



# SMFM Statement: Pharmacological treatment of gestational diabetes

Society of Maternal-Fetal Medicine (SMFM) Publications Committee

**T**reatment for gestational diabetes mellitus (GDM) is associated with improved perinatal outcomes that include reduced frequency of hypertensive disorders of pregnancy, delivery of a large-for-gestational-age (LGA) infant, shoulder dystocia, and cesarean delivery.<sup>1</sup> Although medical nutritional therapy is the first-line intervention for GDM, some evidence suggests that up to 30% of women require pharmacologic treatment to maintain euglycemia.<sup>2</sup>

In the United States, 3 pharmacologic therapies are used to treat GDM: insulin, metformin, and glyburide. Previous recommendations by the American College of Obstetricians and Gynecologists, as well as current recommendations by NICE<sup>3</sup> and others<sup>4,5</sup> support the use of oral hypoglycemic agents as first-line therapy. Despite U.S. providers' decades of experience using oral hypoglycemic agents in pregnancy, a recent Practice Bulletin published by the American College of Obstetricians and Gynecologists now more strongly endorses insulin as the preferred first-line therapy for GDM treatment, with a recommendation that oral hypoglycemic agents be reserved for women unable or unwilling to use insulin.<sup>6</sup> This recommendation has engendered some controversy, particularly as no new evidence has emerged to justify the change. Rather, recent meta-analyses and systematic reviews support the efficacy and safety of oral agents.<sup>7,10</sup> The purpose of this Society for Maternal-Fetal Medicine (SMFM) Publications Committee statement is to review the available scientific literature regarding pharmacological treatment of GDM and to provide additional guidance to obstetric care providers regarding treatment of these women. Although this statement differs in some respects from the the American College of Obstetricians and Gynecologists Practice Bulletin, the SMFM Publications Committee acknowledges that this difference is based on the values placed by different experts and providers on the evidence available in the medical literature and is not meant to represent an exclusive course of management.

Although neither insulin, metformin, nor glyburide use during pregnancy has been associated with newborn birth defects,<sup>11</sup> long-term metabolic effects of offspring exposed in utero to oral hypoglycemic agents are less well known. Because insulin does not cross the placenta, and based on almost 100 years of experience of use in pregnancy, most

experts concur that insulin is safe for the fetus and newborn, and the American Diabetes Association endorses insulin as a first-line treatment for GDM.<sup>12</sup> However, insulin requires multiple daily injections, which can reduce compliance. Studies comparing insulin to metformin have reported a strong patient preference for the oral agent.<sup>13</sup> In addition, insulin use is associated with an increased risk of hypoglycemia, although hypoglycemia in women with GDM is not common and typically is not severe. In a 2017 Cochrane review, the rate of maternal hypoglycemia was not significantly higher in women treated with insulin vs oral agents (RR 3.01, 95% CI 0.74 to 12.27), and several studies report no maternal hypoglycemia in either group.<sup>10</sup>

Metformin is an oral biguanide that primarily acts to decrease hepatic glucose production by inhibiting gluconeogenesis. It also increases glucose uptake in peripheral tissues and decreases glucose absorption in the gastrointestinal tract.<sup>14</sup> Compared with insulin, metformin use in GDM is associated with less maternal weight gain, lower gestational age at delivery, less gestational hypertension, and less neonatal hypoglycemia.<sup>7,15</sup> Maternal side effects of metformin are largely gastrointestinal and include transient anorexia, nausea, and loose stools, causing 2% of pregnant women to discontinue use in one study.<sup>13</sup>

Unlike insulin, metformin readily crosses the placenta, resulting in fetal concentrations similar to those in the maternal circulation and raising concern for impact on neonatal outcomes as well as long-term effects.<sup>16</sup> Reassuringly, in one study, children aged 2 years who were exposed in utero to metformin vs insulin had similar overall body fat but more subcutaneous fat over intraabdominal fat; this effect is postulated to mean that metformin treatment may lead to a more favorable pattern of fat distribution compared with insulin.<sup>17</sup> In this same cohort, these children were also reported to have comparable neurodevelopmental outcomes compared with those exposed to insulin.<sup>18</sup> Thus, although studies on long-term outcomes in offspring exposed to metformin in utero are more limited than those regarding insulin, available data are reassuring.<sup>19</sup>

Glyburide is an oral sulfonylurea that primarily acts by increasing insulin secretion from the pancreas.<sup>20</sup> Although initial studies did not detect glyburide in cord serum of infants whose mothers were treated with glyburide for GDM,<sup>21</sup> subsequent studies suggest that it is present in concentrations averaging approximately 70% of maternal levels.<sup>22</sup> To date, there are no studies evaluating the long-term

effects on metabolic or neurodevelopmental outcomes in offspring exposed to glyburide in utero.

Since the introduction of oral hypoglycemic agents, their use in pregnancy has increased.<sup>23</sup> One study of a cohort of privately insured U.S. women showed that from 2001 to 2011, glyburide use increased from 7.4% to 64.5%.<sup>24</sup> Factors contributing to this increase in use include the fact that, compared with insulin, oral hypoglycemic agents have a lower cost and higher patient acceptance, which may increase patient satisfaction and/or compliance.<sup>13</sup>

Because of its almost limitless ability to escalate and titrate doses to control blood glucose, insulin is presumed to be the most effective means to control hyperglycemia associated with GDM. In more than one-half of GDM pregnancies, oral hypoglycemic agents as monotherapy result in adequate glycemic control. In clinical trials comparing glyburide and metformin to insulin, the need for adjunctive insulin to achieve glycemic control ranges between 26% and 46% for women using metformin and 4% and 16% for women using glyburide.<sup>13,21,25,26</sup> In a randomized controlled trial comparing metformin to glyburide, women using metformin were twice as likely to need insulin as women using glyburide (RR 2.1, 95% CI 1.2–3.9).<sup>25</sup>

In one of the first studies of oral hypoglycemic agents in pregnancy, in 2000 Langer et al. randomized women with GDM to treatment with glyburide vs insulin and found no significant differences in glycemic control or perinatal outcomes.<sup>21</sup> Another randomized trial of GDM management compared metformin to insulin and found no differences in a composite outcome of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, or 5-minute Apgar score <7. Women on metformin experienced higher rates of preterm birth (12.1 vs 7.6%, RR 1.60, 95% CI 1.02–2.52) but lower rates of neonatal hypoglycemia and less gestational weight gain. Both of these trials concluded that oral hypoglycemic agents were an appropriate alternative to insulin for GDM treatment.<sup>13,21</sup>

Most randomized trials of oral hypoglycemic agents vs insulin to treat GDM have been relatively small and underpowered to draw conclusions regarding uncommon or rare outcomes. However, several meta-analyses and systematic reviews have compared the three therapeutic options for GDM treatment. A 2015 meta-analysis by Balsells et al. analyzed 7 studies comparing glyburide to insulin (798 subjects), 6 comparing metformin to insulin (1362 subjects), and 2 comparing glyburide to metformin (349 subjects).<sup>7</sup> Compared with both insulin and metformin, glyburide was associated with higher birth weight and more frequent macrosomia and neonatal hypoglycemia. Metformin was associated with less maternal weight gain and fewer LGA infants but higher rates of preterm birth (pooled risk ratio 1.50, 95% CI 1.04–2.16). The authors concluded that glyburide is inferior to both insulin and metformin, and that metformin (plus insulin when required) performs slightly better than insulin.<sup>7</sup>

More recently, Farrar et al. analyzed 11 studies comparing metformin to insulin (2365 subjects), 9 studies comparing glyburide to insulin (981 subjects), and 4 studies comparing glyburide to metformin (508 subjects). The authors concluded that metformin was associated with the lowest risk of neonatal hypoglycemia, macrosomia, LGA, preeclampsia, and neonatal intensive care unit admission and comparable preterm birth risk. Although acknowledging weaknesses in the data, they describe a general “trend” in favor of metformin over insulin or glyburide and suggest either metformin or insulin if glucose levels are not adequately controlled with dietary and lifestyle modifications.<sup>8</sup> Finally, two Cochrane Reviews in 2017 addressed oral hypoglycemic agents and insulin for management of GDM (9, 10). In these reviews, the authors concluded that there was insufficient high-quality evidence to assess whether one oral hypoglycemic agent is superior to another or to insulin, and note that the choice to use one or the other may reasonably be based on physician or maternal preference, availability, or the severity of GDM.<sup>9,10</sup>

It should be also noted that both maternal and perinatal outcomes are influenced not only by the type of agent that is used to treat GDM, but by many other variables, including indications for screening (who is screened), timing of screening, type of screening (one- vs two-step screening and the screening protocol chosen), criteria for GDM diagnosis, criteria to start therapy after failure of dietary and lifestyle interventions alone, dosage and frequency of initial therapy, frequency of glucose monitoring, target glucose values, criteria for pharmacologic therapy dosage adjustment, and criteria for adding or switching pharmacologic therapy.

Given the available data, the SMFM Publications Committee concludes that in women with GDM in which hyperglycemia cannot adequately be controlled with medical nutrition therapy, metformin is a reasonable and safe first-line pharmacologic alternative to insulin, recognizing that one-half of women will still require insulin to achieve glycemic control. Although concerns have been raised for more frequent adverse neonatal outcomes with glyburide, including macrosomia and hypoglycemia, the evidence of benefit of one oral agent over the other remains limited. Clearly, further data are needed to establish long-term safety of these agents.

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