Which criteria should be used for starting pharmacologic therapy in gestational diabetes in pregnancy? Evidence from randomized controlled trials

Claudia Caissutti MD,[1] Gabriele Saccone MD,[2] Vincenzo Berghella MD[3]

[1]Department of Experimental Clinical and Medical Science, DISM, Clinic of Obstetrics and Gynecology, University of Udine, Udine, Italy; [2]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; [3]Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
E-mail: vincenzo.berghella@jefferson.edu

ABSTRACT

- **Background:** There is inconclusive evidence to support any specific criteria for starting pharmacologic therapy after initial diet therapy in patients with gestational diabetes mellitus (GDM).
- **Objective:** To analyze the criteria for starting pharmacologic treatment for patients with GDM.
- **Data sources:** MEDLINE, OVID and Cochrane Library were searched from their inception to December 2016.
- **Methods of study selection:** Selection criteria included all randomized controlled trials (RCTs) of GDM managed initially by diet and exercise reporting criteria for starting pharmacologic therapy with either oral hypoglycemic agents or insulin. RCTs in women with pregestational diabetes were excluded. For each trial, data regarding glucose values used for starting pharmacologic therapy were extracted and carefully reviewed.
- **Results:** Of 51 RCTs on therapy for diabetes in pregnancy, 15 (4,307 women) were included as they considered GDM only and reported criteria for starting pharmacologic therapy. Two diagnostic tests were used: 8/15 (53%) used the one step approach; 6 (40%) used the two step approach; 1 (7%) used either the one or two step approach. Regarding the type of initial non-pharmacologic treatment, 15 RCTs (100%) reported a new diet was recommended, while 4 RCTs (27%) reported that exercise was recommended. In most RCTs glucose monitoring was assessed four times daily, i.e. fasting (14 RCTs, 93%) and 2 hours (10 RCTs, 67%) after each of the three main meals – breakfast, lunch, and dinner. For fasting glucose target, all used a value <99 mg/dL; 7/14 (50%) used 90 mg/dL as target. Of the 10 RCTs using 2 hour-postprandial value as target, the majority (9/10, 90%) had 120 mg/dL as cutoff. Regarding the criteria for starting pharmacologic therapy, we found seven different criteria. The majority of RCTs (13/15, 87%) used either 1 or 2 values per 1 or 2-week period higher than the target values, of which 7/13 (54%) used 1 value higher than target values, and 6/13 (46%) used 2 values higher than target values. One RCTs (7%) used >50% and 1 (7%) used as criteria >30% of the values higher than the target value.

CONCLUSIONS

When evaluating RCTs which included criteria for starting pharmacologic therapy in women with GDM, the most common criteria for diagnosis was the **one step test**. 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 90mg/dL and 120mg/dL**, respectively. Importantly, we found seven different criteria for starting pharmacologic therapy, with the vast majority (87%) using **very tight criteria of either 1 or 2 values 1 or 2-week period higher than the target values**, of which more than 50% used 2 values.

RESULTS

Table 1: Management of women included in the RCTs.

	Glucose monitoring	Target value for glycemic control	Type of diet	Recommendations about exercise	Glucose values used for starting pharmacologic therapy based on target values
Garner, 1997	4 times daily[A]	F: <4.4 mmol/l (80 mg/dL); 1h: <7.8 mmol/l (140 mg/dL)	35 kcal/kg IBW/day	Not stated	2 or more values higher in 2 weeks
Langer, 2000	7 times daily[B]	F: <5.0 mmol/l (90 mg/dL); Preprandial: <5.3 mmol/l (95 mg/dl) 2h: <6.7 mmol/l (120 mg/dL)	• kcal/day based on BW; • 3 meals and 4 snacks; • 40-45% calories from carbohydrates	Not stated	1 or more preprandial or 2h values higher in 1 week
Mecacci, 2003	9 times daily[C]	F: <5.0 mmol/l (90 mg/dL); 1h: <6.7 mmol/l (120 mg/dL)	ADA recommendations	Not stated	More than 50% values higher after 1 week
Schaefer-Graf, 2004	6 times daily[D]	Intervention group: F: <4.5 mmol/l (80 mg/dL); 1h: <6.1 mmol/l (110 mg/dL) Control group: F: <5.0 mmol/l (90 mg/dL); 1h: <6.7 mmol/l (120 mg/dL)	kcal/day based on BW	Exercise after meals	Intervention group: • F ≥120 mg/dL and/or • 2h ≥200 mg/dL Control group: • 2 or more values or • 4 profiles with at least 1 value higher in 2 weeks
Crowter, 2005	4 times daily[E]	F: <5.5 mmol/l (99 mg/dL); 2h: <7.0 mmol/l (126 mg/dL)	Dietary advice from qualified dietician	Not stated	• 2 values higher in 2 weeks <35 weeks; • 2h >8.0 mmol/l (144 mg/dl) in 2 weeks >35 weeks; • 1 value >9.0 mmol/l (162 mg/dl) in 2 weeks
Anjalakshi, 2006	Not stated	2h: <6.7 mmol/l (120 mg/dL)	Medical Nutrition Therapy	Not stated	1 value 2h higher in 2 weeks
Landon, 2009	4 times daily[E]	F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	ADA recommendations	Not stated	• >50% values higher between 2 study visits; • 1 random value >160 mg/dl (8.9 mmol/l) • 1 F >95 mg/dl, the patient's caregiver initiated treatment
Iljas, 2010	4 times daily[F]	F: <5.3 mmol/l (95 mg/dL); 1.5h: <6.7 mmol/l (120 mg/dL)	Dietary and lifestyle counselling	Not stated	2 values higher in 2-4 weeks
Balaji, 2012	4 times daily[E]	F: <5.0 mmol/l (90 mg/dL); 2h: <6.7 mmol/l (120 mg/dL); Hb1Ac: <6.0 g/dL	Medical Nutrition Therapy	Not stated	1 value higher in 2 weeks
Mukhopadhyay, 2012	7 times daily[B]	F: <5.0 mmol/l (90 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	• kcal/day based on BW; • 3 daily meals; 40-45% of calories from carbohydrates	Not stated	1 value higher in 2 weeks
Niromanesh, 2012	4 times daily[E]	F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	• kcal/day based on BW; • 45% of calories from carbohydrates, 20% from protein and 35% from fat; • 3 meals and 3 snacks	30 minutes of walking per day	2 values higher in one week
Silva, 2012	4 times daily[A]	F: <5.0 mmol/l (90 mg/dL); 1h: <6.7 mmol/l (120 mg/dL)	• kcal/day based on BW; • 3 full meals and 4 light meals; • 35-45% calories from carbohydrates	Not stated	2 values higher after 1 week
Mesdaghinia, 2013	4 times daily[E]	F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	Dietary changes	Not stated	1 value higher in 1 week
Spaulonci, 2013	4 times daily[E]	F: <5.3 mmol/l (95 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	• kcal/day based on BW; • 55% carbohydrates, 15% proteins, 30% fat	30-minute walk 3 times/week	>30% values higher in 1 week
Behrashi, 2016	4 times daily[E]	F: <5.0 mmol/l (90 mg/dL); 2h: <6.7 mmol/l (120 mg/dL)	Education for lifestyle change (exercise and diet)	Education, lifestyle change	1 value higher in 1 week

A Fasting and 1 hour after each main meal – breakfast, lunch, and dinner. B Fasting, before lunch and dinner, 2 hours after main meals – breakfast, lunch, and dinner, and at bedtime. C Fasting, preprandial before lunch and dinner, 1 and 2 hours after each main meal – breakfast, lunch, and dinner. D Fasting, preprandial before lunch and dinner, 1 hour after each main meal – breakfast, lunch, and dinner. E Fasting and 2 hours after each main meal – breakfast, lunch, and dinner. F Fasting and 1.5 hours after each main meal – breakfast, lunch, and dinner.
F, fasting; 1h, 1 hour postprandial; 2h, 2 hours postprandial, BW, body weight

Table 2: Primary and secondary outcomes.

Criteria for starting pharmacologic therapy	Number of studies included	Macrosomia	Cesarean delivery	Maternal hypoglycemia	Neonatal hypoglycemia
1 or 2 values higher than the target values	13	437/4,137 (10.5%)	1,289/3,598 (35.8%)	38/530 (7.2%)	332/3,512 (9.5%)
>50% of the values higher than the target values	1	5/49 (10.2%)	13/49 (26.5%)	Not reported	Not reported
>30% of the values higher than the target values	1	3/92 (3.3%)	63/92 (68.5%)	Not reported	13/92 (14.1%)