Pharmacological Management of Gestational Diabetes

An overview

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OBJECTIVE — To provide a review of the background literature regarding the pharmacological management of gestational diabetes.

RESEARCH DESIGN AND METHODS — This is a literature review.

RESULTS — Information is available regarding the use of some, but not all, oral antidiabetes agents in pregnancy.

CONCLUSIONS — Available evidence supports the use of glyburide during pregnancy. Evidence is inadequate to support or refute the use of metformin, an agent that has been shown to cross the placenta and thus could be helpful or harmful to the developing fetus.

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Because insulin preparations tested to date have been determined not to cross the placenta or to cross minimally, insulin has been the treatment of choice in most parts of the world for patients with gestational diabetes whose circulating glucose levels exceed predetermined thresholds. Although advances have been made in developing insulins that may be administered by alternative routes, insulin is typically injected subcutaneously. This poses a barrier to utilization and has been one of the factors that kindled interest over many years in treating gestational diabetes with oral antidiabetic agents. This and the following presentations describe oral agents that have the potential to be used as alternatives to insulin for the treatment of gestational diabetes. In this overview, I shall outline some guiding principles in determining whether a particular agent is appropriate for use in pregnancy and then apply these principles to the most commonly used oral antidiabetes agents.

GUIDING PRINCIPLES — As our understanding of the physiology and pharmacology of both pregnancy and diabetes has increased, some guiding principles have emerged to help us decide which medications are safe and effective for pregnant women. Any medication must, of course, be safe for the person who takes it, or at least the benefits of its use must outweigh the risks. However, when a pregnant woman takes a medication, we are also concerned about that medication's effects on her unborn fetus. Starting with the thalidomide experience in the 1960s, our view of the placenta has shifted from that of a barrier, serving to protect the fetus from harm, to that of a sieve, allowing entry of all kinds of chemicals and substances to the fetal circulation. Whereas neither point of view is entirely accurate, the latter is probably a safer perspective. Thus, the first question one should ask about a medication to be used by pregnant women is whether it crosses the placenta. If it does not, then presumably the fetus is relatively protected from any direct effects. An example of such a medication would be heparin, which as a relatively large and highly charged molecule, does not traverse the placenta to any measurable extent. Heparin is generally considered to be safe for the fetus, although of course it poses significant risks such as hemorrhage and bone demineralization for the mother.

If a medication is shown to cross the placenta, that is not necessarily a contraindication to its use in pregnancy. For example, we frequently prescribe dexamethasone or betamethasone to pregnant women to take advantage of transplacental passage of these drugs, to enhance fetal lung maturation. The second question is whether a medication that reaches the fetal compartment is neutral, helpful, or harmful to the fetus.

The second safety question above also touches on the subject of efficacy. If a drug crosses the placenta and is helpful to the fetus without causing harm, it could then be considered to be both safe and efficacious. Most often, a drug is prescribed during pregnancy to help the mother. The first efficacy question is whether the drug has been shown to help the condition for which the mother is being treated. If the mother has diabetes, and we are considering oral antidiabetic drugs, the answer would generally be yes. However, this will not always be the case. A medication whose mechanism of action is to stimulate pancreatic insulin secretion and/or release would not be helpful to a mother with type 1 diabetes.

There are situations where treating the mother's condition will also help the fetus indirectly. The second efficacy question is whether the drug's effect on the mother will be beneficial, and not harmful, to the fetus. In keeping with the Pedersen Hypothesis, any medication that tends to normalize maternal glycemic levels should benefit the fetus as well. The third efficacy question is whether the drug crosses the placenta and has a direct benefit to the fetus.

It is my view that all of these questions should be considered in making a deci-

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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sion regarding treatment of gestational diabetes with oral antidiabetes agents.

CLASSES OF ORAL ANTIDIABETES AGENTS

— Oral antidiabetes agents are typically classified as insulin secretagogues, insulin sensitizers, and α-glucosidase inhibitors. Recently, a glucagon-like peptide 1 agonist has also been placed on the market.

Insulin secretagogues

The sulfonylureas and meglitinide are insulin secretagogues. The sulfonylureas bind to sulfonylurea receptors in β-cells, stimulating insulin secretion at all blood glucose levels. For sulfonylureas to be effective, the patient must have residual β-cell function, so these drugs are not at all effective in patients with type 1 diabetes or longstanding type 2 diabetes in the stage of insulinopenia. The primary side effect of sulfonylureas is hypoglycemia. The effect of sulfonylureas is to suppress hepatic glucose production, diminish glucotoxicity, and improve insulin secretion after meals. They generally lower circulating glucose levels by ~20% and work best in patients of normal or slightly increased body weight. The first-generation sulfonylureas include tolbutamide, chlorpropamide, and tolazamide. Second-generation sulfonylureas include glipizide (Glucotrol), which is shorter acting; glyburide or glibenclamide (Diabeta and Micronase), which are longer acting; and gimepride (Amaryl), which is also longer acting.

Meglitinides are structurally different from sulfonylureas, but act similarly via a different receptor. The meglitinides that are currently marketed are nateglinide (Starlix) and repaglinide (Prandin).

If insulin secretagogues cross the placenta, they would be expected to stimulate insulin production in the fetus. Presumably this would make diabetic fetopathy worse, even if circulating glucose levels were lowered. In one study (1), which measured tolbutamide levels in mothers taking tolbutamide as well as their newborns, drug concentrations in placental samples and in neonatal blood samples obtained ~3 h after birth were similar to maternal levels. Using an isolated perfused human placental cotyledon model, Elliott et al. (2) demonstrated minimal placental transfer of glyburide, but greater transport of glipizide and particularly chlorpropamide and tolbutamide (3), from maternal to fetal compartments. Glyburide could not be detected in the cord blood of offspring whose mothers took the drug as part of a randomized trial (4). No information is available regarding nateglinide; the package insert (5) lists the drug as Pregnancy Category C, but states, "There are no adequate and well-controlled studies in pregnant women. Starlix should not be used in pregnancy." For repaglinide, the Physicians' Desk Reference (6) states, "Prandin should be used during pregnancy only if it is clearly needed." Given the available data, glyburide appears to be the best candidate insulin secretagogue for use during pregnancy, since it crosses the placental little or not at all and benefits the mother directly and the fetus indirectly. A subsequent presentation will go into detail regarding the use of this drug for women with gestational diabetes.

Insulin sensitizers

There are two broad types of insulin sensitizers: the biguanides and the thiazolidinediones, also called peroxisome proliferator–activated receptor-γ agonists.

The biguanides enhance insulin action, stimulating glucose uptake in the liver and in the periphery and also suppressing hepatic glucose output. They only work when insulin is present, do not stimulate insulin secretion or release, and do not cause hypoglycemia. They are used for patients with type 2 diabetes who have residual β-cell function, typically when diet and exercise are insufficient for diabetic control. They are also useful in the insulin resistance syndrome and constitute an increasingly popular treatment for polycystic ovarian syndrome, often inducing ovulation and resulting in pregnancy. Phenformin was the original biguanide but was removed from the market in the 1960s because of reports of fatal lactic acidosis. Metformin (Glucophage) is the only biguanide currently available in the U.S.

Metformin is a relatively small molecule with a molecular weight of 105.03. If it were to cross the placenta, it might be expected to enhance the action of fetal insulin, which could be beneficial or deleterious to the fetus, depending on which insulin effects are potentiated. According to the package insert (7), metformin is Pregnancy Category B. The manufacturer also states, "Determination of fetal concentrations demonstrated a partial placental barrier to metformin." In conversations with officials at Bristol-Myers Squibb, the manufacturer, I have been unable to obtain the data supporting the latter statement. However, Hague et al. (8) measured plasma metformin levels in seven women taking metformin at a median daily dose of 2,000 mg and in the cord blood of 23 babies whose mothers took metformin during pregnancy. Median plasma metformin levels were 1.05 μg/ml (range 0.06–2.93) in maternal blood and 0.63 μg/ml (range 0.08–2.55) in cord blood samples. These data suggest that significant amounts of metformin can cross the placenta, with fetal concentrations in the range of half of maternal concentrations. Because it is unknown whether metformin is therapeutic or deleterious to the fetus, it would seem prudent to obtain further data (perhaps from animal models) before metformin becomes commonly prescribed during pregnancy. At the very least, patients taking metformin should be counseled about the unknown risks and benefits for the fetus.

The thiazolidinediones are agonists for the peroxisome proliferator–activated receptor-γ. Such receptors are found in target tissues for insulin action. These drugs enhance peripheral insulin action and are useful for patients with type 2 diabetes who have adequate endogenous insulin; they are only useful if insulin resistance is present. Weight gain is common with these drugs and appears to be dose and time dependent. Fluid retention may occur, and peripheral edema develops in 2–5% of patients. Heart failure may be precipitated that is not responsive to diuretics; it does generally respond to discontinuation of the thiazolidinedione therapy. Troglitazone was the original thiazolidinedione, but was removed from the market in 2000 because ~2% of those treated had to discontinue the drug because of hepatotoxicity, and a number of deaths occurred. Currently there are two thiazolidinediones on the market: rosiglitazone (Avandia) and pioglitazone (Actos). These drugs are less hepatotoxic than troglitazone, but patients still require monitoring of liver function tests. These drugs are increasingly used in treating polycystic ovarian syndrome and other aspects of the insulin resistance syndrome. Because they enhance insulin action, it would be logical to consider their use in insulin-resistant states such as pregnancy. Unfortunately, there are no controlled data available in pregnancy, and one study reported that rosiglitazone crossed the placenta in early human pregnancy at 10–12 weeks, with fetal tissue levels measured at about half of maternal

serum levels (9). Use in pregnancy would best await the availability of further data.

α-Glucosidase inhibitors

The α-glucosidase inhibitors slow the absorption of sugars in the upper gastrointestinal tract, decreasing postprandial glucose excursions. Their major side effects are gastrointestinal, particularly flatulence and borborygmus. These drugs do not depend on the presence of endogenous insulin. There are currently two available preparations: miglitol (Glyset) and acarbose (Precose). Although no data are currently available concerning placental passage, miglitol is highly absorbed from the gastrointestinal tract, whereas acarbose is minimally absorbed, so that, on principle, the latter drug would seem to be preferable in pregnancy. Nevertheless, there have been reports of transient elevations in transaminase levels in acarbose-treated individuals, and a few cases of fulminant hepatitis with fatal outcome have been reported. A literature search revealed only two studies of acarbose in gestational diabetes. The first (10) was a case series of six gestational diabetic patients treated with 50 mg acarbose three times daily with meals. In these six patients, glucose levels were normalized, and all six babies were apparently normal. All mothers reported gastrointestinal discomfort. In a preliminary abstract of a randomized trial (11) of acarbose versus insulin in 91 gestational diabetic women failing diet therapy, glucose control and glycohemoglobin results were similar, and only 6% of acarbose-treated patients required insulin. Gastrointestinal side effects were common. Acarbose is not systemically absorbed to an appreciable extent, so transplacental passage should not be an issue. It is directly beneficial to the mother and indirectly to the fetus. This medication appears to hold promise for the treatment of gestational diabetes.

Exenatide

Exenatide (Byetta) is a glucagon-like peptide (GLP-1) agonist that was approved by the Food and Drug Administration for adjunctive therapy when patients with type 2 diabetes have not been optimally controlled on metformin (12). It is an incretin mimetic and potentiates insulin secretion while inhibiting glucagon secretion and slowing gastric emptying. It also promotes satiety. The drug is administered as a subcutaneous injection, generally concomitantly with a sulfonylurea or metformin. Although it has a modest effect on lowering fasting glucose levels, it markedly reduces postprandial glucose. It is a polypeptide consisting of 39 amino acids with a molecular weight of 4186.6. Ex vivo human placental perfusion studies (13) detected minimal levels on the fetal side (fetal:maternal ratio ≤0.017). There are no data available regarding the use of exenatide in pregnancy, and the fact that it must be injected subcutaneously will probably limit interest.

SUMMARY AND CONCLUSIONS

— Available data including poor transplacental passage support the use of an insulin secretagogue, glyburide, to treat gestational diabetes. The widespread use of metformin should await the demonstration of safety for the fetus, since fetal levels are approximately half of maternal levels. Acarbose may be a worthwhile approach if the published preliminary data from a randomized trial are confirmed in the final report and if the issue of gastrointestinal disturbance can be overcome. Given the available evidence regarding placental transfer, and the lack of data from pregnancy, thiazolidinediones should not be used until more information is available. Incretin mimetics do not yet show promise for use in gestational diabetes.

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