Pharmacy and Wellness Review

Volume 2 | Issue 2 Article 19

May 2011

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Abstract

Gestational diabetes is a concern for a large number of pregnant women due to the potential for long-term complications for both the mother and the fetus. With the increasing prevalence of obesity and diabetes in the general public, the number of pregnant women with undiagnosed type 2 diabetes mellitus has also increased. In order to adequately educate their patients, it is important for pharmacists to be aware of the general practices of treating gestational diabetes. This review will highlight recent updates to initial screening, the criteria for diagnosing gestational diabetes, and current management strategies.

Introduction

Any onset of glucose intolerance that manifests during pregnancy, without previously recognized type 2 diabetes mellitus (T2DM) risk factors, is classified as gestational diabetes mellitus (GDM).[1] Gestational diabetes is a concern for expectant mothers, affecting up to 7 percent of all pregnancies. GDM can lead to maternal and/or fetal complications. Women with this condition are at risk for pre-eclampsia, cesarean section and postpartum T2DM, while the fetus may be at risk of macrosomia (increased birth weight), higher fetal adiposity and abnormal glucose tolerance.[2-5]

Previous guidelines only addressed diagnosis in women who experience hyperglycemia during pregnancy; they did not attempt to determine if the diabetes was pre-existing. As a result of the increased concern of missing pre-existing diabetes, American Diabetes Association (ADA) guidelines dictate that women with risk factors for T2DM be screened at their first prenatal visit using the standard diagnostic criteria shown in Table 1. If unequivocal hyperglycemia is not present, the results should be confirmed by repeat testing. If detection of diabetes is made at the initial screening of a patient with risk factors, a diagnosis of overt, not gestational, diabetes should be made.[6,7]

Table 1: Criteria for the diagnosis of diabetes[6]

Women must present with one of the following criteria:

- Hemoglobin A1C (HbA1C) ≥ 6.5%
- Fasting plasma glucose (FPG) ≥ 126 mg/dl
- 2 hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT) performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
- A random plasma glucose ≥ 200 mg/dl in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

Diagnosis

Women with the risk factors listed in Table 2 should be screened at their first prenatal visit using the standard diagnostic criteria for diabetes (Table 1).[6] Pregnant women who are not diabetic and do not display risk factors for diabetes should be screened for GDM at 24-28 weeks of gestation using a 75 g two-hour OGTT. Diagnosis is made from the OGTT upon exceeding any of the following plasma glucose values: fasting ≥ 92 mg/dl, 1 hour ≥ 180 mg/dl or 2 hour ≥ 153 mg/dl. Based on the new recommendations, only one abnormal value, as opposed to two, is necessary to make the diagnosis; thus, the prevalence of GDM will likely rise. This change in diagnostic practices has been made with the hope of optimizing gestational outcomes.

Table 2: Criteria for testing for diabetes in asymptomatic adult individuals[6]

1. Testing should be considered in all adults who are overweight (body mass index or BMI ≥ 25 kg/m^2*) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing > 9 lb or were diagnosed with GDM
- Hypertension (≥ 140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level < 35 mg/dl and/or a triglyceride level > 250 mg/dl
- Women with polycystic ovarian syndrome
- HbA1C ≥ 5.7%, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease

2. In the absence of the above criteria, testing for diabetes should begin at age 45.

3. If results are normal, testing should be repeated at a minimum of three-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At-risk BMI may be lower in some ethnic groups.

Fetal Complications

Gestational diabetes can cause both short-term and long-term fetal complications.[8] Women with gestational diabetes have an increased resistance to insulin, which alters the uptake of glucose into tissues and decreases the suppression of lipolysis and protein synthesis. These alterations increase the mother's blood glucose, making more available to the fetus, thereby providing more nutrition to the fetus for growth. As a result, the concentration of glucose in the fetal blood will rise and cause the fetus to

secrete more than his or her basal level of insulin. When the baby is born and the umbilical cord is cut, the fetal pancreas will continue to produce excess insulin, and the baby will most likely present with lethargy and hypoglycemia from this large amount of insulin. The surplus of glucose delivered to the fetus may lead to macrosomia, high fetal adiposity and birth trauma. Babies born with high birth weight are at risk of shoulder dystocia and other traumas during birth due to their large size.[9] High birth weight puts the infant at risk of developing adolescent obesity, which can further lead to obesity as an adult.[10] As a result of the obesity, diabetes and cardiovascular disease may also develop later in life. The fetuses of women with undiagnosed glucose intolerance prior to pregnancy are at an even greater risk of acquiring excess adipose tissue.

Prevention

There are many different modifiable and nonmodifiable risk factors for GDM. Modifiable risk factors include being overweight or obese and physical inactivity, while ethnicity, race, family history of GDM, and age are nonmodifiable risk factors. Obese women have been reported to have a 17 percent increased risk of developing GDM. Overweight women with a BMI of 25-30 kg/m^2 are 1.8 to 6.5 times more likely to develop GDM when compared to normal weight women.[8] Lifestyle modifications to help decrease a woman's weight and incorporate more physical activity can help decrease the risk for developing GDM. Dietary education and recommendations can help women at risk of GDM decrease their calorie intake to help reduce their weight. Dietary restrictions will help keep the woman's glucose levels and HbA1C within normal limits and can help prevent the onset of insulin resistance.

Lack of physical activity is a risk factor for both obesity and T2DM. Since 60 percent of women with GDM develop T2DM, increased physical activity as a lifestyle modification can have many health benefits.[8] Women with regular physical activity prior to becoming pregnant have been shown to have less chance of developing GDM. A self-reported questionnaire study conducted by Dempsey compared the effects of physical activity between two groups of women: active during pregnancy and inactive during pregnancy. This study showed a 48 percent reduction of GDM in women with the most activity during the first 20 weeks of their pregnancy. Risk for GDM was reduced by 51 percent in women with the most activity one year prior to the studied pregnancy. According to the authors, these two findings show a combined 60 percent reduction in risk for GDM. However, due to a lack of well-controlled studies, no exercise guidelines can be established.[11]

Treatment

All women diagnosed with GDM should receive nutritional counseling by a registered dietitian whenever possible.[1] The medical nutrition therapy (MNT) should be individualized based upon maternal weight and height. The MNT should allow for adequate calories and nutrients to meet the needs of pregnancy and to be consistent with the established maternal blood glucose goals. Pharmacological treatment is warranted when maternal glucose levels are not controlled by diet and lifestyle modification alone.

Historically, insulin has been the pharmacologic therapy most consistently shown to reduce fetal morbidities when added to MNT.[1] When insulin is prescribed, the dosing and timing should be based upon self-monitored blood glucose levels. The disadvantages of insulin for the mother include the complexity of administering a subcutaneous injection, risks of hypoglycemia and increased appetite and weight gain. The ADA guidelines do not recommend the use of insulin analogs for treating GDM; however, there have been studies reporting safe and effective use of both rapid-acting (lispro) and intermediate-acting insulin (NPH).[12,13] Insulin lispro has actually been reported to be more efficacious than human regular insulin to normalize the blood glucose levels in GDM by lowering postprandial glucose levels and HbA1C levels with fewer hypoglycemic episodes.[12,14] In a large clinical trial (n=213 GDM patients) comparing lispro and regular insulin, there were no significant differences in maternal or fetal outcomes. Additionally, the lispro arm had lower predelivery HbA1C values and higher patient satisfaction compared to the regular insulin arm.[15]

None of the oral glucose-lowering agents have FDA approval for the treatment of GDM.[1] However, metformin and glyburide have both been utilized and studied for GDM over the last two decades. Oral agents are less expensive and complicated to administer than insulin. Additionally, side effects of hypoglycemia and weight gain may be avoided or lessened. Glyburide, or the sulfonylureas in general, are beta cell stimulators, which increase the release of endogenous insulin into the blood stream. Therefore, hypoglycemia and weight gain are potential side effects of these medications. Metformin works primarily by increasing receptor sensitivity to insulin as well as decreasing excessive hepatic glycogenolysis. Metformin is not associated with weight gain or hypoglycemia and may actually cause some weight loss.[16,17]

Metformin appears to be a logical option for women with GDM as it improves insulin sensitivity and is not associated with hypoglycemia or weight gain. Its use in GDM is considered to be unlabeled or investigational.[17] Metformin crosses the placenta, and so it may consequently affect fetal physiology directly; thus, it is classified as FDA pregnancy risk category B and is not recommended for routine use in pregnancy.[13,16,17] However, according to Briggs' *Drugs in Pregnancy and Lactation*, there is no evidence of adverse fetal effects.[18] A study published in *The New England Journal of Medicine* in 2008 examined the use of metformin compared to insulin in the treatment of GDM.[13] The participants were started at a metformin dose of 500 mg once or twice daily with food and increased, typically over a period of one to two weeks to meet glycemic targets, up to a maximum daily dose of 2,500 mg. The rates of neonatal hypoglycemia were similar in the metformin and insulin study groups, but severe hypoglycemia occurred significantly less often in infants whose mothers were taking metformin. There was a higher frequency of preterm births in the metformin group, which may have been due to chance or unrecognized effects of metformin use. However, the difference between the two study groups in mean gestational age at delivery was of no clinical significance. In the study, 46.3 percent of the women in the metformin arm required supplemental insulin. The authors concluded that there was no difference between treatments with metformin as compared to insulin. The study's findings support the use of metformin alone or with supplemental insulin as a safe and effective treatment option for women diagnosed with GDM. The insulin protocol employed in the study was a short-acting insulin analog before meals and an intermediate insulin once or twice daily.[13]

A recent review article on the use of glyburide for GDM examined randomized prospective trials, prospective studies and cohort studies with a total of more than 1,000 patients. The studies demonstrate that glyburide

is as well tolerated, as safe and as useful as insulin for the treatment of GDM. Although, the author suggested that glyburide may become the drug of choice for the treatment of GDM, glyburide's use in GDM is considered to be unlabeled or investigational as it is classified as FDA pregnancy risk category B or C depending on the manufacturer. [19,20,21] Minimal amounts of glyburide have been detected crossing the placenta in an *in vitro* perfusion model.[22] According to Briggs' *Drugs in Pregnancy and Lactation*, neonatal hypoglycemia secondary to glyburide appears to be a low risk.[18] To date, there have not been any trials comparing metformin use to that of glyburide as far as the authors are aware. Therefore, before GDM can become a labeled indication of metformin and glyburide, randomized controlled trials should be completed to compare the two oral glucose-lowering agents to determine the medication of choice for GDM patients.

Role of the Pharmacist

Gestational diabetes is a concern for a large number of pregnant women, and with the recent changes in diagnostic guidelines, it will become more prevalent in the years to come. To help with the predicted rise, pharmacists can play an active role in the prevention, monitoring and treatment of GDM.[6] Many risk factors for GDM, such as increased weight and physical inactivity, can readily be improved by patient education. Pharmacists in both community and clinical settings can educate their pregnant patients on the benefits of maintaining a healthy weight and incorporating exercise into their daily routines. In addition to educating, the pharmacist can continually motivate patients to incorporate these healthy behaviors into their lives once they become pregnant.

GDM can usually be managed with lifestyle modifications, but in some cases pharmacologic therapy is required. In these cases, the pharmacist is a valuable resource to counsel the patient on the proper use, storage and possible side effects of the drugs. Proper insulin administration techniques should be explained and demonstrated to patients. The pharmacist is also an imperative resource on appropriate technique and the use of blood glucose monitoring supplies. Monitoring blood glucose is essential to optimizing the effectiveness of all medications used for GDM. The pharmacist's role in education, prevention and disease state management in patients with GDM is vital to improve the health outcomes of both mother and child.

Conclusion

GDM affects up to 7 percent of all pregnancies and has the potential to cause complications for both the mother and the fetus. Due to the updates to the ADA guidelines for diagnosis of GDM, affected mothers will now be able to receive treatment earlier in pregnancy in order to avoid complications. Although the ADA only endorses the use of regular insulin for the management of GDM, numerous studies have employed short- and long-acting insulin analogs as well as oral glucose-lowering agents. It is important for pharmacists to understand the changes in diagnostic criteria and treatment options in order to effectively educate and treat their patients.

References

1. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2004;27:S88-S90.
2. Al-Rowaily MA, Abolfotouh MA. Predictors of gestational diabetes mellitus in a high-parity community in Saudi Arabia. EMHJ. 2010;16:636-641.
3. Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care. 2009;32:1639-43.
4. Lawlor DA, Fraser A, Lindsay RS, Ness A, Dabelea D, Catalano P, et. al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia. 2010;53:89-97.
5. Osgood ND, Dyck RF, Grassmann WK. The inter- and intragenerational impact of gestational diabetes on the epidemic of T2DM. American Journal of Public Health. 2011;101:173-9.
6. American Diabetes Association. Standards of medical care in diabetes-2011. Diabetes Care. 2011;34:S11-S61.
7. Karagiannis T, Bekiari E, Manolopoulos K, Paletas K, Tsapas A. Gestational diabetes mellitus: why screen and how to diagnose. Hippokratia. 2010;14(3):151-4.
8. Mottola MF. The role of exercise in the prevention and treatment of gestational diabetes mellitus. Curr Sports Med Rep. 2007;6:381-86.
9. Hutcheon JA, Platt RW, Meltzer SJ, Egeland GM. Is birth weight modified during pregnancy? Using sibling differences to understand the impact of blood glucose, obesity, and maternal weight gain in gestational diabetes. Am J Obstet Gynecol. 2006; 195:488-94.
10. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. JN. 2003; 1674S-83S.
11. Dempsey JC, Butler CL, Sorensen TK, Lee I, Thompson ML, Miller RS, et al. A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus. Diabetes Res Clin Pract. 2004; 66:203-215.
12. Jovanovic L, and Pettitt DJ. Treatment With Insulin and Its Analogs in Pregnancies Complicated by Diabetes. Diabetes Care. 2007;30:S220-S224.
13. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003-15.
14. Jovanovic L, Ilic S, Pettitt DJ, Hugo K, Gutierrez M, Bowsher RR, Bastyr EJ. The metabolic and immunologic effects of insulin lispro in gestational diabetes. Diabetes Care. 1999;22:1422-1426.
15. Bhattacharyya a, Brown S, Hughes S, Vice PA. Insulin lispro and regular insulin in pregnancy. QJM. 2001;94:255-260.
16. Metformin [monograph on the Internet]. Hudson (OH): Lexi-Comp; 2011[cited 2011 Mar 2]. Available from 0-online.lexi.com.polar.onu.edu/crlsql/servlet/crlonline.
17. Metformin [monograph on the Internet]. Tampa (FL): Gold Standard/Elsevier; 2011 [cited 2011 Feb 27]. Available from 0-www.clinicalpharmacology-ip.com.polar.onu.edu/Forms/search.aspx?s=Metformin.
18. Briggs g, Freeman R, Yaffe S. Drugs in Pregnancy and Lactation. 8th ed. Philadelphia, Lippincott, 2008.

19. Rosenn BR. The glyburide report card. J Maternal-fetal and Neonatal Med. 2010;23:219-223.
20. Glyburide [monograph on the Internet]. Hudson (OH): Lexi-Comp; 2011 [cited 2011 Mar 2]. Available from 0-online.lexi.com.polar.onu.edu/crlsql/servlet/crlonline.
21. Glyburide [monograph on the Internet]. Tampa (FL): Gold Standard/Elsevier; 2011 [cited 2011 Mar 2]. Available from 0-www.clinicalpharmacology-ip.com.polar.onu.edu/Forms/drugoptions.aspx?cpnum=279&n=Glyburide.
22. Elliott, BD, Schenker S, Langer O, Johnson R, Prihoda T. Comparative placental transport of oral hypoglycemic agents in humans: a model of human placental drug transfer. Am J Obstet Gynecol. 1994;171:653-660.