# Very tight versus tight control: which should be the criteria for pharmacologic therapy dose adjustment in diabetes in pregnancy? Evidence from randomized controlled trials

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## ABSTRACT

- **Background:** There is inconclusive evidence from randomized controlled trials (RCTs) to support any specific criteria for pharmacologic therapy dose adjustment in diabetes (DM) in pregnancy.
- **Objective:** To analyze the criteria for dose adjustment of pharmacologic treatment for DM in pregnancy.
- **Data sources:** MEDLINE, OVID and Cochrane Library were searched from their inception to November 2016.
- **Methods of study selection:** 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 (4,230 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; 3 (19%) used the one step approach; 1 (6%) used either the one or two step approach. Regarding the type of initial therapy, 13 (77%) RCTs used different types and doses of insulin; 9 (53%) used metformin; 4 (24%) used glyburide; 1 (6%) used glybenclamide; and 1 (6%) used placebo. In most RCTs glucose monitoring was assessed four times daily, i.e. fasting (all RCTs) and 2 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; 9 (53%) used 95 mg/dL as target. Of the 15 RCTs using 2 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 1 or 2 values per week higher than the target values, of which two thirds used only 1 value (35% of total), and one third (18% of total) 2 values. Five RCTs (29%) used >50%, 1 (6%) used >30%, and 1 (6%) used >20% of the values higher than the target value; while 1 (6%) used 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 **insulin and metformin**. Regarding glucose monitoring, the most common frequency was **four times per day, fasting and 2 hours after each main meal, using as target glucose values 95mg/dL and 120mg/dL**, respectively. Importantly, we found six different criteria for pharmacologic GDM therapy dose adjustment, with the majority using **very tight criteria of either 1 or 2 values per week higher than the target values**, of which two thirds used only 1 value, and one third 2 values.

## RESULTS

**Table 1**: Management of women included in the RCTs.

| | Glucose monitoring | Target value for glycemic control | Glucose values used for dose modification based on target values | Intervention: dose modification | Control: dose modification |
|---|---|---|---|---|---|
| O'Sullivan, 1966 | 4 times daily[A] | F: <5.5 mmol/l (100 mg/dL); 1h: <8.3 mmol/l (150 mg/dL); 2h: <5.5 mmol/l (100 mg/dL) | Appearance of glycosuria | Insulin: as needed | Diet and exercise |
| Thompson, 1990 | 4 times daily[B] | F: <5.9 mmol/l (105 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | 1 F higher in 1 week or 2 2h higher in 1 week | Insulin: as needed | Diet and exercise, insulin added if needed |
| Kjos, 2001 | 4-7 times daily[B] | Intervention group: F: <4.4 mmol/l (80 mg/dL); 2h: <6.1 mmol/l (110 mg/dL) Control group: F: <5.0 mmol/l (90 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | 1 F > 6.7 mmol/L (120 mg/dL) in 1-2 weeks; or >50% higher in 1-2 weeks | Insulin: as needed | Insulin: as needed |
| Mecacci, 2003 | 9 times daily[C] | F: <5.0 mmol/l (90 mg/dL); 1h: <6.7 mmol/l (120 mg/dL) | ≥50% higher in 1 week | Insulin Lispro: increase of 20–30% until achievement of targets | Regular short acting insulin: increase of 20–30% until achievement of targets |
| Crowther, 2005 | 4 times daily[B] | F: 3.5-5.5 mmol/l (63-99 mg/dL); 2h: <7.0 mmol/l (126 mg/dL) | 2 values higher during 2-week period ≤35 weeks; or 1 postprandial value >8.0 mmol/l (144 mg/dl) >35 weeks; or 1 value ≥9.0 mmol/l (162 mg/dl) during 2-week period | Insulin: as needed | Diet and exercise |
| Landon, 2009 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | Intervention group: > 50% higher in 2 weeks | Insulin: as needed | Diet and exercise |
| Moore, 2010 | 4 times daily[B] | F: <5.9 mmol/l (105 mg/dL); 2h: <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 of 20 mg/day (10 mg twice daily); treatment failures started on insulin and oral medication discontinued | Metformin: increased till maximum of 2 g/day; treatment failures started on insulin and oral medication discontinued |
| Silva, 2010 | 4 times daily[D] | F: <5.0 mmol/l (90 mg/dL); 1h: <6.7 mmol/l (120 mg/dL) | ≥ 2 values in one week | Glyburide: increased by 2.5 to 5 mg each week, maximum 20 mg/day, switch to insulin if needed | Metformin: increased by 500 to 1000 mg each week, maximum 2500 mg/day, switch to insulin if needed |
| Niromanesh, 2012 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | 2 F higher in 1 week or 1 F and 1 2h higher in 1 week or 2 2h 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 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 | 4 times daily[D] | F: <5.3 mmol/l (95 mg/dL); 1h: <7.0 mmol/l (126 mg/dL) | ≥50% F in 2 weeks or ≥50% 1h 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 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | 1 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 | 4-7 times daily[E] | F: <5.3 mmol/l (95 mg/dL); 2h: <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 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL); Hb1Ac: <6.5 g/dL | 1 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 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <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 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL) | 1 F ≥6.1 mmol/l in 1 week (110 mg/dL) or 1 postprandial value ≥8.3 mmol/l in 1 week (150 mg/dL) or > 2 values higher in 1 week | Metformin: increased 500 mg weekly to a maximum of 2500 mg a day allowing a total of 2–3 weeks; after that, insulin was added or women were switched over completely to insulin | Glibenclamide: 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 | 4 times daily[B] | F: <5.3 mmol/l (95 mg/dL); 2h: <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 2,500 mg/day; added insulin if needed | Insulin (regular + NPH): as needed |
| Ashoush, 2016 | 4 times daily[B] | F: <5.5 mmol/l (100 mg/dL); 2h: <7.8 mmol/l (140 mg/dL) | >20% higher in 1-2 weeks | Metformin: increased by 500-850 mg every 1-2 weeks, maximum 2500 mg daily. 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 |

A Fasting value and after each main meal – breakfast, lunch, and dinner - (either 1 or 2 hours). B Fasting and 2 hours after each main meal – breakfast, lunch, and dinner. C Fasting, preprandial before lunch and dinner, 1 and 2 hours after each main meal – breakfast, lunch, and dinner. D Fasting and 1 hour after each main meal – breakfast, lunch, and dinner. E Intervention group: at fasting, 2 hours after each main meal – breakfast, lunch, and dinner. Control group: at fasting, 2 hours after breakfast, 1hour before lunch, 2 hours after lunch, 1 hour before dinner, 2 hours after dinner and at 3am in the morning.
F, fasting; 2h, 2 hours postprandial, BW, body weight

**Table 2:** Primary and secondary outcomes.

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