Pharmacological treatment of gestational diabetes mellitus: point/counterpoint

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Everyone is entitled to his own opinion but not to his own facts.
—Late Senator Patrick Moynihan

Controversies persist over the most efficacious pharmacologic treatment for gestational diabetes mellitus. For purposes of accuracy in this article, the individual American College of Obstetricians and Gynecologists Practice Bulletin and American Diabetes Association Standards of Medical Care positions on each issue are quoted and then deliberated with evidence of counter claims presented in point/counterpoint. This is a review of all the relevant evidence for the most holistic picture possible. The main issues are (1) which diabetic drugs cross the placenta, (2) the quality of evidence and data source validity, (3) the rationale for the designation of glucose control as the primary outcome in gestational diabetes mellitus, and (4) which drugs (metformin, glyburide, or insulin) are most effective in improving secondary outcomes. The concept that 1 drug fits all, whether it be insulin, glyburide, or metformin, is a fallacy. Different drugs provide certain benefits but not all the benefits and not to all patients. In addition, the steps in the gestational diabetes mellitus management decision path and the current cost of the use of insulin, glyburide, or metformin are addressed. In the future, we must consider studying the potential of diabetic drugs that currently are used in nonpregnancy and incorporating the concept of precision medicine in the decision tree to maximize pregnancy outcomes.

Key words: insulin, glyburide, GDM, metformin

The 2017 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on the use of oral hypoglycemic agents to manage gestational diabetes mellitus (GDM) were polarizing. Here, the ACOG conclusions are placed into the greater context of the published literature, providing a more holistic picture of the best approaches to patient care. Patients with GDM traditionally have been treated with diet and insulin when required. Before 2001 in the United States, the use of oral hypoglycemic agents was considered contraindicated in pregnancy because of the risk for fetal anomalies and adverse metabolic effects, such as neonatal hypoglycemia within 4−10 days of birth.[1,2] Castillo et al[3] studied commercially insured women with GDM. The patients were treated with insulin (n=10,778) or glyburide (n=5873) by calendar year, which was documented from pharmacy claims. The authors reported that before 2000, <1.0% of patients used oral hypoglycemic agents, which increased to 7.4% in 2001 and to 64.5% in 2011. The authors concluded that glyburide had replaced insulin as the more common pharmacotherapy for GDM.[3,4] A recent 38-question survey, with a 40% response rate (of 2330 members of the Society of Fetal Maternal Medicine), revealed that glyburide was used by 57% of practitioners as a first-line agent; 4% of them used metformin. Long-acting insulin analogs (glargine and/or detemir) were used by 46% and 33.6%, respectively.[5]

Although the 2013 ACOG Practice Bulletin[4] recommended that, when pharmacologic treatment of GDM is indicated, insulin and oral medications are equivalent in efficacy and either can be appropriate first-line therapies. The 2017 ACOG Practice Bulletin[6] (level C: based primarily on consensus and expert opinion) stated: "Insulin is considered the first-line treatment for diabetes in pregnancy since insulin does not cross the placenta. Glyburide should not be recommended as a first-line pharmacologic treatment because, in most studies, it does not yield equivalent outcomes to insulin. Metformin is a reasonable second-line choice."

These contradictory recommendations have led to confusion and debate and potentially have become major barriers to policy and practice decision-making. Therefore, there are several major questions that practitioners must ask themselves regarding the use of pharmacologic therapy in GDM.

Which diabetic drug(s) cross the placenta?

Point

The 2017 ACOG Practice Bulletin[6] stated that "Insulin should be considered the first-line treatment for diabetes in pregnancy because it does not cross the placenta." The 2017 American Diabetes Association Standards of Medical Care (ADA) stated that insulin is the preferred medication for the treatment of hyperglycemia in GDM because it "does not cross the placenta to a measurable extent. Metformin and glyburide may be used, but both cross the placenta with metformin likely crossing to a greater extent than glyburide."[7]

Counterpoint

The fetus is exposed to most drugs that are taken by the mother. The placenta is capable of limiting fetal exposure to drugs, specifically with respect to glyburide and insulin. Thousands of patients have been treated with glyburide, metformin, and insulin during pregnancy with no teratogenic effects to the fetus.[3-5] Therefore, it is not which drug crosses the placenta but rather which drug may affect the fetus adversely.

Placental transfer of insulin was investigated in several in vitro insulin perfusion studies.[8-14] Bauman and

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Yalow[8] in the 1980s demonstrated that beef-pork-insulin (antibody) crosses the placenta. With the development of human and analog insulins, researchers reevaluated insulin placental transfer. In studies of human insulin,[9-11] 1−5% of insulin concentration in the maternal artery transferred to fetal circulation. In another study of human insulin,[12,13] fetal concentrations corresponded to peak serum insulin levels after doses of 14, 24,104, and 278 units. A study of insulin lispro reported concentration-dependent transfer to fetus at maternal levels of ≥ 580 μU/mL (equaling approximately 75 units). A study of insulin glargine[14] demonstrated transfer across the placenta when the dose was >0.3 unit/kg. In translating these findings into clinical practice and taking into account that two-thirds of women with GDM are obese with maternal weight >70−80 kg, the calculated dose for the initiation of insulin is 0.7−1 units/kg/d. The calculated dose may be increased by 10−20% every 3−7 days. Thus, many fetuses may be exposed to insulin.[15,16]

Elliot et al[17-19] reported that the percent transfer of glyburide within a 2-hour perfusion resulted in negligible levels on the fetal side, even if maternal concentration was >8 times the therapeutic dose. These findings were confirmed by several studies.[20-26] Hebert et al[27] studied glyburide placental transport in vivo. In vivo studies use nanograms in measurement with 1 mg=1.000.000 ng. Umbilical venous concentrations ranged from not detectable to 12.5 ng/mL (mean ratio, 0.7±0.4). The ratio is time-dependent from drug administration to obtaining the sample. In addition, the rate of drug clearance in the mother and fetus potentially affect the concentration. In this study, fetal cord glyburide level was <1 ng/mL (n=4), 1−3 ng/mL (n=7), and 3−12 ng/mL (n=5), with an overall mean of almost 1 ng/mL. Mean drug administration to sampling was 13 hours. Similar findings were reported with umbilical glyburide level with a mean level of 7.5±8.2 ng/mL, a median level of 3.7 ng/mL, and a range of 0.68−32.4 ng/mL.[28]

Metformin transfer across the placenta has been measured with the use of the recirculating single cotyledon model in several studies.[29,30] Vanky et al[31] reported that metformin passes freely across the placenta; fetal serum levels are comparable with maternal values in patients with polycystic ovary. Another study reported that there is a ratio of 0.73 between metformin concentration and umbilical cord/maternal serum.[32]

Importantly, and related to the question of which drugs cross the placenta, do glyburide and/or metformin transfer during lactation? The exposure of infants to second-generation sulfonylureas (eg, glipizide, glyburide) and/or metformin through breast milk is expected to be minimal.[33] The benefits of breastfeeding greatly outweigh the risks of infant exposure to these medications, if any. Only when the drug level in the lactating newborn infant is ≥10% is there reason for concern.[33] In a study of metformin, the infant level was 0.28% weight normalized to maternal dose.[33] In another study by Feig et al,[34] neither glyburide nor glipizide was detected in breast milk, and neonatal hypoglycemia was not observed.

Very little is known about the presence of insulin in human milk. Current guides for medical treatment suggest that insulin does not pass into milk because the general belief is that insulin is too large to cross over from blood into milk. Insulin level rapidly decreases during the first few days of lactation, and then, unlike other serum proteins of similar size, achieves comparable levels with those in serum. Whitmore et al[35] demonstrated that insulin is transported into human milk at comparable concentration with serum, which suggests an active transport mechanism. Although there are a number of potential implications for the infant of the presence of artificial insulins in milk, it is beyond the scope of this article to discuss it in detail.

What is the quality of evidence and data source validity?

Point

The 2017 ACOG Practice Bulletin[6] stated: "Two recent metaanalyses have demonstrated worse neonatal outcomes with glyburide compared with insulin in the treatment of GDM. Specifically, neonates born to women treated with glyburide had higher rates of respiratory distress syndrome, hypoglycemia, macrosomia, and birth injury. These poorer outcomes were reported despite the fact that individual trials comparing glyburide to insulin failed to show any significant difference in degree of glycemic control. Observational studies have reported higher rates of preeclampsia, hyperbilirubinemia, and stillbirth with the use of glyburide as compared with insulin, but many other outcomes have not been significantly different."

Counterpoint

Many factors influence the results of studies on pregnancy outcome and may mask actual results. Among them are misinterpretations of administrative databases and study design of metaanalysis. In addition, a sample size that is too large produces "mass significance" that can be as misleading as a sample size that is too small.[36]

Several metaanalyses of randomized controlled trials and observational studies evaluated the effect of the results of treatment with glyburide or metformin in comparison with insulin therapy.[37-43] However, verification of the methods and the statistical analysis that were used in each study are not feasible because the raw data were not available. Different designs that address the same question often yield different results. Secondary outcomes were conflicting. The chance for error is much less in a single study than in a systematic review or metaanalysis. No agreement was found among neonatal hypoglycemia, increased birthweight, incidence of large-for-gestational-age (LGA), or macrosomia although the authors used the same 8 studies in the analysis. Therefore, we must be vigilant when considering the results and reliability of a metaanalysis. In the aforementioned analyses, both observational and randomized controlled trials were included, with both insulin and metformin studies incorporated into the same metaanalysis. The majority of studies lacked power; 5 different sets of criteria were used to define GDM in the 8 studies, and there was no uniform definition of