Current Management of Gestational Diabetes Mellitus

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Karen von Koeckritz has no actual or potential conflict of interest in relation to this program.

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TARGET AUDIENCE:

This accredited program is targeted pharmacists, pharmacy technicians, and nurses practicing in hospital and community pharmacies. Estimated time to complete this monograph and posttest is 60 minutes.

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Program Overview:

To provide participants with an understanding current management methods and strategies for gestational diabetes mellitus.

OBJECTIVES:

After completing this program, pharmacists and nurses will be able to:

- Describe Gestational Diabetes Mellitus and its potential adverse consequences to the mother and the baby.
- Review the new criteria recommended by the American Diabetes Association for the diagnosis of Gestational Diabetes Mellitus.
- Identify the current therapy recommendations for Gestational Diabetes Mellitus.

Pharmacy technicians will be able to:

- In general terms, describe the signs and symptoms of gestational diabetes mellitus.
- Outline the potential adverse consequences of gestational diabetes mellitus to the mother and the baby.
Definition of Gestational Diabetes (GDM)
Gestational diabetes mellitus (GDM) is defined as the onset or the recognition of any degree of carbohydrate intolerance during pregnancy. Most cases of GDM resolve following delivery.¹ Both type 2 diabetes mellitus (T2DM) and GDM are characterized by peripheral insulin resistance, declining β-cell function and impaired regulation of hepatic glucose production. Patients with GDM account for approximately 90-95% of patients with diabetes during pregnancy.² Insulin resistance normally occurs during pregnancy. To compensate, insulin secretion increases to maintain euglycemia (normal blood glucose). The degree of insulin resistance is greatest in the third trimester; GDM normally develops at this stage. For this reason women are screened for glucose intolerance at 24-28 weeks into their pregnancy.³

Incidence
The incidence of diabetes in pregnancies in the US has been estimated to be approximately 2-14%; as previously mentioned, most of the cases represent women with GDM. ³⁻⁵ There is an increased prevalence of GDM in women of Hispanic, African, Native American, Asian and/or Pacific Island ancestry.⁵ It has been estimated that 50 to 60 percent of women with GDM will develop type 2 diabetes later in life.⁵ The incidence of GDM is increasing as is the increase in T2DM.³

Problems due to GDM
Gestational diabetes mellitus can cause serious glucose-mediated complications. Macrosomia (high birth weight), shoulder dystocia (an obstetrical emergency when the shoulder of the infant cannot pass below the pubic symphysis) with risks of brachial plexus injury and clavicle fracture during birth, and neonatal hypoglycemia occur most commonly.³ Other serious, but less common effects of GDM include still birth, birth trauma, increased need for a cesarean section, pre-eclampsia, respiratory distress, hyperbilirubinemia, increased neonatal intensive care unit visits and neonatal adiposity which may develop into childhood obesity and diabetes.²

During pregnancy, glucose travels freely to the fetus from the mother, but insulin does not. Hyperglycemia from a mother with GDM requires the fetus to increase insulin production. The increased circulating insulin in the fetus may then cause macrosomia either from excessive fat deposition or a direct effect on cell growth.⁶

The American Diabetes Association (ADA) reconsidered the diagnostic criteria for GDM based upon the conclusions from the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study. In 2008, the study researchers concluded that adverse maternal, fetal and neonatal outcomes increased with higher levels of maternal glycemia, even at levels considered normal for pregnancy.¹,⁷ The effects of GDM on the mother and child can be minimized with good glycemic control.³ Consequently, the ADA has tightened the requirements for the diagnosis of GDM in women.¹
Health Risks of Gestational Diabetes

<table>
<thead>
<tr>
<th>Mother</th>
<th>Fetus</th>
<th>Newborn</th>
<th>Child/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth trauma</td>
<td>Hyperinsulinemia</td>
<td>Respiratory distress syndrome</td>
<td>Obesity</td>
</tr>
<tr>
<td>Increased cesarean delivery</td>
<td>Cardiomyopathy</td>
<td>Hypoglycemia</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Preeclampsia/Gestational Hypertension</td>
<td>Stillbirth</td>
<td>Hypocalcemia</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Large for gestational age/macrosomia</td>
<td>Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Birth trauma</td>
<td>Hyperviscosity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycythemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperbilirubinemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>


Risk factors
Risk factors for GDM can be separated into two groups: unmodifiable and modifiable. Known unmodifiable risk factors include age, genetic background, number of previous pregnancies and possibly a short stature. Modifiable risk factors include obesity, lack of exercise, dietary fat and smoking. Women at risk for developing type 2 diabetes and those with a previous diagnosis of GDM are also at risk for developing GDM.

Screening and Diagnosis
Historically, obstetricians selected patients to be tested for GDM based on historical and clinical risk factors. Those factors included a family history of diabetes, a previous stillbirth, the delivery of a malformed or macrosomic infant, obesity, hypertension, glycosuria and age over 25; however, over half of patients diagnosed with GDMs do not exhibit these risk factors. Many GDM patients do not exhibit any signs or symptoms of glucose intolerance. The onset is often insidious; few of the women have classic triad symptoms: polydipsia (excessive thirst), polyphagia (excessive hunger) and polyuria (excessive urine production).

The ADA has put forth guidelines in the screening and diagnosis of pregnant women. The ADA recommends that all women with risk factors contemplating pregnancy be screened for undiagnosed T2DM at the first prenatal visit, using standard diagnostic criteria. Women diagnosed with diabetes at this stage are not considered to have GDM, but rather overt diabetes. Screening for GDM is recommended in pregnant patients at 24–28 weeks gestation, using a 75 gram glucose 2–hour Oral Glucose Tolerance Test (OGTT) and the ranges in the following table.

von Koeckritz – Gestational Diabetes
Screening and Diagnosis for Gestational Diabetes Mellitus

<table>
<thead>
<tr>
<th>TIME</th>
<th>PLASMA GLUCOSE VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fasting</em></td>
<td>$\geq 92$ mg/dL (5.1 mmol/l)</td>
</tr>
<tr>
<td>1 Hour</td>
<td>$\geq 180$ mg/dL (10.0 mmol/l)</td>
</tr>
<tr>
<td>2 Hours</td>
<td>$\geq 153$ mg/dL (8.5 mmol/l)</td>
</tr>
</tbody>
</table>


A diagnosis of Gestational Diabetes Mellitus is made when at least one of the plasma glucose values is in the range of those listed.

*The OGTT is performed after an overnight fast of at least 8 hours.*

The patient is to fast 8 hours prior to the OGTT. A positive diagnosis of GDM is made after only one abnormal reading. The previous guidelines required two high readings for a positive GDM diagnosis. The diagnostic fasting glucose level and the 2-hour glucose level have been reduced to $\geq 92$mg/dL and $\geq 153$ mg/dL respectively in the ADA guidelines. These updates to the diagnostic criteria will increase the number of pregnant patients who will now be diagnosed with GDM. These criteria changes are being made in response to increases in obesity and diabetes rates, with the purpose of optimizing gestational outcomes for women and their babies.¹

**Treatment**

Once a woman has been diagnosed with GDM, a decision must be made as to whether she should be treated and if so for how long. A woman will be diagnosed late in her pregnancy and little time is usually remaining from the time of the GDM diagnosis to the time of delivery. It is important to recognize that delay in therapy may result in irreversible adverse outcomes.⁴ Treatment for GDM can encompass three different therapies: dietary changes, exercise and pharmacotherapy. ⁴

Medical nutritional therapy (MNT) is the mainstay of GDM treatment.⁹ Women with fasting blood glucose levels less than 95 mg/dL qualify for a trial of MNT. Patients who are unable to achieve the desired glycemic levels after two weeks may then need to initiate pharmacologic therapy.⁴ A diet with a reduction in fat intake and a substitution of complex carbohydrates for refined carbohydrates will help achieve and maintain an appropriate maternal blood glucose profile throughout gestation.² A 1900 – 2400 kcal/day diet, limiting carbohydrates to 35% to 40% of calories, and utilizing complex and high-fiber carbohydrates is generally prescribed.⁶ Researchers have found that a low-glycemic index diet decreased the amount of insulin needed by some patients.⁶ It is important that the patient ingest a sufficient amount of calories to prevent excessive weight loss, persistent ketonuria and excessive hunger.⁶ The ADA recommends that the patient consult with a registered dietitian to individualize a nutrition plan for the patient.² The primary goal in MNT is to achieve euglycemia and provide the required nutrients for fetal
growth and maternal health. A secondary goal is to prevent excessive weight gain during the pregnancy.

Exercise decreases peripheral insulin resistance and is an appropriate adjunctive therapy to diet for the GDM patient. Patients are encouraged to participate in exercise 30 minutes several times weekly.

In cases where the patients are unable to achieve glycemic control with diet and exercise, pharmacotherapy with insulin is recommended. One recommended threshold for initiation of pharmacologic therapy requires a fasting glucose ≥ 95 mg/dL in addition to postprandial levels ≥ 120 mg/dL for 2 hours or ≥ 140 mg/dL for 1 hour. Insulin therapy is safe and effective and is the gold standard against which other therapies for GDM are compared. Regular and NPH insulins, and the short-acting insulin analogs lispro (Humalog) and aspart (Novolog) are considered safe for GDM. There is less evidence supporting the use of long-acting insulin analogs, and the use of insulin glargine (Lantus) and insulin detemir (Levemir) for women with GDM is not currently recommended. Although long-acting insulins are being used by women with type 1 diabetes throughout their pregnancies, the safety profile has not been proven.

Insulin treatment for women with GDM can be done on an outpatients basis. The insulin dosage is maternal weight-based. One insulin regimen doses insulin at 0.7 units/kg actual body weight. This dosage is lower than for pregnant, non-GDM diabetic patients. This more conservative therapy is intended to prevent hypoglycemia. After the total daily dose is calculated, two-thirds of the dose is administered before breakfast (two-thirds NPH insulin and one-third regular insulin) and the remaining one-third is broken up into 2 different doses (one-half regular insulin before dinner and one-half NPH insulin at bedtime).

The use of oral hypoglycemic medications in patients with GDM is controversial. Glyburide and metformin are not FDA-approved for GDM, but some clinicians will prescribe them off-label. The use of glyburide stems from a study, “A Comparison of Glyburide and Insulin in Women with Gestational Diabetes Mellitus”, published in The New England Journal of Medicine, in 2000. The researchers compared the efficacy and safety of glyburide versus insulin in 404 women with GDM. The researchers concluded that the levels of glycemic control between the two groups were equal, and there were no differences in the number of babies with macrosomia, neonatal hypoglycemia, and admission to neonatal intensive care units and fetal anomalies. The incidence of maternal hypoglycemia was lower in the glyburide group versus the insulin group (2% vs. 20%). Glyburide does not significantly cross the placenta. Glyburide, a second-generation sulfonylurea, enhances insulin secretion, which then suppresses the production of hepatic glucose, the main cause of fasting hyperglycemia. Insulin secretion after meals is improved, thus reducing postprandial hyperglycemia. Glyburide is effective in patients who are normal weight or obese, have increased blood glucose levels for less than 5 years and will follow a dietary plan. These features often match that of a woman with GDM. The dose for glyburide in treating GDM is 2.5 mg in the AM or 2.5 mg every 12 hours (may increase weekly by 2.5 mg up to 10 mg every 12 hours).
Metformin is also used off-label to treat GDM in women. Metformin reduces insulin resistance by increasing insulin sensitivity, reduces basal plasma insulin levels and stabilizes or facilitates weight reduction. Additionally, metformin does not stimulate insulin secretion and subsequently does not cause hypoglycemia. Several clinical trials have examined the safety and efficacy of metformin in GDM. Most of the trial researchers conclude that metformin is effective for GDM and safe in the short-term. However, metformin crosses the placenta; any resultant metabolic or teratogenic effects on the fetus are unknown.

### Pharmacologic Agents for Gestational Diabetes

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Insulin</th>
<th>Glyburide</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor-mediated glucose uptake; other actions</td>
<td>Stimulates pancreatic beta cell insulin release</td>
<td>Increases sensitivity to insulin; stimulates insulin-induced glucose uptake</td>
<td></td>
</tr>
<tr>
<td>Onset of action</td>
<td>Varies</td>
<td>Approximately 1 hour</td>
<td>Approximately 1 hour</td>
</tr>
<tr>
<td>Peak</td>
<td>Varies</td>
<td>4 hours</td>
<td>2 to 4 hours</td>
</tr>
<tr>
<td>Dosing</td>
<td>2.5 mg in AM or every 12 hours, increase weekly by 2.5 mg up to a maximum of 10 mg every 12 hours</td>
<td>500 mg in AM or every 12 hours; maximum of 1000 mg every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Placental Transport</td>
<td>Minimal (only-antibody-bound fraction)</td>
<td>Minimal</td>
<td>Yes</td>
</tr>
</tbody>
</table>


In 2008, results from the Metformin versus Insulin for the Treatment of Gestational Diabetes (MiG Trial) study were published in The New England Journal of Medicine. Researchers prospectively assigned 751 women diagnosed with GDM, who were unable to maintain acceptable glycemic control, to treatment with either metformin (with supplemental insulin when required) or insulin alone. The purpose of the trial was to assess the safety and efficacy of metformin during pregnancy. In the metformin treatment arm of the study, 46.3% of the patients received supplemental insulin. Patients receiving the combined metformin/insulin therapy required less insulin plus gained less weight than the insulin only patients. Additionally, the patients preferred metformin to insulin treatment. The researchers concluded that the administration of metformin with or without supplemental insulin is not associated with increased complications as compared with insulin and that metformin alone or with supplemental insulin is a safe and effective treatment option for women with GDM.
Though off-label and controversial, some practitioners advocate the use of metformin for their GDM patients. The doses used for metformin are 500 mg in the AM or 500 mg every 12 hours, up to 1000 mg every 12 hours.\(^6\)

**Monitoring**

In addition to treatment for GDM, close monitoring is important for the long-term health of the mother and the baby. Patients being treated with MNT alone will be advised to check glucose levels 4 times daily (one fasting glucose level and three postprandial levels). Patients on pharmacologic therapy should test 4-6 times daily, including pre-prandial levels. To assess fetal size, the patient should have ultrasound performed every 4 to 6 weeks, or more frequently if macrosomia is suspected.\(^8,13\) The patient is also monitored by her obstetrician on a weekly basis. It is important to recognize that delay in therapy may result in irreversible adverse outcomes.\(^6\)

**Follow-up**

Women with a history of GDM have an increased lifetime risk for diabetes. Patients diagnosed with GDM should be screened 6-12 weeks postpartum for persistent diabetes.\(^1\) It is recommended that a 75-g 2-hour glucose tolerance test be performed at the routine postpartum visit.\(^6\) Additionally, GDM patients should also have lifelong screening for the development of prediabetes or diabetes every 3 years.\(^1\) It may be prudent to increase the testing frequency if the patient is contemplating further pregnancies.\(^6\)

**Pharmacist’s Role**

A diagnosis of GDM implies that the patient and baby will have an increased chance of complications before, during and after delivery and that future pregnancies are also more likely to be complicated by diabetes or GDM.\(^24\) It is important for the woman with GDM to be proactively treated and followed after delivery to prevent or minimize unfavorable outcomes. Pharmacists can help educate the patient regarding the various pharmacotherapy options available to her, including insulin, glyburide and metformin. A diagnosis of GDM is understandably an additional complication when so much is already happening to the patient’s body. The woman will need guidance in blood glucose testing. It is important that we as pharmacists encourage the woman with GDM to be compliant with recommendations for her diet, exercise, blood glucose monitoring and medications she needs to be taking.\(^15,16\) Well controlled glycemia is important for preventing serious medical problems for the mother and the fetus.\(^6\)
References