques to give an overall measure of effect (55,56).

The data analysis of the indirect meta-analysis was completed independently by two authors (C.C., G.S.) using REVIEW MANAGER v. 5.3 (The Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion with a third reviewer (V.B.) (54).

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A 2 × 2 table was assessed for relative risk (54).

Indirect meta-analysis was performed using the random effects model of DerSimonian & Laird (54) to produce summary treatment effects in terms of relative risk with 95% confidence interval (CI).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (57). Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42016053067).

Results

We identified 51 RCTs on therapy for GDM or pregestational diabetes, and assessed these for eligibility (Figure 1) (1–51). Of them, 34 were excluded, and therefore 17 including 4230 women were included (1–3,5–14,16–19). Figure 2 shows the risk of bias of the included trials. Most of them had low risk of bias in selection, attrition, and reporting.

No trials compared differing criteria for pharmacologic therapy dose adjustment. Most of them (88%, 15/17) included women with GDM only (1–3,5,7–13,16–19).

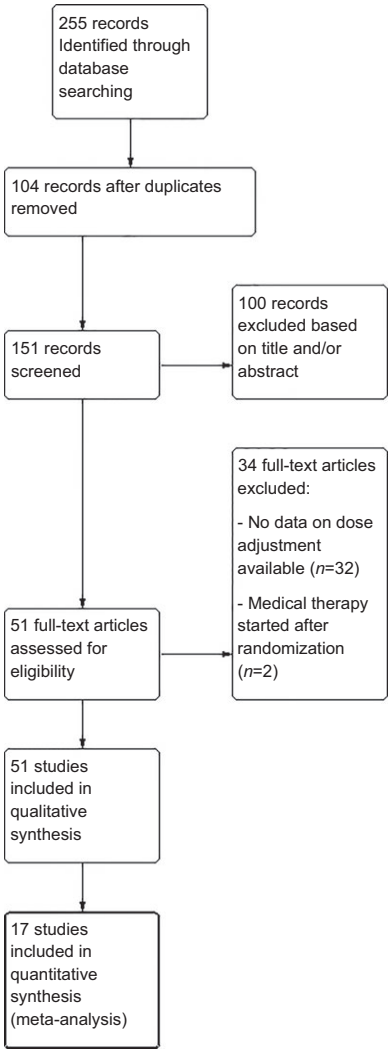

Figure 1. Flow diagram of studies identified in the systematic review. PRISMA template (Preferred Reporting Item for Systematic Reviews and Meta-analyses).

Refuerzo et al. (14) included women with type II pregestational diabetes only. Hickman et al. (6) included women with both GDM and type II pregestational diabetes. For RCTs including women with GDM, 12/16 (75%) used the two-step test (2,5–13,18,19) and three trials the one-step test (1,3,16). Spaulonci et al. (17) used either the one- or two-step approach (17). Sample size ranged from 21(14) to 1000 women (3). Regarding the type of initial therapy, 13 (77%) trials used different types and doses of insulin (NPH, regular short-acting, lispro) (1,3,6–10,12–14,17–19), nine (53%) trials tested metformin (1,5,6,10–12,14,16,17), five (30%) trials tested glyburide (2,5,8,11,18), and one (6%) trial used placebo (2) (Table 1).

Table 2 shows the management of women included in trials. In most of them (14 RCTs, 82%) glucose monitoring was assessed four times daily, i.e. fasting and either one or two hours after each of the three main meals – breakfast, lunch, and dinner (1–3,5,6,8,10–14,16,18,19); two (12%) trials assessed four to seven times daily, i.e. fasting, preprandial before lunch and dinner, one and two hours after each main meal – breakfast, lunch, and dinner (7,17). Only one (6%) trial carried out monitoring nine times a day, i.e. fasting and one and two hours after each main meal – breakfast, lunch, and dinner (9). All 17 RCTs used fasting glucose as a target, and 100% had a value <105 mg/dL; nine (53%) used 95 mg/dL as target. Of the 15 RCTs using the two-hour postprandial value as target, 11 (73%) had 120 mg/dL as cutoff. Of the four RCTs using a one-hour postprandial value as target, two (50%) had 120 mg/dL as cutoff, and the others used 150 mg/dL (Table 2). One RCT also considered the Hb1Ac value (18).

Regarding the glucose values used for dose modification:

- Nine trials (53%) used one or two values higher than the target values (3,5,7,10–12,16,18,19) (i.e. very tight control group); 6/17 (35%) used one value higher than target values (3,5,7,10,18,19), and 3/17 (18%) used two values higher than target values (11,12,16). Of these nine trials, five (56%) used their criteria over 1 week (5,10,12,16,19), two over 2 weeks (3,11), one over either one or 2 weeks (7), and one over 3 days (18).
- Five trials (29%) used >50% of the values higher than the target values (2,6,8,9,14) (i.e. tight control group).
- One trial (6%) used >30% of the values higher than the target values (17).
- One trial (6%) used >20% of the values higher than the target values (1).
- One trial (6%) used appearance of glycosuria (13).

Table 3 shows individual data for the primary and secondary outcomes in the overall analysis. Indirect meta-analysis showed no statistically significant difference in the incidence of macrosomia comparing a very tight with a tight policy (8.3 vs. 7.0%; relative risk 1.20, 95% CI 0.87–1.64). Tables 4 and 5 show primary and secondary outcomes in sensitivity analyses in insulin- and metformin-only trials.

Discussion

This systematic review from 17 RCTs, including 4230 women, evaluated the criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy. We failed to find any RCT comparing differing criteria for pharmacologic therapy dose adjustment. The majority of the 17 RCTs included women with GDM (88%); used the two-

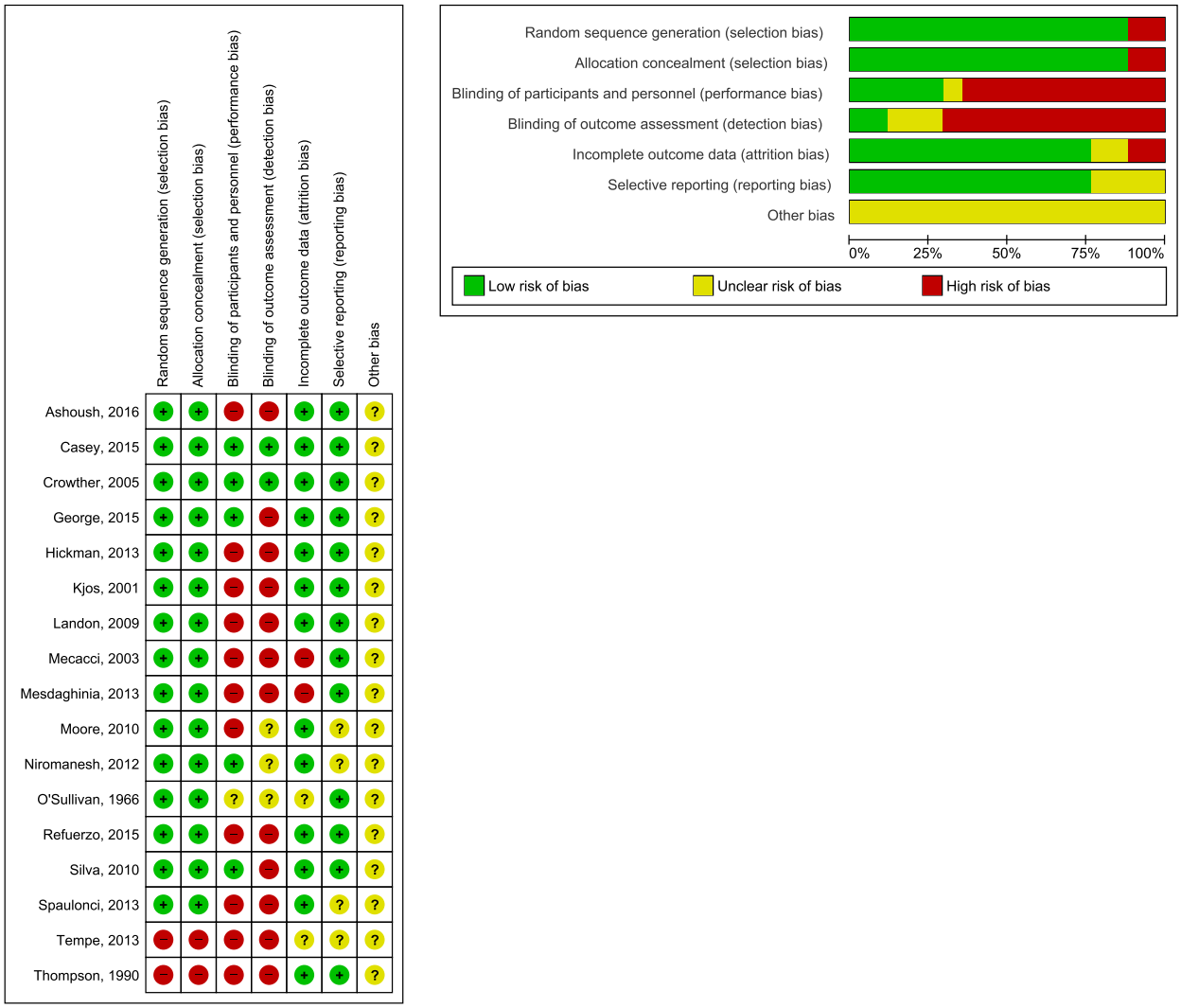

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies. [Color figure can be viewed at wileyonlinelibrary.com].

step test (with 100 g glucose load as second step) for GDM diagnosis (75%); insulin (77%) and metformin (53%) as therapies; monitored glucose values four times per day, i.e. fasting and usually two hours after each main meal – breakfast, lunch and dinner (82%); and used as targets a fasting glucose target of 95 mg/dL (53%) and two hours of 120 mg/dL (65%). As described in a review of the Endocrine Society from 2013, a fasting glucose target of <90 mg/dL is associated with a lower risk of macrosomia and other outcomes in women with gestational diabetes, whereas this is unclear in pregestational diabetes (58). Moreover, therapy adjustment based on the results of postprandial, rather than preprandial, blood glucose values in women with GDM improves glycemic control and decreases the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery (59).

Regarding our main aim, i.e. evaluating criteria for pharmacologic DM therapy dose adjustment, we found six different criteria. The majority of RCTs (53%) used either one or two values per week higher than the target values, of which two-thirds used only one value (35% of total), and one-third (18% of total) two values.

There are at least 11 variables regarding management of GDM which could affect the outcomes, macrosomia etc. These include:

Table 1. Characteristics of the included trials.

	Origin	Type of diabetes	Sample size[a]	Diagnostic test used[b]	Intervention: daily starting dose	Control: daily starting dose
O'Sullivan, 1966 (13)	USA	GDM	615 (307/308)	Two-step	Insulin (NPH): 10 IU	Diet and exercise only
Thompson, 1990 (19)	USA	GDM	95 (45/50)	Two-step	Insulin (NPH + regular): 10 IU + 10 IU	Diet and exercise only
Kjos, 2001(7)	USA	GDM	98 (49/49)	Two-step	Insulin (NPH + regular): 0.8, 0.9, 1.0, 1.1, or 1.2 IU/kg if any ultrasound examination >70th percentile for GA	Insulin (NPH + regular): 0.8, 0.9, 1.0, 1.1, or 1.2 IU/kg
Mecacci, 2003 (9)	Italy	GDM	49 (25/24)	Two-step	Insulin (lispro): 1 IU/10 g of carbohydrates in the meal, 3 times a day	Insulin (regular short acting): 1 U/10 g of carbohydrates in the meal, 3 times a day
Crowther, 2005 (3)	Australia	GDM	1000 (490/510)	One-step	Insulin: as needed	Diet and exercise only
Landon, 2009(8)	USA	GDM	958 (485/473)	Two-step	Insulin: as needed	Diet and exercise only
Moore, 2010(11)	USA	GDM	149 (74/75)	Two-step	Glyburide: 2.5 mg twice a day	Metformin: 500 mg
Silva, 2010(16)	Brazil	GDM	72 (40/32)	One-step	Glyburide: 2.5 mg twice a day	Metformin: 500 mg twice a day
Niromanesh, 2012(12)	Iran	GDM	160 (80/80)	Two-step	Metformin: 500 mg twice a day	Insulin (NPH): 0.2 IU/kg
Hickman, 2013 (6)	USA	PDM II + GDM	28 (14/14)	Two-step	Metformin: 500 mg once or twice a day	Insulin (NPH + regular): 0.7 IU/kg/day
Mesdaghinia, 2013 (10)	Iran	GDM	200 (100/100)	Two-step	Metformin: 500 mg	Insulin (NPH + regular): 0.5 IU/kg/day
Spaulonci, 2013 (17)	Brazil	GDM	92 (46/46)	One or two step	Metformin: 850 mg twice a day	Insulin (NPH): 0.4 IU/kg/day
Tempe, 2013 (18)	India	GDM	64 (32/32)	Two-step	Glyburide: 2.5 mg	Insulin (regular): 4 IU regular before each major meal
Casey, 2015 (2)	USA	GDM	375 (189/186)	Two-step	Glyburide: 2.5 mg	Placebo
George, 2015 (5)	India	GDM	159 (79/80)	Two-step	Metformin: 500 mg	Glyburide: 2.5 mg
Refuerzo, 2015 (14)	USA	PDM II	21 (8/13)	–	Metformin: 500 mg	Insulin (NPH + regular): I tr 0.7 IU/kg/day, II tr 0.8 IU/kg/day, III tr 0.9–1.0 IU/kg/day
Ashoush, 2016 (1)	Egypt	GDM	95 (47/48)	One-step	Metformin: 1000 mg	Insulin (NPH + regular): 0.7 IU/kg/day
Total		–	4230	–	–	–

GDM, gestational diabetes mellitus; NPH, neutral protamine Hagedorn; PDM II, pregestational diabetes mellitus type II; tr, trimester.

[a]Data are presented as total number (number in the intervention group/number in the control group).

[b]One-step, i.e. 75 g two-hour glucose load; Two-step, i.e. 50 g one-hour glucose load, followed if abnormal by a 100 g three-hour glucose load test.

Table 2. Management of women included in the trials.

	Glucose monitoring	Target value for glycemic control	Glucose values used for dose modification based on target values	Intervention: dose modification	Control: dose modification
O'Sulliva, 1966 (13)	4 times daily[a]	F: <5.5 mmol/L (100 mg/dL); 1 h: <8.3 mmol/L (150 mg/dL); 2 h: <5.5 mmol/L (100 mg/dL)	Appearance of glycosuria	Insulin: as needed	Diet and exercise
Thompson, 1990 (19)	4 times daily[b]	F: <5.9 mmol/L (105 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	• one F higher in 1 week or • two 2 h higher in 1 week	Insulin: as needed	Diet and exercise, insulin added if needed
Kjos, 2001 (7)	4–7 times daily[b]	Intervention group: F: <4.4 mmol/L (80 mg/dL); 2 h: <6.1 mmol/L (110 mg/dL) Control group: F: <5.0 mmol/L (90 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	• 1 F > 6.7 mmol/L (120 mg/dL) in 1–2 weeks (after-before 34 weeks); or • >50% higher in 1–2 weeks (after-before 34 weeks)	Insulin: as needed	Insulin: as needed
Mecacci, 2003 (9)	9 times daily[c]	F: <5.0 mmol/L (90 mg/dL); 1 h: <6.7 mmol/L (120 mg/dL)	≥50% higher in 1 week	Insulin lispro: increase of 20–30% until the achievement of targets	Regular short acting insulin: increase of 20–30% until the achievement of targets
Crowther, 2005 (3)	4 times daily[b]	F: 3.5–5.5 mmol/L (63–99 mg/dL); 2 h: <7.0 mmol/L (126 mg/dL)	• two values higher during 2-week period ≤35 weeks; or • 1 postprandial value >8.0 mmol/L (144 mg/dL) >35 weeks; or • one value ≥9.0 mmol/L (162 mg/dL) during 2-week period	Insulin: as needed	Diet and exercise
Landon, 2009 (8)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	Intervention group: >50% higher in 2 weeks	Insulin: as needed	Diet and exercise
Moore, 2010 (11)	4 times daily[b]	F: <5.9 mmol/L (105 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	≥2 values in the same meal exceed targets by ≥10 mg/dL for 2 weeks	Glyburide: increased till maximum dose of 20 mg/day (10 mg twice daily); treatment failures started on insulin and oral medication discontinued	Metformin: increased till maximum dose of 2 g/day; treatment failures started on insulin and oral medication discontinued
Silva, 2010 (16)	4 times daily[d]	F: <5.0 mmol/L (90 mg/dL); 1 h: <6.7 mmol/L (120 mg/dL)	≥ two values in 1 week	Glyburide: increased by 2.5–5 mg each week, maximum 20 mg/day, switch to insulin if needed	Metformin: increased by 500–1000 mg each week, maximum 2500 mg/day, switch to insulin if needed

Table 2. Continued

	Glucose monitoring	Target value for glycemic control	Glucose values used for dose modification based on target values	Intervention: dose modification	Control: dose modification
Niromanesh, 2012 (12)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	• two F higher in 1 week or • one F and one 2 h higher in 1 week or • two 2 h higher in 1 week	Metformin: increased by 500–1000 mg every 1–2 weeks, maximum daily dose of 2500 mg; insulin added if needed	Insulin NPH: if F high, given before bedtime, if postprandial high, short-acting insulin before meals based on postprandial glucose level (1 IU/10 mg/dL over target value), and if both fasting and postprandial were high it was started at a total dose of 0.7 units/kg
Hickman, 2013(6)	4 times daily[d]	F: <5.3 mmol/L (95 mg/dL); 1 h: <7.0 mmol/L (126 mg/dL)	• ≥50% F in 2 weeks or • ≥50% 1 h postprandial >7.2 mmol/L (130 mg/dL) in 2 weeks	Metformin: maximum 2500 mg daily; added insulin if needed	Insulin (regular + NPH): as needed
Mesdaghinia, 2013 (10)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	one value in one week	Metformin: up to 2500 mg/day	Insulin (NPH + regular): as any 10 mg/dL of glucose level more than target, 1 IU of NPH or regular insulin added to initial insulin dose
Spaulonci, 2013 (17)	4–7 times daily[e]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	>30% values higher in 1 week	Metformin: raised the next week to 2550 mg/day (850 mg 3 times a day); insulin added, if needed	Insulin NPH: as needed; regular insulin was added if needed
Tempe, 2013 (18)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL); Hb1Ac: <6.5 g/dL	one value higher every 3 days	Glyburide: add 2.5 mg every 3 days till targets reached. Maximum dose of 20 mg/day. If not enough, switch to insulin	Insulin: increased by 4 IU every 3 days till targets reached in all meals
Casey, 2015 (2)	4 times daily (only intervention group)[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	>50% higher in 1 week	Glyburide: till 20 mg daily; increase by 5 mg daily	Placebo
George, 2015 (5)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	• one F ≥ 6.1 mmol/L in 1 week (110 mg/dL) or • one postprandial value ≥8.3 mmol/L in 1 week (150 mg/dL) or • > two values higher in 1 week	Metformin: increased 500 mg weekly to a maximum of 2500 mg/day allowing a total of 2–3 weeks; after that, insulin was added or women were switched over completely to insulin	Glyburide: increased once a week, maximum total dose of 15 mg/day in 2–3 weeks; after that, insulin was added or women were switched over completely to insulin
Refuerzo, 2015 (14)	4 times daily[b]	F: <5.3 mmol/L (95 mg/dL); 2 h: <6.7 mmol/L (120 mg/dL)	Metformin: >50% higher in 1 week; Insulin: criteria for dose modification not reported	Metformin: increased to 500 mg twice a day, maximum dose of 2500 mg/day; added insulin if needed	Insulin (regular + NPH): as needed

Table 2. Continued

	Glucose monitoring	Target value for glycemic control	Glucose values used for dose modification based on target values	Intervention: dose modification	Control: dose modification
Ashoush, 2016 (1)	4 times daily[b]	F: <5.5 mmol/L (100 mg/dL); 2 h: <7.8 mmol/L (140 mg/dL)	>20% higher in 1–2 weeks	Metformin: increased by 500–850 mg every 1–2 weeks, maximum daily dose of 2500 mg. Insulin was added, with reduction of the daily dose of metformin to 1000 mg, if needed after 1 week on maximum metformin dose	Insulin (regular + NPH): increments of 1 IU/10 mg glucose higher than the desired cut-off; short-acting insulin was added whenever needed

F, fasting; GA, gestational age; NPH, neutral protamine Hagedorn.
[a]Fasting value and after each main meal – breakfast, lunch, and dinner – (either one or two hours).
[b]Fasting and two hours after each main meal – breakfast, lunch, and dinner.
[c]Fasting, preprandial before lunch and dinner, one and two hours after each main meal – breakfast, lunch, and dinner.
[d]Fasting and one hour after each main meal – breakfast, lunch, and dinner.
[e]Intervention group: at fasting, two hours after each main meal – breakfast, lunch, and dinner. Control group: at fasting, two hours after breakfast, one hour before lunch, two hours after lunch, one hour before dinner, two hours after dinner and at 03:00 hours in the morning.

- indications for screening (who)
- timing of screening (when)
- type of screening (one- vs. two-step) (how) (60,61)
- criteria for diagnosis
- criteria to start therapy using diet alone
- type of initial therapy (for example insulin vs. oral hypoglycemic agent)
- dose and frequency of initial therapy
- frequency of glucose monitoring
- target glucose values
- criteria for pharmacologic therapy dose adjustment
- criteria for adding or switching pharmacologic therapy

While very tight (one or two abnormal target vales) vs. tight criteria for pharmacologic therapy dose adjustment did not seem to affect outcomes (Table 3), it is impossible to really assess this comparison given the other 10 variables listed above, which could not be controlled for.

Strengths of the study include the use of the most rigorous methodology for an indirect meta-analysis of RCTs. We are not aware of any other meta-analysis evaluating a policy of very tight vs. tight glycemic control to assess the criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy. The variables which may affect pregnancy outcomes in GDM management were carefully reviewed. The most common management strategies for GDM used in RCTs were identified.

There are several limitations in our study. Four RCTs used a different definition of macrosomia. No trials comparing a policy of very tight vs. tight glycemic control to assess the criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy could be identified. Therefore, a standard meta-analysis was not feasible. An indirect meta-analysis has wide statistically inconsistency compared with standard meta-analysis. In addition, the risk of overestimation could be high when the indirect comparison of interest relies on only a few trials. The clinical heterogeneity within the trials was very high. Trials included used different protocol management, different diagnostic tests, different sample size, different initial therapy, different glucose monitoring, different target glucose values. Moreover, not all RCTs considered the same outcomes.

Finally, the majority of included RCTs considered neutral protamine Hagedorn (NPH) and regular insulin to be the only options. Nowadays, the use of insulin analogues, in particular the rapid-acting bolus analogues aspart and lispro, achieve postprandial targets with less hypoglycemia compared with regular insulin, with similar fetal outcomes, and.the long-acting insulin analogues glargine and detemir appear safe with similar maternal/fetal outcomes compared with NPH (62). We included only trials of diabetes in pregnancy managed by oral

Table 3. Primary and secondary outcomes.

Criteria for dose adjustment	Number of studies included	Macrosomia	Cesarean delivery	Maternal hypoglycemia	Neonatal hypoglycemia
Very tight control group	9 (3,5,7,10–12,16,18,19)	120/1,442 (8.3%)	375/1,162 (32.3%)	8/342 (2.3%)	108/1,442 (7.5%)
Tight control group	5 (2,6,8,9,14)	65/922 (7.0%)	288/921 (31.3%)	8/28 (28.6%)	68/756 (9.0%)
>30% of the values	1 (17)	3/92 (3.3%)	37/92 (40.2%)	Not reported	16/92 (17.4%)
>20% of the values	1 (1)	7/95 (7.4%)	46/95 (48.4%)	Not reported	13/95 (13.7%)
Appearance of glycosuria	1 (13)	13/305 (4.3%)	Not reported	Not reported	Not reported

Table 4. Primary and secondary outcomes in only insulin trials.

Criteria for dose adjustment	Number of studies included	Macrosomia	Cesarean delivery	Maternal hypoglycemia	Neonatal hypoglycemia
Very tight control group	6 (3,7,10,12,18,19)	85/850 (10.0%)	220/732 (30.1%)	0/34	67/850 (7.9%)
Tight control group	3 (6,8,9)	34/539 (6.3%)	147/538 (27.3%)	7/14 (50.0%)	62/381 (16.3%)
>30% of the values	1 (17)	3/46 (6.5%)	20/46 (43.5%)	Not reported	10/46 (21.7%)
>20% of the values	1 (1)	2/47 (4.3%)	22/47 (46.8%)	Not reported	6/47 (12.8%)
Appearance of glycosuria	1 (13)	13/305 (4.3%)	Not reported	Not reported	Not reported

Table 5. Primary and secondary outcomes in only metformin trials.

Criteria for dose adjustment	Number of studies included	Macrosomia	Cesarean delivery	Maternal hypoglycemia	Neonatal hypoglycemia
Very tight control group	5 (5,10–12,16)	21/366 (5.7%)	98/266 (36.8%)	5/154 (3.2%)	20/366 (5.5%)
Tight control group	2 (6,14)	0/8	4/8 (50.0%)	1/14 (7.1%)	Not reported
>30% of the values	1 (17)	0/46	17/46 (37.0%)	Not reported	6/46 (13.0%)
>20% of the values	1 (1)	5/48 (10.4%)	24/48 (50.0%)	Not reported	7/48 (14.6%)
Appearance of glycosuria	–	–	–	–	–

hypoglycemic agents or insulin. Trials in women treated only with exercise or diet at the time of randomization were excluded. Exercise in pregnancy has been shown to reduce the risk of diabetes in both normal-weight and overweight and obese women (63–66), as well as to improve pregnancy outcome in those with GDM (67).

When evaluating RCTs which included criteria for pharmacologic GDM therapy dose adjustment, the most common criteria for GDM diagnosis was the two-step test, and the most common therapies used were insulin and metformin. Regarding glucose monitoring, the most common frequency was four times per day, i.e. fasting and after each main meal, using a fasting level of 95 mg/dL and a two-hour level of 120 mg/dL as targets. Importantly, we found six different criteria for pharmacologic GDM therapy dose adjustment, with the majority using very tight criteria of either one or two values per week higher than the target values, of which two-thirds used only one value (35% of total), and one-third (18% of total) two values. While very tight (one or two abnormal target vales) vs. tight criteria for pharmacologic therapy dose adjustment did not seem to affect outcomes (Table 3), it is impossible to really assess this comparison given no head-to-head RCTs with this study design. Future well-designed, properly powered RCTs are needed to answer this important clinical question.

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