CONTEMPORARY REVIEW ARTICLE

Diabetes in Pregnancy

Neeta Deshpande

Consultant, Diabetologist and Bariatric Physician, Belgaum Diabetes Center, Belgaum, Karnataka, India

Correspondence: Consultant, Diabetologist and Bariatric Physician, Belgaum Diabetes Center, Belgaum, Karnataka, India Phone: 9880271313, e-mail: neetarohit@gmail.com

Abstract

Gestational diabetes mellitus is carbohydrate intolerance with onset or first recognition during pregnancy. Pregnancy could also occur in a woman with pre-existing diabetes. Congenital anomalies, macrosomia, birth injuries, obstetric and neonatal complications are associated with diabetes in pregnancy. The long-term implications in both mother and offspring include the development of obesity, metabolic syndrome and diabetes. Screening would identify patients and many guidelines exist for the same. Universal screening is advocated. The glycemic goals are stringent, although data indicate that thresholds should be lowered further. Nutritional therapy is the mainstay of treatment. Insulin is the agent of choice if glycemic goals are not met. Newer insulin analogs are advantageous. Oral anti-diabetic agents show promise for the future, although more long-term trials are needed. Self monitoring of glucose is an important tool in the management of diabetes in pregnancy.

Rates of cesarean section are high in diabetic pregnancies. If macrosomia occurs, other obstetric complications ensue. Maternal hyperglycemia can lead to neonatal hypoglycemia. Postpartum, maternal glycemic status should be reassessed and treatment modified accordingly. In the long-term, both mother and offspring are ideal candidates for lifestyle modification for the prevention of type 2 diabetes.

Preconception care in women with pre-existing diabetes and/or its complications is desirable to minimize complications and congenital anomalies.

Keywords: Diabetes, pregnancy, screening, macrosomia, preconception care.

INTRODUCTION

Pregnancy is a potentially diabetogenic condition due to numerous hormonal and metabolic changes that occur. An inherent genetic predisposition to insulin resistance and/or insulin deficiency can get unmasked, though temporarily, in the pregnant woman. This then needs to be identified speedily as otherwise, both maternal and fetal outcomes can be adversely affected. Therefore, screening tests for the condition are warranted. Over the years, several criteria have evolved for the diagnosis of diabetes in pregnancy, as the values are necessarily different from the usual diagnostic criteria in the nonpregnant state. There are subtle differences between the pre-existing diabetes in a pregnant woman [Diabetes with pregnancy (DWP)] and the diabetes developing for the first time after the onset of pregnancy [gestational diabetes mellitus (GDM)], although the glycemic goals remain the same. GDM usually surfaces between 24 to 28 weeks of gestation. A diagnosis of diabetes earlier on in pregnancy usually implies hitherto undiagnosed pre-existing diabetes.

DEFINITION

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[1] This is regardless of the therapy used and the reclassified status after pregnancy. For example, it could be unrecognized type 1 or type 2 diabetes.

SCREENING (ADA 2009) [2]

At the first prenatal visit, a risk assessment is done. The risk factors under consideration for very high-risk are:

- Severe obesity
- Prior history of GDM or delivery of large for gestational age infant
- Presence of glycosuria
- Diagnosis of PCOS
- Strong family history of type 2 diabetes.

At this stage the usual criteria for diagnosis of diabetes should be applied.

All women of greater than low-risk of GDM, including those above not found to have diabetes early in pregnancy, should undergo GDM testing at 24 to 28 weeks of gestation. Low-risk status, which does not require GDM screening, is defined as women with ALL of the following characteristics:

- Age < 25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetrical outcome.

Two approaches may be followed for GDM screening at 24 to 28 weeks:

Two-step approach:

1. Perform initial screening by measuring plasma or serum glucose 1 hour after a 50 gm oral glucose load. A glucose threshold after 50 gm load of ≥ 140 mg/dl identifies ~ 80% of women with GDM, while the sensitivity is further increased to ~ 90% by a threshold of ≥130 mg/dl.
2. Perform a diagnostic 100 gm OGTT on a separate day in women who exceed the chosen threshold on 50 gm screening.

One-step approach: (may be preferred in clinics with high prevalence of GDM): Perform a diagnostic 100 gm OGTT in all women to be tested at 24 to 28 weeks.

The 100 gm OGTT should be performed in the morning after an overnight fast of at least 8 hours.

To make a diagnosis of GDM, at least two of the following plasma glucose values must be found:

- Fasting: ≥ 95 mg/dl
- 1 hour ≥ 180 mg/dl
- 2 hours ≥ 155 mg/dl
- 3 hours ≥ 140 mg/dl

However, the most commonly used OGTT across the world is the 75 gm glucose test. It is recommended by the WHO. In the USA, the 100 gm OGTT is still predominantly used. Different cut-off values are in use for the OGTT 100 gm and 75 gm.

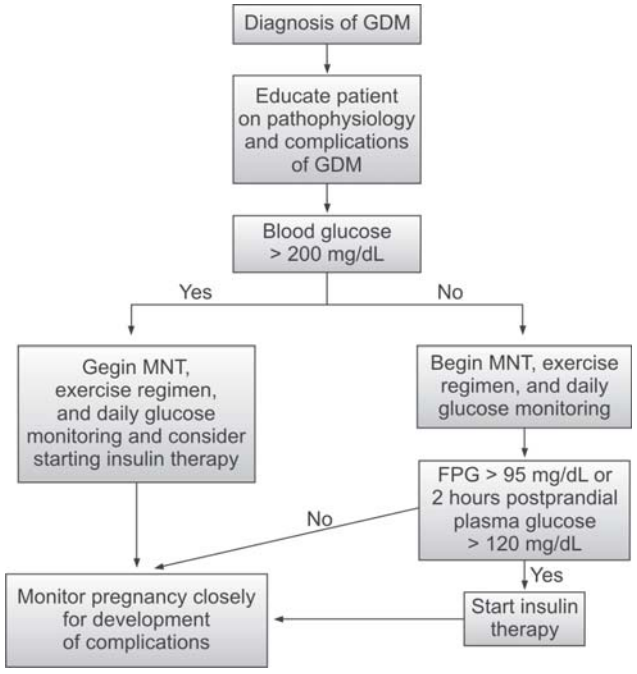
The hyperglycemia and adverse pregnancy outcomes study is a large multicentric epidemiological study that included about 25000 patients globally. The results of this study demonstrated that adverse maternal and fetal outcomes could occur as a continuum across blood glucose values at 24 to 28 weeks, even at those levels currently considered as normal glucose tolerance.[3] Therefore there is probably a need for revision for the current diagnostic criteria for GDM, as the study showed no specific threshold for risk.

Women diagnosed with GDM are at much greater risk for future development of type 2 diabetes.[4] They should be first tested 6 to 12 weeks postpartum, with nonpregnant criteria, and regularly thereafter. Moreover, this is a group that can greatly benefit from primary prevention strategies and all efforts should be directed towards aggressive lifestyle modification for prevention of diabetes.

MANAGEMENT

Although the glycemic goals are identical, there are some differences in management strategies between DWP and GDM (Flow Chart 1). In general, women of DWP have to be switched to insulin as soon as pregnancy is diagnosed, if they were on

Flow Chart 1: Treatment algorithm for GDM



Cut-off Values for the OGTT 100 and 75 gm

Study	*Fasting*	*1 hour*	*2 hours*	*3 hours*
100 gm Carpenter and Coustan	95 mg/dl, 5.3 mmol/l	180 mg/dl, 10.0 mmol/l	155 mg/dl, 8.6 mmol/l	140 mg/dl, 7.8 mmol/l
100 gm National Diabetes Data Group	105 mg/dl, 5.8 mmol/l	190 mg/dl, 10.6 mmol/l	165 mg/dl, 9.2 mmol/l	145 mg/dl, 8.0 mmol/l
75 gm WHO	126 mg/dl, 7.0 mmol/l	–	140 mg/dl, 7.8 mmol/l	–
75 gm American Diabetes Association	95 mg/dl, 5.3 mmol/l	180 mg/dl, 10.0 mmol/l	155 mg/dl, 8.6 mmol/l	–
75 gm Canadian Diabetes Association	95 mg/dl, 5.3 mmol/l	190 mg/dl, 10.6 mmol/l	160 mg/dl, 8.9 mmol/l	–

oral antidiabetic agents (OADs). Women with GDM can be given a trial of nutrition therapy before initiating insulin.

Blood sugar monitoring pen (Fig. 1) is mandatory for a successful outcome. There are no definite guidelines indicating the frequency of monitoring in diet controlled cases. In insulin requiring cases, fasting and preprandial monitoring is recommended every day. However, postprandial values at both 1 hour and 2 hours have been recommended by various authors. Continuous glucose monitoring (CGM) is also being advocated recently.

Nutritional therapy is the mainstay of treatment, whether or not insulin is begun. The aim is to provide adequate calories and nutrients and at the same time achieve euglycemia as per the set targets. The caloric allowance is about 30 kcals/kg of present weight for normal weight women and about 25 kcal/kg for overweight and obese women. Severe caloric restriction should be avoided as there is some data showing a relationship between severe caloric restriction and reduced psychomotor development in offspring.[5] Fat intake should be reduced and complex carbohydrates are preferred over the refined variety. Overall, carbohydrates should contribute about 40% to the total caloric intake.[6] There is some evidence that consumption of low glycemic index carbohydrates is beneficial.[7] Noncaloric sweeteners are best avoided. Frequent meals are recommended (3 meals and 3 snacks). A bedtime snack may need to be included especially in those women on pharmacological therapy, to minimize nocturnal hypoglycemia.

A smaller weight gain of about 7 kg is recommended in women with a Body mass index (BMI) of 30 kg/m^2 or more. There are no data on optimal weight gain for women with GDM.[8]

There is very little data to support physical activity as a significant contributor to therapy in GDM. But the ADA has endorsed exercise as 'a helpful adjunctive therapy' for GDM when euglycemia is not achieved by diet alone. Also, exercise addresses the issue of insulin resistance and may thus be a useful add-on therapy.

Fig. 1: Blood sugar testing pen

If nutritional therapy fails to attain the targets (which comprise ≤ 95 mg% FPG and preprandial glucose and ≤ 120 mg% postprandial glucose), *insulin therapy* is instituted. Conventional insulins, both short and long acting, are used in various combinations. In general, multiple injections are required for optimal control, especially in DWP. Some of the rapidly acting insulin analogs are currently approved for use in pregnancy, namely, insulin lispro and insulin aspart. They have some advantages over regular insulin. These insulins are shorter acting and hence there is lesser chance of hypoglycemia. There is more flexibility in dosing as they can be injected just prior to a meal. There is data to show that the efficacy of analogs is comparable to that of regular insulin, with lesser incidence of hypoglycemia.[9]

Since long, research has been ongoing for the use of OADs in the treatment of GDM/DWP. Although there is no recommendation yet for their use, there is encouraging data with OADs in the recent past. From the pathophysiological standpoint, insulin therapy does not address the issue of insulin resistance that exists in GDM. Perhaps OADs can. The main deterrent to their usage is the possibility of congenital anomalies and fetal hypoglycemia through stimulation of fetal pancreas. However, congenital anomalies are not a concern if OADs were to be used after the first trimester. In some countries, glibenclamide and metformin have been used for many years without any adverse fetal outcomes. Many studies have confirmed the efficacy of glibenclamide. A comparison of insulin and glibenclamide showed similar glycemic and pregnancy outcomes.[10] It has very little transfer across the placenta and is not found in milk of lactating mothers. Potentially, it is an acceptable alternative to insulin and naturally better for compliance.

There is no evidence of teratogenicity to metformin. A recent metanalysis shows that metformin does not cause any major malformations.[11] Metformin is being increasingly used to treat polycystic ovarian Syndrome. It is not unusual to find that metformin is continued over the first trimester in such cases. In PCOS, use of metformin is associated with a tenfold reduction in gestational diabetes (from 31 to 3%). There is no evidence of congenital defects, intrauterine growth retardation and neonatal hypoglycemia requiring intervention.[12,13]

In summary, most current studies demonstrate that oral hypoglycemic agents, such as glyburide and metformin, are safe to use in pregnancy, but there is a need for a randomized controlled trial in women with type 2 diabetes and GDM in pregnancy with long-term follow-up of both mothers and children.[14]

COMPLICATIONS

Macrosomia is the hallmark of GDM and is defined as an infant's weight greater than 4000 gm. Prolonged labor, postpartum hemorrhage, shoulder dystocia and infections occur more frequently in macrosomic infants. Increased abdominal circumference as seen on fetal ultrasonography can detect macrosomia. Congenital malformations occur with far more frequency in GDM than in normal pregnancies. Normalizing the macrosomia rate is the primary goal in treating women with pregnancies complicated by GDM. Macrosomia is not only associated with a higher rate of birth injury for the mother and newborn, but it is also associated with higher weight and accumulation of fat in childhood, with a higher rate of obesity in adulthood. Macrosomia rates in mothers with GDM when compared to mothers without GDM still remain elevated even with maternal glucose normalization. Other factors that contribute to the development of macrosomia are:

- Obesity of the mother
- Excessive weight gain in pregnancy.

TIMING OF DELIVERY

If the glycemic control is good and there are no maternal or fetal indications, there are no compelling reasons to advocate delivery before 40 weeks gestation. However, risk of shoulder dystocia may be reduced if labor is induced at about 38 weeks.[15]

INTRAPARTUM MANAGEMENT

Neonatal hypoglycemia has to be prevented. Patients on nutrition therapy alone do not need any insulin therapy or monitoring during labor. Women on insulin therapy need to be monitored hourly for capillary blood glucose to maintain the glucose level between 80 to 110 mg%. There are 2 approaches to the intravenous fluid management at this time. One is to keep the patient on a maintenance glucose containing fluid with a concurrent adjustable insulin drip. The second is to just alternate between glucose containing and nonglucose containing fluids based on the blood sugars.

POSTPARTUM MANAGEMENT

Neonatal hypoglycemia is a real threat in GDM and should be actively looked out for. Diet controlled GDM patients generally do not require monitoring. About 15 % of GDM patients continue to be glucose intolerant postpartum. Most GDM patients do not require insulin in the postpartum period. However, insulin requiring patients and those whose diabetes antedated pregnancy will require close monitoring of blood glucose. There is no validated screening policy, but an OGTT at least once in 3 years is advocated for all GDM patients. Women with GDM are more likely to develop GDM in future pregnancies.

PRECONCEPTION CARE

It is mandatory for diabetic women desiring pregnancy to receive preconception counseling in order to avert maternal and fetal complications, especially congenital malformations. It is necessary to attain Hba1C levels as close to normal as possible before conception. Effective contraception needs to be practiced until glycemic goals are achieved. Ideally, it is wise to switch to insulin even before conception is attempted. All other drugs such as statins, ACE inhibitors, ARBs, etc need to be reviewed. Long-term complications of diabetes such as retinopathy, nephropathy and cardiovascular disease need to be identified and treated prior to conception.

FUTURE DIRECTIONS

As recent trials have demonstrated the safety and efficacy of oral antidiabetic agents in diabetic pregnancies, they could well be accepted therapies in the future. However, more randomized controlled trials are needed before any recommendations can be made. Also, long-term studies in the offspring of those mothers who have been given these agents, is necessary to ascertain the safety.

SUMMARY

Pregnancy can occur in a known diabetic and diabetes can complicate a pregnancy. In either case, glycemic goals are the same and research shows that attainment of these goals is desirable in order to optimize maternal and fetal outcomes. The cutoff values are probably still evolving as adverse outcomes have been seen even in the seemingly normal ranges. Nutrition therapy and insulin remain the mainstays of therapy until we can get more data on oral antidiabetic drugs. Antenatal surveillance, close monitoring of blood glucose and judicious use of insulin during labor are conducive to favorable outcomes. Preconception counseling is extremely important as a preventive measure. Long-term screening of GDM patients and lifestyle modification will help prevent the development of type 2 diabetes in these women.

REFERENCES

1. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
2. Diabetes Care. January 2009;32(S1):S13-S61.
3. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA: Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
4. Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes: A systematic review. Diabetes Care 2002;25:1862-68.

5. Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol 1995;173(6):1753-58 .
6. Major CA, Henry MJ, De Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol 1998;91(4):600-04.
7. Diabetes Care 2009;32:996-1000.
8. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and Reccomendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30:S251-S260.
9. Lapolla A, Dalfra MG, Fedele D. Insulin therapy in pregnancy complicated by diabetes: Are insulin analogs a new tool? Diabetes Metab. Res Rev 2005;21(3):241-52.
10. Langer O, Yogev Y, Xenakis EMG. Insulin and glyburide therapy: Dosage, severity level of gestational diabetes and pregnancy outcome. Am J Obstet Gynecol 2004;192:134-39.
11. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: A meta-analysis. Fert Steril 2006;86(3):658-63.
12. Glueck CJ, Wang P, Kobayashi S, et al. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil. Steril 2002;77(3):520-25.
13. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycistic ovary syndrome treated with metformin. Hum. Reprod 2002;17(11):2858-64.
14. Hawthorne G. Metformin use and diabetic pregnancy: Has its time come? Diabetic Med 2006;23:223-27.
15. Lurie S, Insler V, Hagay ZJ. Induction of labor at 38 to 39 weeks of gestation reduces the incidence of shoulder dystocia in gestational diabetic patients Class A2. Am J Perinatol 1996;13:293-96.