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MANAGING GESTATIONAL DIABETES: A REVIEW

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that is first recognized during pregnancy.[1] It is characterized by insulin levels that are not sufficient to meet the body's demand, much like other forms of hyperglycemia.[2] In some cases, undiagnosed diabetes and/or glucose intolerance that existed before pregnancy may reveal itself during gestation; this is termed pregestational diabetes. This article will review the current strategies for identifying and treating women with GDM. It will highlight the criteria for screening and diagnosis of GDM, and the available methods of treatment.

EPIDEMIOLOGY

Diabetes complicates approximately 7% of all pregnancies,[2] resulting in over 200,000 GDM cases annually. Usually, women return to normoglycemia after childbirth, but 30-50% of women will develop type 2 DM later in life. A meta-analysis by Chueng and colleagues found the population-attributed risk of GDM to be between 10-31%, which means that 10 -31% of parous women with diabetes would have experienced GDM during pregnancy.[3] The relative risk of developing diabetes later in life is 6 times higher in women who have GDM compared to those that do not.

PATHOPHYSIOLOGY

Insulin is secreted from the pancreatic beta-cells in response to intracellular glucose concentrations. The intracellular concentration of glucose is in equilibrium with serum glucose concentrations. When secreted, insulin binds to insulin receptors on target cells in liver, muscle, and fat tissues. After binding, the receptor is activated, leading to a phosphorylation cascade within the cell that ultimately leads to translocation of the GLUT 4 glucose transporter and increased glucose uptake.

In the muscle, insulin stimulates glycogen synthesis and inhibits glycogenolysis to promote glucose storage. In fat tissue, increase glucose uptake and stimulation of lipoprotein lipase promote storage of fat. In the liver, insulin stimulates glycogen synthesis and storage.

During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester.[4] Increases in the levels of chorionic somatomammotropin, progesterone, cortisol, and prolactin lead to counter-regulatory

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Table 1. Risk factors for gestational diabetes

- Family history of diabetes
- Pre-pregnancy weight > 110% IBW or BMI > 30 kg/m^2
- Age > 25 years
- Previous delivery of baby > 9 pounds
- History of abnormal glucose tolerance
- Member of ethnic group with higher than background rate of type 2 diabetes
- Maternal birthweight > 9 pounds or < 6 pounds
- Essential hypertension or pregnancy-related hypertension
- Glycosuria at first prenatal visit
- Current use of glucocorticoids
- Polycystic ovary syndrome
- Previous unexplained stillbirth or birth of malformed child

Adapted from Jovanovic L.[9]

anti-insulin effects.[5] This increased insulin resistance causes an insufficient response to insulin, leading to maternal and fetal hyperglycemia that typically manifests as postprandial hyperglycemic episodes. The hyperglycemic episodes contribute to accelerated growth of the fetus.

As a result of surging glucose levels in the blood, fetal hyperinsulinemia occurs. Fetal hyperinsulinemia promotes excessive nutrient storage, resulting in macrosomia, or large birth weight. Complications of macrosomia include birth trauma, increased maternal morbidity during labor, increased risk of glucose intolerance and DM in offspring and increased risk of obesity.[2]

Other complications that can occur in neonates born to women with GDM include neonatal hypoglycemia, jaundice, polycythemia, hypocalcemia, birth injury, hyperbilirubinemia, pre-term delivery, and need for neonatal intensive care.[6,7] Risks to the mother with uncontrolled GDM include preeclampsia, polyhydramnios, birth trauma, operative delivery, and perinatal mortality.

DIAGNOSIS & SCREENING

The practice of screening for GDM is controversial. Some data suggest that screening is only marginally beneficial at reducing the complications associated with GDM. The United States Preventive Services Task Force concluded that current clinical evidence is not strong enough to prove screening is beneficial.[8] However, the American Diabetes Association (ADA) and the American College of Obstetrics and Gynecology (ACOG) continue to recommend screening during pregnancy.

Table 1 summarizes risk factors for developing gestational diabetes. The ADA suggests that all pregnant women should be assessed for these risks at the first prenatal visit and screening should occur at 24-28 weeks of pregnancy.

Some data suggest that universal screening has added benefits compared to selective screening.[10] However, the ADA suggests that women who present with a low risk for diabetes do not require screening. The criteria for exclusion from GDM screening are listed in Table 2. A woman must meet ALL the criteria to be excluded from screening.

Screening for diabetes during pregnancy can be performed in two ways: a one-step approach, using a diagnostic oral glucose tolerance test (OGTT) without prior blood glucose screening; or a two-step approach, which involves screening the blood glucose level 1 hour after a 50 g oral glucose load and then performing the 100 g OGTT separately in women who have plasma glucose levels > 130 or 140 mg/dL. Using the two-step approach and the 130 mg/dL threshold, the glucose challenge test identifies 90%

Table 2. Criteria for exclusion from GDM screening

- Age <25 years
- Normal weight before pregnancy
- Member of ethnic group that has low prevalence of DM
- No known family history of DM in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetrical outcome

Adapted from ADA Position Statement on Gestational Diabetes.[6]

of women with GDM.[7] The 140 mg/dL threshold identifies 80% of women with GDM.

The one-step approach and the second step of the two-step approach use the 100 g OGTT. It should be performed after an overnight fast of at least 8 hours and requires two above-threshold plasma glucose levels.

TREATMENT

The ADA and ACOG have published practice guidelines for the management of GDM. Treatment of GDM should be aimed at maintaining therapeutic plasma glucose levels, reducing the risk of macrosomia in the fetus, and lowering the risk of peri- and postnatal complications in the mother. Table 3 lists the threshold glucose levels suggested by several evidence-based practice guidelines.

Medical Nutrition Therapy

To achieve glycemic control in diabetic patients, clinicians suggest medical nutrition therapy (MNT), defined as a carbohydrate-controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycemia, and the absence of ketosis.[12] The ADA recommends that all women with GDM should receive nutritional counseling and individualized MNT based on individual weight and height. For women with a BMI > 30 kg/m^2, a 30-33% total caloric restriction can reduce hyperglycemia and triglycerides without adversely increasing ketonuria. Similarly, a reduction of carbohydrate intake to 35-40% of total calories can decrease maternal glucose levels and improve outcomes for the mother and fetus.[13]

Pharmacological Management

Medical nutrition therapy alone does not uniformly achieve adequate glycemic control, especially in obese women and those women who have long-standing and/or severe hyperglycemia. In these women, MNT should be supplemented with pharmacological treatment. However, questions remain whether the treatments for DM in the non-pregnant population are safe and effective in pregnant women.

Currently, several different classes of oral drugs are available to treat DM: insulin sensitizers, namely the biguanides and the thiazolidinediones (TZDs); insulin secretagogues, such as the sulfonylureas and the meglitinides; and alpha-glucosidase inhibitors like acarbose. Additionally, injectable medications are available, including insulin in various forms and newer agents like exenatide (Byetta®), an incretin mimetic, and pramlintide (Symlin®), a synthetic amylin analogue. These agents will be described and their role in managing GDM will be discussed.

Insulin

Historically, insulin therapy has been the treatment of choice for GDM. Clinical evidence for current insulin products demonstrates no crossing of the human placenta and minimal risk to the fetus, making insulin a safe option for gestational diabetes management.[14]

Human insulin is the least immunogenic of the available insulin products, therefore it is the most widely used for the treatment of GDM. Each pa-

Table 3. Recommended glycemic thresholds (mg/dL)[11]

	ACOG (2001)	ADA (2004)	4th Int'l Workshop Conf. (1998)	CDA (2003)	Thresholds in Non-DM patients
Fasting	60-90	<105	<95	----	75 +/- 12
Premeal	60-105	----	----	95	78 +/- 11
1hr post-prandial	<130-140	<155	<140	<140	105 +/- 13
2hr post-prandial	<120	<130	<120	<120	97+/- 11
Mean post-prandial	100	----	----	----	84 +/- 18
Night-time	60-90	----	----	----	68+/- 10

Abbreviations: ACOG=American College of Obstetricians and Gynecologists, ADA= American Diabetes Association, CDA=Canadian Diabetes Association
Data are means +/- 1 SD

tient's dose should be individualized to meet her specific goals, and is based on the patient's current level of glycemic control and carbohydrate intake.

Currently, the only insulin analogs FDA-approved for GDM are isophane insulin (NPH), and regular insulin.[15] Lente insulin once carried this indication, but it is no longer available in the US. Regular and NPH insulin are used in combination to manage fasting and post-prandial glucose levels in GDM. Doses typically start at 0.3-0.7 units/kg/day, but must be individualized to each patient to achieve desired glucose levels.

A study in women with GDM investigated the short-term effects of insulin aspart compared to regular insulin or no insulin in controlling glucose levels.[16] It found that higher post-prandial insulin peaks could be attained with insulin aspart (95.9 mcU/mL) compared to regular insulin (84.7 mcU/mL) vs. no insulin (72.6 mcU/mL). Additionally, insulin aspart (Novolog®) was very effective in reducing the peak postprandial glucose concentration, resulting in a significantly lower glucose than without insulin ($p<0.001$). The difference with regular insulin compared to no insulin was modest ($p=0.034$). The study also found that at 3 hours post-prandial, there was a lower demand for endogenous insulin with insulin aspart than with regular insulin. Because elevated post-prandial glucose levels are associated with an increased risk of macrosomia, the study suggested that administering insulin aspart 5 minutes before a meal can reduce this risk.

Currently there are no published large-scale controlled studies investigating the use of long-acting insulins in GDM patients. While several small studies suggest that long-acting insulin analogs can be effective in managing GDM,[17,18] these studies have failed to show that long-acting insulins are superior to intermediate- or short-acting insulins, even though they carry an increased risk of hypoglycemic episodes. Currently, long-acting insulins are used predominantly in pregnant women with pre-existing type 1 DM. There is not enough clinical evidence to support the use of long-acting insulin analogs including insulin glargine (Lantus®) or insulin detemir (Levemir®) in GDM.

While insulin is the cornerstone of GDM treatment, the aversion to multiple daily injections has prompted research of the oral anti-diabetes medications with regard to their efficacy and safety in pregnancy.

Metformin

Metformin increases the body's sensitivity to insulin without directly stimulating insulin secretion. It acts by decreasing hepatic gluconeogenesis production, decreasing intestinal absorption of glucose, and increasing peripheral glucose uptake and utilization in the muscle and fat tissues via increased cell membrane glucose transport.[19]

Metformin is the first-line treatment of type 2 DM in non-pregnant states.[20] It significantly lowers HbA1c, has favorable effects on the lipid profile, is associated with less weight gain than with other oral agents, and is useful in treating the insulin resistance in polycystic ovarian syndrome (PCOS).

Metformin was investigated for the management of GDM in the Metformin in Gestational Diabetes (MiG) trial.[21] The study compared the effects of metformin versus insulin in 751 women with GDM (more than one fasting glucose of > 97.2 mg/dL or more than one 2hr-postprandial glucose of > 120.6 mg/dL). The metformin group received 500 mg once or twice daily, up to a maximum daily dose of 2500 mg, to achieve glycemic control of fasting glucose < 99 mg/dL or a 2-hour postprandial level < 126 mg/dL.

The median daily dose that achieved glycemic control in the metformin group was 2500 mg. Forty-six percent of the women in the metformin group were given insulin supplementation to achieve recommended glucose levels. At the end of the study, there was no significant difference between the two groups in the primary outcome, a composite of neonatal complications that included neonatal hypoglycemia (2 blood glucose readings < 46.8 mg/dL), respiratory distress that required at least 4 hours of oxygen support, birth trauma, pre-mature birth (<37 weeks), and 5-minute APGAR scores <7 points. The secondary outcomes measured were birth weight and anthropometric measures, maternal hypertensive complications, and maternal glycemic control up to 6 -8 weeks postpartum. The study also found no significant difference in these outcomes.

Investigators also assessed the patients' acceptability of their respective treatment assignments using a questionnaire at 2 weeks post-partum. Seventy-six percent of the women in the metformin group said they would choose metformin again in a subsequent pregnancy, whereas 27% would prefer insulin in a subsequent pregnancy. More women in the insulin group rated taking the medication as the most dif-

ficult part of the treatment.

The MiG trial demonstrated that metformin is a safe alternative to insulin for the management of GDM. While roughly half of the patients on metformin required insulin, it is important to note that these patients generally had higher baseline glucose levels and/or were significantly obese. Therefore, in patients with milder hyperglycemia, metformin is a reasonable initial option for treating GDM, offering more ease of use with no additional risk of maternal or neonatal complications.[21]

For more information on metformin in GDM, a recent comprehensive review is available in the latest issue of *Annals of Pharmacotherapy*:

Wensel TM. Ann Pharmacother 2009;43 [Epub]. DOI 10.1345/aph.1L562

Sulfonylureas

Sulfonylureas act by stimulating pancreatic islet cells to secrete insulin. Several studies have investigated sulfonylureas in pregnancy. Older studies suggested that treatment with sulfonylureas could increase the fetal anomaly rate and neonatal hypoglycemia.[22,23] These studies primarily investigated the first-generation sulfonylureas including chlorpropamide (Diabenese®) and tolbutamide (Orinase®), which cross the maternal placenta and lead to neonatal complications. The second-generation sulfonylureas, however, have minimal human placental transfer.[24]

Langer and colleagues compared glyburide and insulin in 404 pregnant women between 11 and 33 weeks gestation.[25] Glyburide at a starting dose of 2.5 mg orally in the morning was titrated weekly to achieve glycemic control, to a maximum dose of 20 mg. The authors reported no significant differences between the two treatment groups in rates of macrosomia (birth weight of 4000 g or more), lung complications, hypoglycemia, neonatal intensive care unit admission, or fetal anomalies. In addition, they observed similar levels of glucose control in both groups, with the exception of 8 patients in the glyburide group requiring insulin to achieve target glucose levels (90 mg/dL fasting and 100 mg/dL postprandial).

A smaller study by Bertini and colleagues compared insulin, glyburide, and acarbose in 70 patients.[26] Patients in the glyburide group were given a starting dose of 5 mg in the morning, increasing every 7 days until achieving glucose control with maximum dosage of 20 mg per day. The investigation found a higher rate of large for gestational age (LGA) fetuses in the glyburide group compared to the acarbose and insulin groups (p=0.073). Also, the rate of neonatal hypoglycemia was higher in the glyburide group (33.3%; p=0.006), but the babies were well-managed on their mothers' milk. Neonatal capillary glucose levels did not differ significantly at one, three, and six hours after birth. The investigation acknowledged that while insulin is a more effective choice in managing GDM, glyburide is an acceptable alternative when considering ease of use and costs.

Acarbose

Acarbose (Precose®) is an oligosaccharide that inhibits carbohydrate absorption from the gut to reduce post-prandial glucose levels. Because it is associated with a reduced risk of placental transfer and is not systemically absorbed, acarbose has been of significant interest for use in GDM.

At an initial dose of 50 mg before main meals, titrated by 50 mg/day to a maximum total dose of 300mg/day, acarbose treatment resulted in fewer cases of hypoglycemia than glyburide (5.3% vs 33.3%; p=0.006), but required insulin treatment in a larger proportion of patients compared to glyburide (42.1% vs 20.8%).[26] The investigators suggested that acarbose may be an option in GDM patients wishing to delay the need for insulin injections.

Other Therapies

Other oral options for treating diabetes outside the setting of pregnancy include the thiazolidinediones, meglitinides, and the newer class DPP-IV inhibitor, sitagliptin (Januvia®). For many of these options, animal studies have illustrated placental transfer with no teratogenic effects. However, there have not been adequate human studies looking at the effects of these drugs in pregnancy. These agents should not be used in the treatment of GDM unless the benefits of therapy clearly outweigh the potential risks, and when other better-studied options have been exhausted.

In cases when monotherapy does not achieve optimal glucose control, combination therapy may be considered. Combination therapy offers the opportunity to decrease doses on individual agents and to decrease the side effect profile. Currently, the Re-

Table 4. Average retail costs of selected GDM medications

DRUG	UNIT SIZE	PRICE PER UNIT ($)
Insulin NPH		
Novolin N 100u/ml	10ml vial	57.81
Novolin Penfill 100u/ml	5 pens x 3ml	133.28
Humulin N 100/ml	10ml vial	54.00
Regular Insulin		
Novolin R 100u/ml	10ml vial	57.81
Humulin R 100u/ml	10ml vial	54.00
Metformin		
500mg tablet	30 tablets	12.99
1000mg tablet	30 tablets	17.99
Glyburide		
2.5mg tablet	30 tablets	12.99
5mg tablet	30 tablets	11.99
Acarbose		
50mg tablet	100 tablets	87.99
100mg tablet	100 tablets	89.99

Adopted from www.drugstore.com Prescription Price Checker.[28]

gional Obstetrical Consultants group in Tennessee is investigating the use of Glucovance®, a combination of glyburide and metformin, with a starting dose of 1.25/250 mg twice daily.[27] Until this and other study results are available, there is limited data to routinely recommend combination oral therapy in gestational diabetes.

COST

Table 4 summarizes the average retail price of the agents discussed in this article. Using these prices, the cost of treating a patient with metformin 2500 mg daily would be $61.96 (two 100 mg tablets and one 500mg tablet each day) or $64.95 (500 mg tablets only) for 30 days. Glyburide would cost $12.99-44.95, depending on the dose. Insulin prices vary by brand and dose.

SUMMARY

Tight control of plasma glucose is important during pregnancy to reduce the risk of GDM and its complications in the mother and neonate. The ADA recommends that all pregnant women be screened for the risk of GDM at 24-28 weeks gestation, and that women at risk be screened using the one-step or two-step glucose challenge test.

Insulin continues to be the standard of treatment for GDM. In patients in whom glycemic control is not achieved by medical nutrition therapy, NPH or regular insulin can be used to achieve normoglycemia and reduce the risk of maternal and neonatal complications. Insulin aspart is pregnancy category B and has favorable data supporting its use in GDM, but awaits approval.

Oral options for treating GDM include metformin, glyburide, and acarbose. Metformin, at a dose of 2500 mg daily, achieves normoglycemia in women with GDM. It is a more widely accepted dosage form and can be used in patients who are averse to multiple insulin injections. Glyburide is used to manage GDM at a starting dose of 2.5 mg daily titrated to a maximum dose of 20 mg daily. Acarbose, in small studies, is somewhat effective in treating GDM. No definitive conclusions can be drawn about its use in GDM; it is an area of research that requires

further exploration. Other oral antidiabetic agents should not be used for the management of GDM unless a thorough risk:benefit evaluation is made and other better-studied options are exhausted.

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DRUG UPDATES

Golimumab (Simponi®) - *Centocor Ortho Biotech, Inc*

In April, 2009, the FDA granted approval for a new monoclonal antibody, golimumab, for the treatment of moderate-to-severe rheumatoid arthritis, ankylosing spondylitis, and active psoriatic arthritis. Golimumab is injected subcutaneously on a monthly basis and is approved in combination with methotrexate in rheumatoid arthritis and active psoriatic arthritis. However, it may also be used as monotherapy in active psoriatic arthritis and ankylosing spondylitis.

As with other tumor necrosis factor alpha inhibitors, golimumab has been associated with an increased risk of tuberculosis and other invasive fungal infections.

New indication for tigecycline

On March 20, 2009, the FDA approved a tigecycline for use in community-acquired bacterial pneumonia (CABP) caused by susceptible strains of *S. pneumoniae, H. influenzae,* or *Legionella pneumophila*. The approval was based on the results of two randomized trials showing non-inferiority to levofloxacin 500 mg dosed once or twice daily. Dosing for CABP is equivalent to previous indications (100 mg loading dose then 50 mg every 12 hours).

MEDICAL NEWS

Swine Influenza Update

As of April 29, 2009, 91 cases of Swine influenza, an influenza A (H1N1) strain, have been confirmed in the U.S. Although most cases in the U.S. and elsewhere have resulted in clinically mild disease, at least 1 death in Texas and > 150 deaths in Mexico have been attributed to this virus. Subsequently, the FDA has authorized Emergency Use Authorization (EUA) for the influenza antivirals, oseltamivir and zanamivir. The EUA temporarily lifts restrictions on the use of these antivirals and allows a variety of healthcare workers as well as volunteers to dispense these medications.

The CDC is recommending that nasopharyngeal swabs/aspirates be collected from patients with suspected swine influenza infection and transported to state public health departments for confirmatory analysis. In addition, recommendations for the use of each of influenza antivirals can be found on the CDC website available at:

http://www.cdc.gov/swineflu/

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