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Comparing Rates of Macrosomia and Neonatal Hypoglycemia of Differing Treatment Modalities of Gestational Diabetes Mellitus

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by

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Table of Contents

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Abstract

Gestational diabetes mellitus (GDM) is a known potential complication that can occur during pregnancy. Unmanaged GDM can result in maternal hyperglycemia, which can cause increased neonatal complications, two of which are macrosomia and neonatal hypoglycemia. To prevent maternal hyperglycemia, treatment of GDM typically begins with dietary changes, home glucose monitoring, increased exercise patterns and other lifestyle modifications. However, if maternal hyperglycemia persists after two weeks of maternal lifestyle modifications, there are not current best practice guidelines established for the treatment of GDM. Historically, subcutaneous multiple daily dosed insulin (MDI) has been the gold standard for treatment after lifestyle modification. However, in more recent years oral antihyperglycemic medications, glyburide and metformin, have seen increased use for the treatment of GDM. Additionally, with advancing technology and the development of continuous subcutaneous insulin infusion (CSII), there is discussion regarding which insulin delivery method will achieve more consistent rates of euglycemia to help reduce rates of neonatal hypoglycemia and macrosomia. This scholarly literature review will provide a general overview of GDM, compare treatment modalities (subcutaneous multiple daily dosages of insulin, continuous subcutaneous insulin infusion, metformin and glyburide) of GDM in terms of rates of neonatal hypoglycemia and macrosomia, and compare the safety of differing treatment modalities.

Key Words: Gestational diabetes mellitus, macrosomia, neonatal hyperglycemia, glyburide, metformin, insulin, continuous subcutaneous insulin infusion (CSII)

Comparing Rates of Macrosomia and Neonatal Hypoglycemia of Differing Treatment Modalities of Gestational Diabetes Mellitus

Gestational diabetes (GDM) rates are increasing in the United States, and there are currently no best practice recommendations for treatment (SMFM, 2018). It is known that persistent hyperglycemia in pregnancy will result in complications such as neonatal macrosomia or hypoglycemia (Poomalar, 2015). Options for treatment of GDM/ hyperglycemia begin with diet alone, advancing to oral pharmacological therapy, or insulin delivered either subcutaneously or continuous subcutaneous insulin infusion (CSII). If unable to control gestational diabetes with diet alone, treatment must be advanced to pharmacologic interventions. It is at this point, when treatment needs to be advanced, that there is no well-established current best practice recommendation to further manage gestational diabetes.

This review will compare differing pharmacological GDM treatment modalities to assess how each affects neonatal outcomes to include macrosomia and neonatal rates of hypoglycemia. Treatment modalities compared will include: metformin, glyburide, subcutaneous insulin injections, and CSII. While the focus of the review will be on which treatment(s) result in lower rates of macrosomia and neonatal hypoglycemia, potential side effects of each treatment must be considered and will also be discussed.

Statement of the Problem

Beyond lifestyle modification, including dietary changes and exercise, there is no gold standard recommendation for the treatment of GDM. Historically, insulin therapy was thought to be second-line treatment if diet/exercise failed to achieve euglycemic control (Poomalar, 2015). With the development of oral antihyperglycemics there is controversy of what is appropriate for

second-line therapy. Additionally, with the development of new technology, such as an insulin pump, there must be further discussion as to what method of insulin delivery is best for women with GDM in order to achieve euglycemia and prevent complications of gestational diabetes including macrosomia and neonatal hypoglycemia. It is necessary to compare rates of both macrosomia and neonatal hypoglycemia when assessing the efficacy of GDM treatment modalities, including: oral antihyperglycemics (metformin or glyburide), subcutaneous insulin injections, and CSII.

Research Questions

In patients with GDM, is there a difference in rates of macrosomia and neonatal hypoglycemia when comparing metformin, glyburide, insulin via subcutaneous injections, and insulin via CSII?

In patients with GDM, will taking metformin, glyburide, subcutaneous insulin injections or insulin via CSII, yield safer and more efficacious results?

Research Methods

A scholarly literature review using the PubMed database yielded multiple literature reviews, randomized clinical trials, one nested case-control study, and several expert opinion articles regarding treatment modalities and potential treatment side effects for GDM. Terms searched included: Gestational Diabetes (GDM), insulin, metformin, glyburide, insulin pumps, subcutaneous insulin injections, pharmacological therapy, oral agents, macrosomia, pregnancy, neonatal hypoglycemia, outcomes. Review articles, expert opinions and studies were limited to those with the highest level of evidence and those published after the year 2005. However, due to a limited number of studies and reviews conducted regarding insulin pump therapy for the

management of GDM, the search was expanded to include studies and reviews dating as far back as 2000. Studies and literature reviews included only articles in English and human studies. This article is not a complete literature review including all studies and reviews regarding the management of gestational diabetes and comparison of treatment modalities on rates of macrosomia and neonatal hypoglycemia. Excluded studies include those published prior to the year 2000, those in a language other than English, and those completed on animals.

Literature Review

Overview of Gestational Diabetes and Potential Fetal Risk Factors

Gestational Diabetes is a common condition that can develop during pregnancy. In the 2018 ACOG bulletin, it was found that, "In 2009, 7% of pregnancies were complicated by any type of diabetes, and 86% of the cases represented women with GDM." (Caughey & Turrentine, 2018, p. e49). A 2017 review by Dirar and Doupis define GDM as, "…any degree of hyperglycemia recognized for the first-time during pregnancy," with suspicion for both undiagnosed type 2 diabetes, and true gestational diabetes (p. 489). It is a condition of glucose intolerance due to increased insulin resistance (Dirar, 2017). The pathophysiology behind the development of GDM is thought to be multifactorial including increased secretion of pregnancy-associated hormones, placental hormone production, increased adipose tissue, and beta-cell dysfunction all of which lead to increased cellular insulin resistance (Kamana, Shakya, & Zhang, 2015). Increased insulin resistance can lead to maternal hyperglycemia. Persistent maternal hyperglycemia associated with GDM raises the risk of neonatal hypoglycemia. Neonatal hypoglycemia occurs due to fetal hyperinsulinemia in response to exposure to glucosemia in the mother (Dirar, 2017; Kamana et al., 2015). If GDM is untreated, maternal hyperglycemia will persist, which will allow more glucose to pass through the placenta and into the fetal blood

supply (Kamana et al., 2015). Ultimately, the fetus will be exposed to extra glucose, which it will store as body fat, resulting in macrosomia (Kamana et al., 2015). Kamana et al. (2015) also found that, "macrosomic neonates have 5-fold higher rates of severe hypoglycemia" (p. 15). Therefore, macrosomia, otherwise known as large-for-gestational-age, in addition to neonatal hypoglycemia, is a common fetal outcome related to maternal hyperglycemia and subsequent glucosemia associated with GDM (Kamana et al., 2015). While this literature review does not address the following additional factors, it must be noted macrosomia is a risk due to increased rates of shoulder dystocia, brachial plexus trauma, and increased risk of the need for emergent delivery via cesarean section, which may lead to both maternal and other neonatal complications (Kamana et al., 2015).

While it is known macrosomia and neonatal hypoglycemia are fetal risk factors associated with unmanaged GDM, McCance's 2015 review and meta-analysis of randomized control trials found the appropriate treatment of GDM showed reduced rates of birth weight. Furthermore, Caughey's 2018 ACOG practice bulletin reviewed the 2005 Australian Carbohydrate Intolerance Study in Pregnant Women trial and found treatment of GDM reduced rates of macrosomia as well as other fetal risk factors. Review of an additional randomized, multicenter control trial in the United States found that while there was no reduction in rates of neonatal hypoglycemia with treatment of GDM, there was reduction in the rate of macrosomia and large-for-gestational-age infants (Caughey, 2018).

While it is not a question of whether treatment of GDM and the prevention of maternal hyperglycemia will produce better fetal outcomes, the question of ***what*** treatment option will yield better outcomes still stands.

Rates of Neonatal Complications Associated with Specified GDM Treatment

Continuous subcutaneous insulin infusion versus multiple daily insulin injections.

Insulin has been the longstanding treatment for GDM after dietary changes have failed to control hyperglycemia after one to two weeks of dietary modification (Poomalar, 2015). Insulin can be administered in two different forms, either via multiple daily injections (MDI) or using a continuous subcutaneous insulin infusion system (CSII), otherwise known as an insulin pump. While studies have demonstrated use of an insulin pump can reduce rates of hypoglycemia, as well as improve overall blood glucose control, there is discussion of the usefulness of insulin pump therapy in pregnancy (Kesavadev, 2016). Kesavadev (2016) found that a 2004 meta-analysis of six small randomized control trials failed to demonstrate better glycemic control or improved fetal outcomes with a CSII compared to insulin delivery via MDI. A review conducted by Castorino, Paband, Zisser, & Jovanovic (2012) provided a comparison of the use of CSII with the use of MDI in the treatment of diabetes in pregnancy. While the study population was primarily limited to type 1 diabetes in pregnancy, there was no significant difference in blood glucose control with the use of either CSII versus MDI (Castorino et al., 2012). In contrast, Simmons, Conroy, Thompson, & Scott's 2001 nested case control study compared pregnancies (complicated by GDM or DM2) who used CSII versus MDI for blood sugar management. It was found that mothers who used CSII to control blood glucose levels had greater insulin requirements, greater weight gain, and neonates more likely to be admitted to a NICU; but they did not have higher rates of macrosomia or greater rates of neonatal hypoglycemia compared to mothers who used MDI for blood sugar control (Simmons et al., 2001). A more recent 2016 Cochrane interventional review conducted by Farrar, Tuffnell, West J., & West HM., found there was insufficient evidence to conclude whether CSII or MDI will produce better outcomes for diabetes in pregnancy. Overall, due to the limited number of trials, as well as design limitations

and small sample sizes, the evidence available to assess rates of macrosomia and neonatal hypoglycemia in GDM and diabetes complicating pregnancy is low in quality. More trials, with larger sample sizes and more consistent study limitations, need to be conducted to further assess the efficacy of CSII vs MDI for the treatment of GDM.

Glyburide versus multiple daily injections of insulin.

While insulin has historically been the initial go-to for treatment of GDM, since 2007 glyburide has become the most commonly prescribed medication for management of GDM, if dietary modifications fail to control hyperglycemia (Corcoy, 2018). However, there is still discussion whether glyburide is a better initial treatment when compared to insulin. In Coustan and Barbour's 2017 expert opinion article, the authors reviewed a multi-institutional randomized control trial by Senat et al. that was designed to assess if glyburide was inferior to insulin in the treatment of GDM in terms of preventing perinatal complications. Out of the 809 women included in the per-protocol analysis, the potential outcomes of macrosomia, hypoglycemia and/or hyperbilirubinemia occurred in 23.4% infants born to insulin treated GDM, and 27.6% of infants born to glyburide treated GDM (Coustan et al., 2017). While the study was attempting to show that glyburide was inferior to insulin, it did not find conclusive evidence to prove glyburide's inferiority in terms of preventing macrosomia or neonatal hypoglycemia (Coustan et al., 2017). Additionally, a 2005 expert opinion article by Saade reviewed a 2000 study conducted in the United States that compared MDI versus glyburide to treat GDM. It was found that blood sugar concentrations before and during treatment, as well as neonatal outcomes, were not significantly different. Saade's article did, however, point out that there were lower rates of maternal hypoglycemia in the glyburide treated group than in the MDI group (Saade, 2005). To contrast, a more recent review by the Society for Maternal Fetal Medicine found that in a meta-

analysis conducted in 2015 of seven different studies comparing insulin to glyburide, glyburide was associated with both increased rates of macrosomia and neonatal hypoglycemia (SMFM, 2018). To further support this data, a 2018 review looking at pooled data from seven different randomized control trials found glyburide use in the treatment of GDM will cause fetal hyperinsulinemia, later resulting in macrosomia and neonatal hypoglycemia (Corcoy, Balsells, Garcia-Patterson, Shmueli, & Hadar, 2018).

Metformin versus multiple daily injections of insulin.

While insulin and glyburide have been the preferred treatments in the United States for GDM, other countries have been using metformin more routinely for the treatment of GDM. In New Zealand, for example, metformin use has increased and is now being more widely researched as a treatment alternative to insulin (Corcoy, 2018). In Corcoy's 2018 review of randomized control trials comparing treatments of GDM it was found that when comparing metformin versus insulin, there are lower rates of both macrosomia and neonatal hypoglycemia with the use of metformin. However, there is also an increased rate of preterm births and increased use of supplemental insulin as gestational age advances (Corcoy et al., 2018). SMFM's review supported Corcoy's findings, noting, "Metformin was associated with less maternal weight gain and fewer large-for-gestational-age infants but higher rates of preterm birth (pooled risk ration 1.50, 95%, CI 1.04-2.16," (2018, p. B3). Additionally, there were lower rates of neonatal hypoglycemia with GDM treated with metformin versus insulin (SMFM, 2018). An early review written by Poomalar in 2015 discussed a systemic review by Su et al, which looked at 6 randomized clinical trials involving 1420 patients. It was found that when compared to insulin, metformin treated groups saw no increase in adverse maternal or fetal outcomes, but instead saw less overall maternal weight gain as well as lower rates of neonatal hypoglycemia

(Poomalar, 2015). Poomalar also discussed an additional review by Niromanesh et al., which illustrated that when compared to insulin treated groups, there were lower birth weights observed in the metformin treated group, although rates were not statistically significant (Poomalar, 2015). Following suit, Su and Wang's 2014 review of six randomized control trials all dating 2012 or earlier, n= 1420 subjects, showed statistically lower rates of neonatal hypoglycemia (RR= 0.77, 95% CI 0.60-0.99) with metformin use compared to insulin use (Su, 2014). However, data analysis showed no difference in rates of macrosomia with either treatment group (RR= 0.87, 95% CI 0.69-1.11) (Su, 2014). Although not used as a measurement of outcomes in this scholarly project, it should be noted that metformin treated groups had increased rates of preterm delivery (Su et al., 2014). In a 2015 meta-analysis including eight randomized control trials, Kitwitee et al., found metformin treated groups had lower rates of neonatal hypoglycemia and fewer NICU admissions, p= 0.01 and p= 0.03, respectively. There was not a statistically significant difference between metformin and insulin groups regarding rates of macrosomia, however. (Kitwitee et al., 2015).

Glyburide versus metformin.

While insulin therapy has long been thought of as the mainstay treatment for GDM, oral medications, metformin and glyburide, represent an additional treatment option. Poomalar's 2015 review found glyburide and metformin, in the treatment of GDM, to be relatively comparable. There was a small, non-statistically significant, difference in the rates of macrosomia and neonatal hypoglycemia, with glyburide groups having a higher rate of both outcomes (Poomalar, 2015). SMFM's 2018 review found there were four studies in Farrar et al.'s meta-analysis comparing glyburide to metformin, yielding a total of 508 subjects. It was found that metformin, when compared to glyburide, showed the lowest risk of neonatal

hypoglycemia and macrosomia, and had similar rates of preterm births (SMFM, 2018). Similar results were found in Corcoy's 2018 review. The 2018 review of randomized control trials was conducted to assess neonatal outcomes comparing oral antihyperglycemics versus insulin in terms of neonatal outcomes. Corcoy also assessed if there are long-term outcomes of metformin use to treat GDM on the offspring. The literary review of pooled data from seven randomized control trials found, "…higher birth-weight (MD 109 g, 95% CI 35.9-181), and more macrosomia (RR= 2.62, 95% CI 1.35-5.08) and neonatal hypoglycemia (RR= 2.04, 95% CI 1.30-3.20) in the group treated with glyburide," when compared to the group treated with insulin (Corcoy, 2018, p. 2). However, treatment of GDM with metformin yielded opposing results: lower rates of macrosomia and less neonatal hypoglycemia (Corcoy, 2018). Corcoy's 2015 review of the Metformin in GDM (MiG) study of 2008, which randomized a total of 363 women with GDM to either treatment with metformin or insulin, and found women treated with metformin had, "…a trend towards less neonatal hypoglycemia (RR= 0.78, 95% CI 0.60-1.01)," (2018, p. 3). Other outcomes noted, although not assessed in this scholarly project included lower maternal total weight gain, lower overall rates of blood glucose levels, and higher rates of pre-term birth in the group of GDM treated with metformin (Corcoy, 2018). Corcoy has further assessed six other meta-analyses of RCTs comparing GDM treated with metformin vs insulin and has continued to find consistent results including lower rates of macrosomia in women treated with metformin (2018). When comparing glyburide therapy to metformin therapy, a meta-analysis of one study reviewed offspring had less macrosomia (RR= 0.33, CI 95% 0.13-0.81) and a lower rate of neonatal hypoglycemia (0 vs 12.5%) with metformin therapy (Corcoy, 2018). There was, nonetheless, a higher rate of 'metformin failure', in which more women

treated with metformin had to take supplemental insulin, when compared to the number of women treated with glyburide whom required supplemental insulin (Corcoy, 2018).

To contrast, a 2017 Cochrane review by Brown, Martis, Hughes, Rowan & Crowther, found no difference between rates of macrosomia or neonatal hypoglycemia when comparing six randomized control trials that were designed to compare metformin to glyburide. "For the infant, there was no evidence of a difference in the risk of being born LGA between infants whose mothers had been treated with glyburide and those in the placebo group (RR 0.89, 95% CI 0.51 to 1.58, one study, n= 375, low quality evidence)," (Brown et al., 2017). Additionally, the review found no difference in the rates of neonatal hypoglycemia (average RR 0.67, 95% CI 0.24 to 1.83, two studies 246 infants) or macrosomia (RR 6.33, 95% CI 0.54 to 10.46) when comparing different oral antihyperglycemics including metformin and glyburide (Brown et al., 2017).

Safety and Efficacy of Specified GDM Treatment Modalities

When choosing an appropriate treatment modality for GDM, it is important to not only look at the rates of macrosomia and neonatal hypoglycemia, but also other key factors such as neonatal exposure to glyburide or metformin and maternal weight fluctuations, rates of maternal hypoglycemia, and frequency of neonatal admission to the NICU when comparing insulin delivery methods (Simmons et al., 2001). While outcome measures of rates of macrosomia and neonatal hypoglycemia are comparable with either insulin delivery method, CSII or MDI, GDM treated with CSII had higher rates of maternal weight gain as well as higher rates of neonatal admission to the NICU (Simmons et al., 2001). In a more recent Cochrane review of insulin pump therapy use in pregnancy it was determined that due to a lack of both the number of trials as well as a lack of high-quality trials it is impossible to determine which method of insulin

delivery achieved lower rates of macrosomia and neonatal hypoglycemia, and saw less maternal weight gain, maternal hypoglycemia, and lower rates of NICU admissions (Farrar, 2016). On the other hand, a 2016 review of insulin pump therapy in pregnancy found that the American Association of Clinical Endocrinologists Consensus Panel on insulin pump management recommended, "…insulin pump therapy to be safer and effective for maintaining glycemic control in pregnancies complicated by GDM or DM2 requiring large insulin doses," (Kesavadev, 2016, p. S-40). It must also be acknowledged, when comparing MDI versus CSII, that there is a significant difference in the amount of education required to use each delivery method. It takes nearly 2-12 weeks of education regarding the use of CSII, whereas the typical patient with GDM is diagnosed at 24-28 weeks gestation (Kesavadev, 2016). Additionally, "Insulin pump therapy during pregnancy is a safe and reasonable alternative, but women should be competent users before conception and should consider backup nighttime basal insulin to safeguard against nocturnal disruptions in insulin infusion," (Castorino, 2011, p. 58).

"Insulin has been used for many years to normalize maternal glucose levels in GDM; because it does not significantly cross the placenta or raise fetal insulin levels," (Coustan et al., 2018, p. 1769). Glyburide's use in the treatment of GDM increased around the year 2007 (Corcoy, 2018). It was initially thought glyburide did not cross placental barriers as it was not detected in cord serum of neonates (Saade, 2005). Conversely, more current research has proven that to be incorrect. Newer research methods using high performance liquid chromatography with mass spectrometry assays with smaller detection limits showed glyburide does cross the placental barrier (Malek & Davis, 2016). When compared to other sulfonylureas, glyburide only circulated at 0.2%, compared to a second-generation sulfonylurea, tolbutaminde, which circulated at a rate of 4% (Malek, 2016). Therefore, while glyburide has a lower concentration

available to cross the placenta, it still has the potential to cross (2016). Subsequent studies suggested serum glyburide concentrations in the umbilical cord reached 70% of maternal levels (SMFM, 2018).

Additionally, Malek's 2016 review found that when assessed retrospectively and through meta-analysis, glyburide treated GDM pregnancies had increased rates of higher rates of neonatal hypoglycemia and macrosomia (RR= 1.40, 95% CI 1.00-1.95 and RR= 1.43, 95% CI, 1.16-1.76, respectively) (Malek, 2016). It was also found neonates had a, "…higher risk for NICU admission (RR= 1.41, 95% CI 1.00-1.95), respiratory distress (RR= 1.63, 95% CI 1.23-2.15), and birth injury (RR= 1.35, 95% CI 1.00-1.82)," (Malek, 2016, p. 696). In a retrospective analysis of a study conducted by Kaiser Permanente of Northern California, Malek noted there were higher rates of neonatal hypoglycemia in the GDM group treated with glyburide (n= 78) compared to those treated with insulin (n= 44) (34% vs 14%, respectively, p= 0.01) (2016). Malek also reviewed a retrospective cohort study of women with GDM who were treated with either glyburide (n= 2073) or insulin (n= 8609) from 2001-2004 who were part of the Sweet Success California Diabetes and Pregnancy Program (Malek, 2016). In this retrospective study, there was found to be higher rates of macrosomia (aOR= 1.29, 95% CI, 1.03-1.64) in the glyburide treated group (Malek, 2016). Malek also reviewed a larger retrospective cohort study that drew its patient population from a US employer based insurance claims for women with GDM who were treated with either glyburide (n= 4982) or insulin (n= 4191), and found the glyburide treated group had higher rates of macrosomia (RR= 1.43, 95% CI, 1.16-1.76) and neonatal hypoglycemia (RR= 1.40, 95% CI, 1.00-1.95) (2016).

Metformin also crosses the placenta (SMFM, 2018). Fetal concentration of metformin is like maternal circulation rates of metformin (SMFM, 2018). SMFM's 2018 review found one

study that looked at two-year-old children who were exposed to metformin in utero compared to two-year-old children who had been exposed to insulin. Children exposed to metformin, "…had similar overall body fat but more subcutaneous fat over intraabdominal fat; this effect is postulated to mean metformin treatment may lead to a more favorable pattern of fat distribution compared with insulin," (SMFM, 2018, p. B2). The same study found comparable neurodevelopmental outcomes in both treatment groups (SMFM, 2018).

Corcoy's 2018 review also assessed long-term outcomes of treatment of GDM with insulin, metformin and glyburide. Use of metformin, for the treatment of GDM and its long-term effect on offspring, has been followed more closely due to metformin crossing the placental barrier at a higher rate than glyburide (Corcoy, 2018). Corcoy reviewed the MiG trial for long-term implications of metformin use in GDM, as the trial included a two-year follow-up of 323 children (2018). Follow-up from the trial revealed, "…children exposed to in utero metformin, had measures of subcutaneous peripheral fat (mainly upper arm- subscapular and biceps skinfolds), with no differences in central fat and total fat deposits, compared to children whose mothers were treated with insulin," (Corcoy, 2018, p. 6). This finding allows for the speculation that metformin use in utero can contribute to increased peripheral subcutaneous fat stores, without additional visceral fat stores (Corcoy, 2018). Thus far, research has been limited by poor study attenuation, and it is unclear if exposure to metformin in utero will have effects on offspring. No information is available thus far of the effects of glyburide on offspring. Corcoy reviewed the Australian Carbohydrate Intolerance Study in Pregnant Women by Crowther et al. (ACHOIS) for long-term follow-up applications (2018). Corcoy found follow-up of height and weight at 4- or 5-year-old follow-up appointments revealed no difference in childhood weight gain when comparing women with GDM treated with either diet alone or insulin (2018).

Unfortunately, data was limited due to poor follow-up as the ACHOIS attenuation rate was only 199 of the original participants compared to 526 mothers and 542 children (2018).

Further longitudinal studies are needed to assess long-term effects of GDM treatment on offspring. I anticipate attenuation will continue to be a main limitation in further research. An additional limitation of Corcoy's 2018 study is that to truly assess long-term implications follow-up must be extended to late-childhood and pre-pubescent years. Furthermore, Corcoy's review also found in one randomized control trial, management of GDM with metformin needed supplemental insulin to manage hyperglycemia in 46% of the participants (2018). Therefore, it is difficult to assess if treatment outcomes are related to metformin alone, or metformin plus insulin. Additionally, there is currently no information regarding the long-term outcomes of GDM treatment with glyburide on offspring. To fully assess the safety of GDM treatment modalities, there needs to be additional research conducted on long-term glyburide effects in utero as well as metformin.

Malek's 2016 review assessed glyburide from a pharmacological perspective regarding its safety and efficacy by comparing early reviews of glyburide to more current reviews of glyburide use in the management of GDM. Compared to initial research which showed glyburide did not cross placental barriers, was similarly effective when compared to insulin, and had similar neonatal outcomes, newer research using high performance liquid chromatography with mass spectrometry assay with a smaller detection limit, shows glyburide does cross the placental barrier (Malek, 2016). Additionally, retrospective studies and meta-analyses conducted on GDM treated with glyburide depict increased rates of macrosomia and neonatal hypoglycemia when compared to the treatment of insulin (Malek, 2016). Barriers to the overall review of the safety and efficacy of glyburide use in pregnancy are the limited amount of studies conducted, the need

for more information regarding patient preference and adherence to medication regimens, and the need for additional research assessing long-term effects of glyburide on offspring, especially since there is a known, albeit small, amount of glyburide that can transfer through placental tissue. Just as with metformin, one main limitation to further longitudinal studies of the offspring of glyburide treated mothers with GDM will be study attenuation.

Saade's 2005 expert opinion editorial and review regarding the use of glyburide compared to insulin in the treatment of GDM, found glyburide was not detected in the cord serum of the infant, there were higher rate of maternal hypoglycemia with the use of insulin compared to glyburide therapy, and because second generation sulfonylureas do not cross the placenta, there were less risks of adverse effects incurred by the fetus. Newer research technology and an increased number of studies conducted comparing insulin therapy to glyburide therapy have shown contrasting information: that glyburide does cross placental barriers, that neonates of glyburide treated GDM have higher rates of NICU admission, neonatal hypoglycemia, and macrosomia compared to neonates of insulin treated GDM, and that there is controversy regarding maternal rates hypoglycemia of glyburide vs insulin treated GDM (Malek, 2016). While Saade's 2005 expert opinion provided an unbiased view of oral antihyperglycemics, at the time of publication, there was only one trial conducted in the United States assessing the use of glyburide in the management of GDM. The study consisted of 404 women with GDM who required pharmacologic treatment for the management of GDM (Saade, 2005). There was an additional study conducted in South Africa (n- unknown) studying the use of first-generation sulfonylureas in the management of GDM, which yielded similar results to the randomized control trial conducted in the United States. Although the randomized trial from the United States had a large patient population, Saade's publication is limited by its age, the lack of

technology available at the time of publication, and the lack of overall studies available at that time.

Discussion

While the pathophysiology of GDM is understood as being a condition of maternal hyperglycemia related to increased insulin resistance and glucose intolerance that develops in response to placental hormones, there is no consensus among experts on how to treat hyperglycemia associated with GDM if diet therapy fails to achieve euglycemia (Kamana, 2015). Insulin has long been thought of as the mainstay in treatment, however since 2007 two oral medications, glyburide and metformin, have become increasingly popular and are comparably safe and effective (Dirar et al., 2017). However, while insulin does not cross the placental barrier, both metformin and glyburide do cross the placental barrier (SMFM, 2018). Long-term implications of in utero exposure to glyburide and metformin are unknown (Dirar, 2017). Additionally, while insulin has been a staple in the treatment of GDM, and historically has been administered as multiple daily subcutaneous injections (MDI), insulin pump therapy, otherwise known as continuous subcutaneous insulin injections (CSII), is another method of insulin delivery that can be used in the treatment of GDM. Last, in determining which GDM treatment modality is more effective, it is important to compare rates of macrosomia and neonatal hypoglycemia, both of which are potential complications of maternal hyperglycemia associated with uncontrolled GDM.

Oral Antihyperglycemics

Cochrane's 2017 literature review by Brown et al, focused on the use of oral antihyperglycemic medications in the treatment of GDM. It compared the benefits of oral

antihyperglycemics to placebo treatment for management of GDM in pregnancy. Oral antihyperglycemics studied include glyburide, metformin and acarbose. The review assessed a total of 11 studies (n=1487 women and their infants), 8 of which were able to be used as a part of meta-analysis (Brown, 2017). Overall quality of the evidence in Brown's review was difficult to assess as there was not consistent reporting of study methodology in all the studies used for the meta-analysis. There was no significant difference in rates of macrosomia or neonatal hypoglycemia when comparing glyburide vs metformin in the treatment of GDM. Again, the quality of the studies used in the meta-analysis was difficult to assess. Due to the lack of high-quality evidence, there needs to be more research done comparing metformin to glyburide in the treatment of GDM. In study development, there needs to be an improvement in methodology documentation, as well as improved controls regarding when to initiate pharmacologic therapy. Also, when assessing outcomes, women who need to be advanced to insulin therapy in either the glyburide or metformin arms of the study should have separate treatment outcomes calculated, as opposed to being included in their respective glyburide or metformin arm.

Coustan, in 2018, looked more closely at glyburide compared to insulin in the treatment of GDM. In this expert opinion article, the authors reviewed a multi-institutional randomized control trial by Senat et al. that was designed to assess if glyburide was inferior to insulin in the treatment of GDM in terms of preventing perinatal complications. Out of the 809 women included in the per-protocol analysis, the potential outcomes macrosomia, hypoglycemia and/or hyperbilirubinemia occurred in 23.4% infants born to insulin treated GDM, and 27.6% of infants born to glyburide treated GDM (Coustan, 2018). The study failed to show that insulin was superior to glyburide in the management of GDM regarding the prevention of negative perinatal outcomes (Coustan, 2018). Despite the study failing to prove glyburide's inferiority to insulin,

expert opinion authors could also not conclude that glyburide is inferior (Coustan, 2018). Overall, more research needs to be done assessing immediate and long-term outcomes regarding glyburide as a treatment of GDM. Additionally, factors including cost, patient satisfaction, and patient compliance need to be given consideration when choosing between treatment modalities of insulin or glyburide. A limitation of the study is that in the per-protocol analysis, women who failed glyburide treatment and were changed to insulin therapy for treatment of GDM were not included in the statistical analysis. It is debatable whether these women should be included in the analysis, which would ultimately modify the statistical analysis of the study. Moreover, the lack of research looking at long-term offspring outcomes associated with glyburide use in GDM need to be investigated, as it is known that glyburide crosses the placental barrier.

Mirzamoradi et al completed a randomized clinical trial in 2014 to compare the safety and efficacy of glyburide versus insulin therapy in the management of GDM. Qualifiers for the study included singleton pregnancy, age 18-45, and between 24-36 weeks gestation (Mirzamoradi et al., 2014). From within that cohort, women with GDM were randomly assigned to either a glyburide or insulin treatment group. Both maternal and neonatal outcomes were then compared. Comparison outcomes included: duration of treatment, time to control, time of treatment to delivery, maternal rates of preeclampsia, vaginal versus cesarean delivery, neonatal birth weights, NICU admission rates, endotracheal intubation rates, neonatal rates of hypoglycemia, hypocalcemia and polycythemia (Mirzamoradi et al., 2014). There was no statistically significant difference in birth weight between the insulin treated group and the glyburide treated group (P= 0.84) (Mirzamoradi, 2014). There were no cases of neonatal hypoglycemia (Mirzamoradi et al., 2014). Due to the lack of statistically significant differences between the two treatment modalities, it can be understood that both glyburide and insulin

contributed in a similar manner to the control of GDM. The study was not able to prove which treatment was safer and more effective due to the lack of statistically significant outcomes. However, it was able to determine that both treatment modalities result in similar outcomes and can achieve euglycemic outcomes in GDM. While the study controlled which type of treatment modality study participants received, in a real-world situation, there are other factors including cost, availability, injection fears, or patient preference. More studies will need to be done to account for those factors and assess whether patient preference of therapy will affect outcome. Another limitation to this study is that patient follow-up will be less tightly regulated in a real-world application, which may affect effectiveness of the therapy. Overall the study provides a well-controlled, unbiased look at glyburide versus insulin therapy in the treatment of GDM.

SMFM's 2018 review compared scientific reviews of the treatments of insulin, metformin, and glyburide in management of GDM. Overall, SMFM's review illustrated that glyburide, when compared insulin or metformin, has higher rates of neonatal hypoglycemia and macrosomia (SMFM, 2018). Additionally, metformin, when compared to insulin or glyburide, has the lowest risk of neonatal hypoglycemia and macrosomia (SMFM, 2018). One major limitation to SMFM's review was related to the overall weakness of data included in the publications assessed in the review. Overall, there is a lack of statistically significant differences when comparing metformin, glyburide, and insulin and rates of neonatal hypoglycemia and macrosomia. Additionally, the studies are limited due to both maternal and neonatal outcomes being influenced by lifestyle variables including medication compliance, treatment preferences, screening criteria, blood glucose monitoring compliance, target blood glucose values, differing provider preferences for treatment, and differing clinical policies for treatment. More controlled

randomized trials that account for the above variables need to be conducted to better analyze the efficacy and safety of metformin, glyburide and insulin in the treatment of GDM.

Su's 2014 review was conducted to compare metformin and insulin treatments of GDM and their effects on maternal and neonatal outcomes. The review assessed a total of six randomized control trials totaling 1420 subjects. Limitations to this literature review are the low number of trials (6) included in the review and the lack of definition of neonatal hypoglycemia. Some studies measured neonatal hypoglycemia at 46 mg/dL, and others measured it at 40 mg/dL, therefore it is difficult to compare data accurately. Overall the review illustrates metformin may be useful as a treatment for GDM. Still, more research needs to be done with standardized measurements, larger samples, and further investigation into the increased rates of preterm labor associated with metformin treated GDM to fully ascertain the safety and efficacy of metformin use in the management of GDM.

The focus of Gabbe and Grave's 2003 expert view, was on the management of pregnancies complicated by diabetes mellitus, including pre-existing diabetes and GDM. The expert view provided an overview of GDM, diagnostic criteria, management of GDM, potential complications of hyperglycemia in pregnancy, and maternal post-partum follow-up of GDM. Regarding management of GDM, the expert view discussed when to initiate therapy beyond lifestyle management and compared the use of oral antihyperglycemics to insulin to prevent maternal complications and optimization of neonatal outcomes. Both Dr. Gabbe and Dr. Graves are experts and specialists in Maternal/Fetal Medicine within Obstetrics and Gynecology. They both have received numerous accolades within their specialty and have multiple published works regarding Maternal/Fetal Medicine. There were no disclosed biases in the writing of this expert view. There was however, at the time of publication, limited supporting research for the use of

glyburide in the management of GDM, which was disclosed by the authors. At the time of publication, there was one study supporting the use of glyburide in the management of GDM. Since publication, there has been more research done comparing glyburide and insulin in the management of GDM. There is still a need for an increased number of randomized control trials conducted on a larger, more widespread, and more diverse patient population. Gabbe and Grave's 2003 publication is useful for the purpose of a historical assessment of the treatment of GDM, but, given the date of publication, it should not be used for current clinical recommendations regarding the treatment of GDM.

CSII versus MDI

In comparing CSII to MDI in the treatment of GDM, there are difficulties in assessing rates of macrosomia and neonatal hypoglycemia due to the lack of studies. A 2016 Cochrane review by Farrar et al in 2016 compared continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI) of insulin for GDM. Reviewers used five randomized control trials to compare delivery methods of insulin during GDM. The review examined five single center trials, for a total of 153 women and 154 pregnancies, for differences in primary outcomes, including caesarean section, macrosomia, and perinatal mortality (Farrar, et al, 2016). In two of the trials, totaling 61 infants, "CSII was associated with an increase in mean birthweight compared with MDI, P= 0.05. However, the large confidence interval including anything from a small reduction to an increase in mean birthweight and the lack of a difference in macrosomia rate, CI= 0.14 to 72.62," (Farrar et al., 2016). Regarding neonatal hypoglycemia, "…there was very low graded evidence of a difference between MDI and CSII, CI 0.07 to 14.64, 32 infants," (Farrar et al., 2016). Overall quality of evidence in the five trials is very low, and due to the lack of difference in rates of macrosomia or neonatal hypoglycemia there is no way to ascertain

which treatment modality provides better neonatal outcomes. Limitations to the review are due to the low quality of evidence available within the randomized control trials analyzed in the review. To have a more effective assessment of which insulin delivery method yields lower rates of macrosomia and reduced rates of neonatal hypoglycemia there needs to be a greater number of trials conducted comparing CSII and MDI, as well as a larger population studied, and longer-term assessments of offspring. Trials need to continue to use the most current pump technology, as well as the newest insulins possible to yield the most pertinent results.

In Simmon's 2001 nested case-control study, pregnancies complicated by GDM or pre-existing DM2 treated with insulin pump therapy (CSII) were compared to pregnancies complicated by GDM or pre-existing DM2 treated with MDI of insulin. The patient population was obtained by conducting a service audit of deliveries from 1991-1994, screening for singleton pregnancies, as well as GDM or pre-existing DM2. There was a total of 251 singleton pregnancies complicated by GDM or pre-existing DM2 during the 1991-1994 service audit (Simmons, 2001). Out of those 251 pregnancies, 30 subjects used an insulin pump. None of the women using an insulin pump experienced severe hypoglycemia, although 79% of the women had improved glycemic control in 1-4 weeks (Simmons, 2001). None of the women on a pump had hypoglycemic episodes. The study found the women on insulin pump therapy versus MDI of insulin had similar rates of neonatal hypoglycemia and birth weight but had higher fasting blood sugars (if GDM), greater total daily insulin use, greater weight gain rates, and were more likely to have neonates admitted to the neonatal intensive care unit (Simmons, 2001). Overall study conclusions were that insulin pump therapy in GDM is well tolerated and achieves similar rates of euglycemia and neonatal outcomes when compared to MDI of insulin. One main limitation to this nested case control study is the period that was studied. The reviewed charts are now over 20

years old, and since that time newer insulins have been developed and studied, in addition to advances in insulin pump technology. Additionally, the patient population using insulin pump therapy was only 12% of the surveyed population.

Castorino et al.'s 2012 review assessed the use of insulin pump therapy in the management of diabetes in pregnancy. The review provides a comparison of the use of continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI) in the treatment of diabetes in pregnancy. Studies used in this review focused on the treatment of DMI in pregnancy. Castorino reviewed Murphy et al's study evaluating glycemic control of a closed-loop insulin delivery system on 10 pregnant women who had preexisting DM1 who were studied during both early pregnancy and late pregnancy (Castorino, 2012). Median glycemic control during early pregnancy was 117 mg/dL and 126 mg/dL during late pregnancy (P= 0.72) (Castorino, 2012). Castorino's review of Murphy's ten patient study illustrated that a closed-loop system, such as CSII, may be able to be safely used during pregnancies with preexisting DM1, however, it did not evaluate the use of CSII in pregnancies complicated by the development of GDM. Therefore, the main limitation to this literature review is that it focused primarily on management of pre-existing diabetes in pregnancy. While the overall management goal of diabetes in pregnancy, achieving blood sugars as close to normal as possible without causing hypoglycemia and preventing neonatal and maternal complications, is the same whether dealing with GDM or pre-existing diabetes, the pathophysiology behind the disease processes are different. GDM rates of insulin resistance may cause different insulin requirements than pre-existing DM1 with pregnancy. While information gained in this literature review can still be applied to the treatment of GDM using either insulin pump therapy or multiple daily insulin injections, each population will likely have different total or bolus insulin requirements. There

will also be different teaching methods required for each patient population. Further studies need to be done on the use of insulin pumps with GDM exclusively, as well as studies looking at the initiation of insulin pump therapy during pregnancies complicated by pre-existing diabetes.

Kesavadev's 2016 review assesses the use of insulin pump therapy in pregnancy for the management of DM1, DM2, and GDM and compares the advantages and disadvantages by reviewing current literature. The review concluded that insulin pump therapy in pregnancy can be a safe and successful treatment to help reduce the risk of hypoglycemia and attain euglycemic outcomes during pregnancy (Kesavadev, 2016). The review also concluded that a component of the successful treatment of diabetes in pregnancy is screening patients for their appropriateness for use of insulin pump therapy. Kesavadev did not disclose biases, however, in the introduction, it stated the review was written based on current literature as well as clinical experience. It did not state what the clinical experience included, therefore it is difficult to assess the review for biases or expertise level of the authors. Additionally, six out of the seven studies in the review assessed pregnant patients with DM1. There was one study assessing pregnant patients with DM2 or GDM. Individuals with DM1 on insulin pumps may have had more time on their pump prior to pregnancy, therefore helping them attain better glycemic control. Whereas mothers diagnosed with GDM during pregnancy have less time to learn how to properly use an insulin pump and may have a more difficult time attaining glycemic control.

Clinical Application

Regarding the various treatment modalities available for the management of GDM, there is one broad conclusion that can be drawn- more research needs to be conducted to truly evaluate which treatment modality will best manage hyperglycemia to help prevent neonatal risk factors, two of which are macrosomia and neonatal hyperglycemia. Regarding CSII, new technology has

made insulin pump therapy more appealing, however due to the length of education needed to use a pump correctly and efficiently, using CSII for the treatment of GDM may not be as helpful as it would be for the pregnant woman with pre-existing diabetes. CSII may be an optional tool for a mother who has had GDM previously and is pregnant again, as earlier screening and monitoring of blood sugars could be done, and she may be able to learn how to use a CSII early enough and quickly enough to make it be worthwhile. There is not enough research to validate if the use of CSII in GDM is effective or efficient. Use of MDI compared to CSII in clinical practice is faster and more efficient than CSII. Patients could be taught to use MDI faster than they could CSII, which is important as patients are not diagnosed with GDM until week 24-28 gestation, plus there is typically a two-week trial of diet therapy. The use of MDI may be intimidating, difficult, or too costly for some patients, therefore the option of oral medications is appealing. It is known that both metformin and glyburide cross the placental barrier, but their effect on the fetus, and later infant and then child are not known at this point. Thus far, research has shown lower rates of macrosomia and neonatal hypoglycemia with metformin, yet these results have not been statistically significant. Glyburide, at this point, may feel like the safer option for providers, as it has been more readily used since 2007. Although in other countries, New Zealand for example, metformin is used more often to treat GDM after dietary therapy failed. Metformin provides one additional appealing factor, which is that it will not cause maternal hypoglycemia. ACOG's 2018 bulletin still recommends insulin as the preferred treatment when dietary therapy fails, level A evidence (Caughey & Turrentine, 2018). However, ACOG's recommended treatment if insulin is not appropriate for the patient or if insulin bears too high of a cost, is metformin, level B evidence (Caughey, 2018). ACOG removed glyburide as a first-line treatment for GDM due to its lack of comparison with insulin in terms of unequivocal

results. Treatment of patients with GDM will not be an obvious choice. Insulin is still considered first-line option if diet therapy fails. But, should the provider conclude that the patient is not an appropriate candidate for insulin therapy, whether it be due to cost of insulin, fear of needles, or overall patient preference, metformin should be considered the next option. Both metformin and glyburide need to be researched in terms of long-term effects on the infant. Overall, the treatment plan, after dietary therapy, should consist of a fluid discussion with the patient and overall shared decision-making process.

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