Alternatives To Insulin For Gestational Diabetes

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- Gestational diabetes mellitus (GDM) is a common medical complication associated with pregnancy.
- GDM is defined as any degree of glucose intolerance that occurs with pregnancy or is first discovered during pregnancy

- Gestational diabetes (GD) develops because pregnancy increases requirements for insulin secretion while increasing insulin resistance.
- Women with GD often have impaired pancreatic beta-cell compensation for insulin resistance.
- The nature of GD is currently contentious, with debate about its existence, diagnosis and ramifications for both mother and offspring from pregnancy into later life

For The Mother

- Maternal complications include pre-eclampsia, hyperglycemic crisis, urinary tract infections that may result in pyelonephritis, need for cesarean sections, morbidity from operative delivery, increased risk of developing overt diabetes, and possibly cardiovascular complications later in life, including hyperlipidemia and hypertension.
- Mothers with GDM have a 50% chance of developing type 2 diabetes mellitus (T2DM) for the 20 years following their diagnosis of GDM .

For The fetus Or Neonate

- Foetuses from pregnancies with GD have a higher risk of macrosomia (associated with higher rate of birth injuries), asphyxia, and neonatal hyperbilirubinemia , hypoglycaemia and hyperinsulinaemia , respiratory distress syndrome, cardiomyopathy, and hypocalcemia with higher rates of perinatal mortality
- Uncontrolled GD predisposes foetuses to accelerated, excessive fat accumulation, insulin resistance, pancreatic exhaustion secondary to prenatal hyperglycaemia and possible higher risk of child and adult obesity and type 2 diabetes mellitus later in adult life

The Cause Of Fetal Congenital Anomalies

The poorly controlled glycaemic state was associated with the development

of foetal anomalies and not the agents used to control blood sugar levels.

Diagnosis of Gestational Diabetes

- A 50-g, one-hour glucose challenge test at 24 to 28 weeks of gestation. Patients do not have to fast for this test. To be considered normal, serum or plasma glucose values should be less than 140 mg per dL
- An abnormal one-hour screening test should be followed by a 100-g, three-hour venous serum or plasma glucose tolerance test. After the patient has been on an unrestricted diet for three days, venous blood samples are obtained following an overnight fast, and then one, two, and three hours after an oral 100-g glucose load. During the test period, patients should remain seated and should not smoke. Two or more abnormal values are diagnostic for gestational diabetes .

Criteria for Abnormal Result on 100-g, Three-Hour Oral Glucose Tolerance Tests in Pregnant Women*

Blood sample	*National Diabetes Data Group*	*Carpenter and Coustan*
Fasting	105 mg per dL (5.8 mmol per L)	95 mg per dL (5.3 mmol per L)
1-hour	190 mg per dL (10.5 mmol per L)	180 mg per dL (10.0 mmol per L)
2-hour	165 mg per dL (9.2 mmol per L)	155 mg per dL (8.6 mmol per L)
3-hour	145 mg per dL (8.0 mmol per L)	140 mg per dL (7.8 mmol per L)

**—*Gestational diabetes mellitus is diagnosed if two or more of the values (venous serum or plasma glucose levels) are met or exceeded.*

Accepted Treatment Goal

(BLOOD GLUCOSE MONITORING)

- The commonly accepted treatment goal is to maintain a fasting capillary blood glucose level of less than 90 to 105 mg per dL
- The postprandial treatment goal should be a capillary blood glucose level of less than 160 mg per dL at one hour and less than 140 mg per dL at two hours

- When treatment for gestational diabetes is indicated, the drug of choice, insulin,
- It can be problematic for some women because of the need for daily injections, which can affect compliance.
- Insulin therapy can also cause low blood glucose and weight gain in the mother.
- The cost of therapy may also be an issue for women in lower socioeconomic groups

TTT

Exercises

- Regular exercise (30 minutes/day, 5 days/week following the largest meal of the day) has been shown to improve glycemic control in women with gestational diabetes, but it has not been shown to affect perinatal outcomes
- Ensure adequate hydration and avoid overheating during all physical activity , actual heart rate should not exceed 140 beats/minute
- Although it is not recommended in high risk pregnancies

Diet

- No difference in the prevalence of birth weights greater than 4,000 g or cesarean deliveries in women with gestational diabetes who were randomly assigned to receive primary dietary therapy or no specific treatment.
- The ideal diet for women with gestational diabetes remains to be defined, and current recommendations are based on expert opinion

- The use of oral hypoglycaemic drugs in pregnancy is not recommended in the past because of reports of foetal anomalies, neonatal hypoglycaemia and the development of pre-eclampsia in animal studies and in some human cases.
- However, recent studies have suggested that some oral hypoglycaemic drugs may be used in pregnancy.

Glibenclamide , Glyburide (Doanil)

- Among the sulphonylureas, only glibenclamide has been shown not to cross the placenta

Dose

- **Begin at a low dose of 2.5 mg (half tablet) once or twice per day the dose should be given 30–60 minutes before breakfast and dinner and should not be given before bedtime (Glyburide peaks 2–3 hours) but if the response has been inadequate within a week, it is usually safe to double the initial dose.**
- **It is generally recommended that the total 24-hour dose of glyburide not exceed 20 mg (4 tablets)**
- **If adequate glycemic control is not achieved within 3 weeks, consider changing over to insulin.**
- **Side-effects are usually minimal but women will complain of episodic hypoglycemia and, in some cases, the use of glyburide is accompanied by *excessive weight gain* unless dietary intake (and exercise) is adjusted to compensate for the increased efficiency of utilization of the ingested calories!**

Not To Cross The Placenta

- There was no significant transport of glibenclamide in the maternal-to-foetal and foetal-to-maternal directions.
- Glibenclamide remained undetected when cord blood was analysed using high performance liquid chromatography.
- At least 99.8% of the glibenclamide was bound to protein so it was neither metabolised nor appropriated by the placenta

Metformin (Glucophage)

- The use of metformin, which usually returned blood glucose to normal, rather than dropping it too low, and also is associated with maternal weight loss

Dose

- Usually begin at 500 mg twice per day.
- If the response has been inadequate within a week, the dose can be increased by 500 mg per day on a weekly basis until 2,000 (occasionally 2,500 mg) per day is reached.
- If adequate glycemic control is not achieved within 3 weeks, one can either change to or add insulin to the current metformin regimen
- Side-effects of metformin include gastrointestinal intolerance and, even though food decreases its absorption, it is still suggested that metformin be given with meals during pregnancy to minimize this complication. Hypoglycemia is generally rare with metformin, but it can occur and in rare circumstances (0.03 cases per 1,000 patients) lactic acidosis has been described

Metformin and Early Pregnancy Loss

- women with PCOS who became pregnant while taking metformin and remained on metformin throughout their pregnancy
- the pregnancy loss rate of the metformin was quite similar to the rate of 10% to 15% reported for clinically recognised pregnancies in normal women.

Metformin and Insulin, Insulin Resistance and Testosterone Levels

- Pregnancies in women with PCOS who took metformin throughout their pregnancy.reduces the likelihood of diabetes developing and prevents androgen excess for the foetus.

Metformin and Development of Gestational Diabetes

- Non-diabetic women with PCOS who were on metformin during pregnancy
- GD was developed in only 3% of the women who took metformin as compared to 27% of those who did not

Metformin and Pre-eclampsia

- Pregnancies of women with PCOS taking metformin did not differ between the metformin group and the control group

Metformin and Foetal Outcomes

- Metformin-treated pregnant women that infant morbidity was low and mortality rates were not higher in the metformin-treated patients compared to insulin-treated patients

Metformin and Infant Development

- Neonates born to women with PCOS who conceived while taking metformin and continued taking it through their pregnancy.
- There were also no motor-social developmental delays noted in the drug-exposed infants

Metformin May Have Higher Failure Rate Than Glyburide for Gestational Diabetes

- The failure rate of metformin was approximately twice that of glyburide when used in the management of gestational diabetes mellitus (GDM)

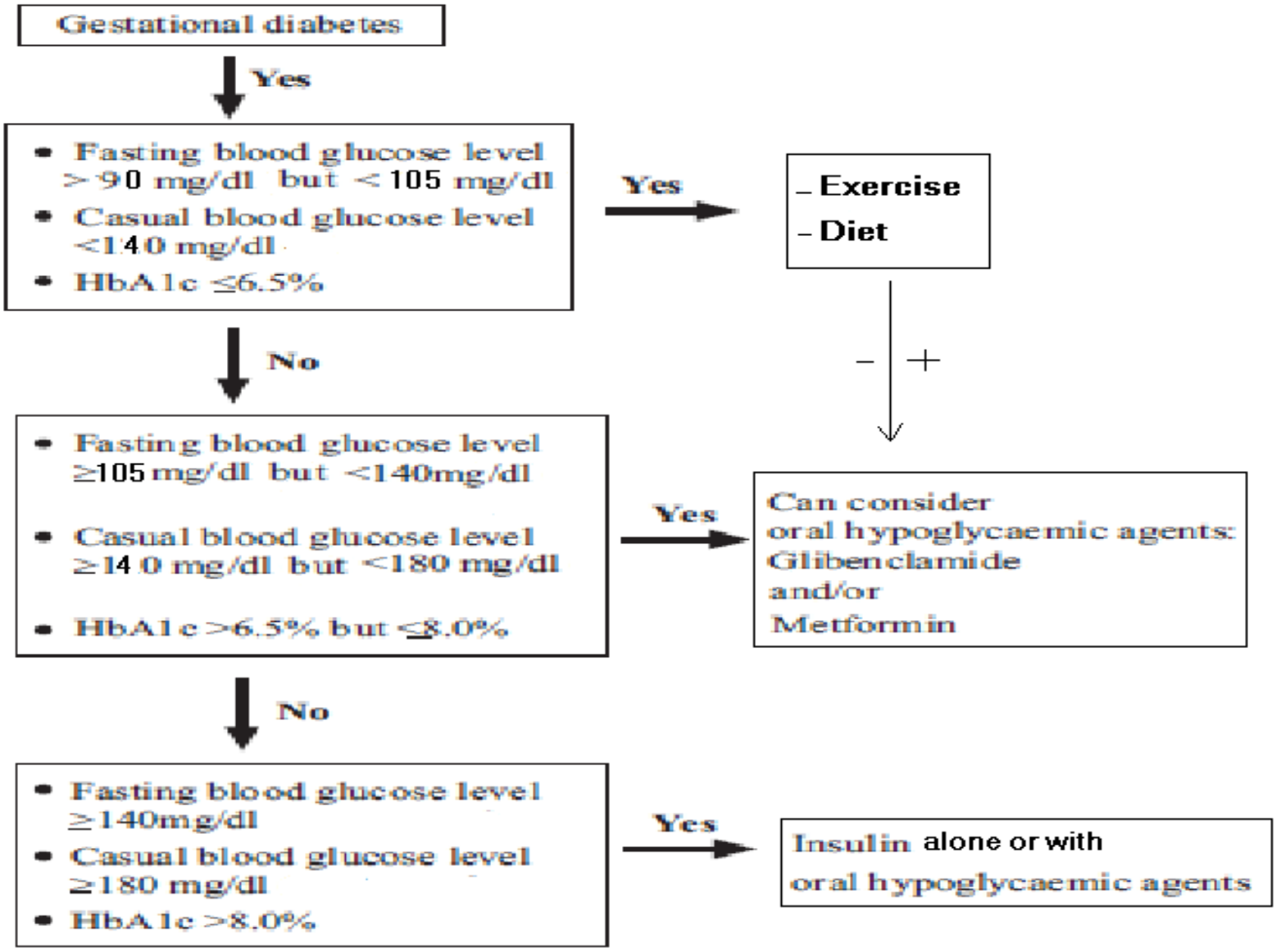
Insulin

- Insulin therapy traditionally has been started when capillary blood glucose levels exceed 105 mg per dL in the fasting state and 140 mg per dL two hours after meals
- There are no specific studies declaring one type of insulin or a certain regimen as superior in affecting any perinatal outcome

Dose

- A common initial dosage is 0.7 units per kg per day,
- one dose consisting of two thirds of the total amount given in the morning and one dose consisting of one third of the total amount given in the evening.
- One third of each dose is given as regular insulin, and the remaining two thirds as NPH insulin.
- A recent study of women with gestational diabetes supports the safety of very-short-acting insulin lispro, which can be used with once-daily extended insulin ultralente.
- The simplest regimen that will control blood glucose levels is the best

Suggested Flow Chart For GD Treatment



	diet , exercise	oral hypoglycemic	insulin
fasting	90-105	105-140	↑ 140
postprandial	↓140	140-180	↑ 180

Conclusions

- There is now a changing trend in the acceptability of using oral hypoglycaemic agents in non-insulin dependent pregnant diabetics
- Both glibenclamide and metformin are currently classified by the FDA as Category B drugs for use in pregnancy, which means that there is no evidence of risk in humans.

TIMING AND ROUTE OF DELIVERY

- A reasonable approach is to offer elective cesarean delivery to the patient with gestational diabetes and an estimated fetal weight of 4,500 g or more, based on the patient's history and pelvimetry, and the patient and physician's discussion about the risks and benefits.
- There are no indications to pursue delivery before 40 weeks of gestation in patients with good glycemic control unless other maternal or fetal indications are

INTRAPARTUM MANAGEMENT

- The goal of intrapartum management is to maintain normoglycemia in an effort to prevent neonatal hypoglycemia. Patients with diet-controlled diabetes will not require intrapartum insulin and simply may need to have their glucose level checked on admission for labor and delivery.
- While patients with oral hypoglycemic or insulin-requiring diabetes are in active labor, capillary blood glucose levels should be monitored hourly. Target values are 80 to 110 mg per dL

POSTPARTUM MANAGEMENT

- Patients with diet-controlled diabetes do not need to have their glucose levels checked after delivery.
- In patients who required oral hypoglycemic or insulin therapy during pregnancy, it is reasonable to check fasting and two-hour postprandial glucose levels before hospital discharge
- Because women with gestational diabetes are at high risk for developing type 2 diabetes in the future, they should be tested for diabetes six weeks after delivery via fasting blood glucose measurements on two occasions or a two-hour oral 75-g glucose tolerance test.
- Normal values for a two-hour glucose tolerance test are less than 140 mg per dL.
- Values between 140 and 200 mg per dL represent impaired glucose tolerance, and
- Greater than 200 mg per dL are diagnostic of diabetes.
- Screening for diabetes should be repeated annually thereafter, especially in patients who had elevated fasting blood glucose levels during pregnancy

Breastfeeding

- Breastfeeding improves glycemic control and should be encouraged in women who had gestational diabetes

Metformin And hypoglycemic drugs with breastfeeding

- Metformin is considered a first-line agent for the management of type 2 diabetes or gestational diabetes.
- The very limited amounts of metformin observed in breast milk are highly unlikely to lead to substantial exposure in the breastfed baby.
- Metformin can be considered a safe medication for the treatment of type 2 diabetes in a breastfeeding mother.
- The levels of glyburide and glipizide in milk are negligible and would not be expected to cause adverse effects in breastfed infants
- monitoring of the breastfed infant for signs of hypoglycemia is advisable during maternal therapy with any of these agents

Table 1. Selected Studies Using Oral Hypoglycaemic Agents in Pregnancy

Drugs	Authors	Year	No. of subjects	Study design	Outcomes
Glibenclamide (Glyburide)	Langer et al[12]	2000	404	Randomised Controlled Trial	Glyburide's efficacy was comparable to insulin in the control of blood sugar levels. There were no significant differences in the neonatal outcomes between the 2 groups.
	Kremer et al[13]	2004	73	Prospective Cohort Study	No congenital anomalies were found in the neonates of those treated with glyburide.
Metformin	Jakubowicz et al[14]	2002	96	Retrospective Study	Reduced the rate of early pregnancy loss in women with PCOS.
	Glueck et al[16]	2002	70	Prospective and Restrospective	Reduced the development of gestational diabetes in women with PCOS with no foetal malformations in the neonates of the treated subjects.
	Glueck et al[15]	2004	42	Prospective Observational Study	Reduced preconception insulin levels, insulin resistance, and testosterone levels while maintaining insulin-sensitising effects throughout pregnancy.
	Glueck et al[18]	2004	349	Prospective Case Series	No significant difference in pre-eclampsia rates between treatment and control groups.
	Glueck et al[17]	2004	126	Prospective Case Series	No systematic differences in growth between the drug-exposed and non-exposed infants. There were also no motor-social developmental delays noted in the infants of treated subjects.
Acarbose	Zarate et al[21]	2000	6	Prospective Case Series	Blood sugar levels were adequately controlled. The pregnancies were uneventful and the newborn babies were normal.

PCOS: polycystic ovary syndrome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