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

Ashleigh Milbrath
University of North Dakota

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Ashleigh Milbrath, PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

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.

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

Introduction

- GDM rates are rising in the United States, but there are no current best practice recommendations for treatment beyond initial diet/exercise modifications (SMFM, 2018).
- As of 2009, 7% of pregnancies were complicated by diabetes, with GDM representing 86% of that population (Caughey & Turrentine, 2018).
- Persistent hyperglycemia will result in complications such as neonatal macrosomia or hypoglycemia (Poomalar, 2015).
- Historically, insulin therapy was thought to be second-line treatment if diet/exercise failed to achieve euglycemic control (Poomalar, 2015)
- Since 2007, in the United States, glyburide has become the most frequently prescribed medication for GDM management beyond diet/exercise modifications (Corcoy, 2018).
- Outside the United States, particularly in New Zealand, GDM treatment with metformin is becoming increasingly popular (Corcoy, Balsells, Garcia-Patterson, Shmueli, & Hadar, 2018).
- Insulin delivery can either be via subcutaneous multiple daily injections (MDI) or a continuous subcutaneous insulin infusion system (CSII), aka insulin pump.

Statement of the Problem

Beyond diet/exercise modifications, there are no best practice treatment recommendations for GDM. Therefore, it is necessary to compare rates of neonatal macrosomia, neonatal hypoglycemia, and safety and efficacy of GDM treatment modalities including: oral antihyperglycemics (metformin and glyburide), subcutaneous MDI, and CSII.

Research Question

- In patients with GDM, is there a difference in rates of macrosomia and neonatal hypoglycemia when comparing metformin, glyburide, insulin via MDI, and insulin via CSII?
- In patients with GDM, will taking metformin, glyburide, insulin via MDI or insulin via CSII, yield safer and more efficacious results?

Literature Review

- MDI vs CSII:
  - 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 (Kesavadev, 2014).
  - A review of glycemic control of DM1 in pregnancy found no difference between MDI and CSII regarding glycemic control (Castorino, Paband, Zisser, & Jovanovic, 2012)
  - A 2016 Cochrane review found there to be insufficient evidence to conclude whether CSII or MDI would produce better outcomes for diabetes management in pregnancy (Farrar, Tuffnell, West, J. & West, HM., 2016)
  - Safety:
    - The American Association of Clinical Endocrinologist's Consensus Panel on insulin pump management recommended CSII for glycemic control in pregnancies complicated by DM2 or GDM if large amounts of insulin are required (Kesavadev, 2016).
    - Castorino's 2011 review recommended women be competent pump users prior to conception if they consider CSII use in pregnancy.
- Glyburide vs Insulin:
  - Out of 809 women included in a multi-institutional randomized control trial by Senat et al., outcomes including macrosomia or neonatal hypoglycemia occurred in 23.4% of infants born to insulin treated GDM vs 27.6% of infants born to glyburide treated GDM (Coustan and Barbour, 2018).
  - Reviews comparing insulin to glyburide showed higher rates of macrosomia and neonatal hypoglycemia in GDM pregnancies treated with glyburide (SMFM, 2018 and Malek & Davis, 2016).
  - GDM pregnancies treated with glyburide or insulin failed to show statistically significant differences in rates of macrosomia or neonatal hypoglycemia (p= 0.84) (Mirzamoradi, Heidar, Faalpoor, Naeiji, & Jamali, 2014).
  - Safety:
    - Glyburide crosses the placental barrier, whereas insulin does not. Serum glyburide concentrations in the umbilical cord have been found to be 70% of maternal levels (SMFM, 2018).
- Metformin vs Insulin:
  - Despite a lack in statistically significant data, metformin has shown lower rates of macrosomia and neonatal hypoglycemia in multiple studies when compared to insulin treated GDM (Corcoy et al., 2018), (SMFM, 2018), (Poomalar, 2015), (Su & Wang, 2014), and (Kitwitee et al., 2015)
  - Safety:
    - Metformin as shown higher rates of preterm births, but less maternal weight gain (SMFM, 2018).
    - Metformin crosses the placental barrier and reaches a fetal concentration rate similar to the maternal concentration rates (SMFM, 2018).
    - 2-year old children, whom were exposed to metformin in utero due to the treatment of GDM, were found to have similar body fat but more subcutaneous body fat compared to intraabdominal body fat when compared to insulin treated GDM 2-year old's (SMFM, 2018).
- Glyburide vs Metformin:
  - Metformin, compared to glyburide, showed lower risk of neonatal hypoglycemia and macrosomia, and had similar rates of preterm births (SMFM, 2018) and (Corcoy et al, 2018).
  - However, a 2017 Cochrane review found no difference in rates of neonatal hypoglycemia or macrosomia (Brown et al., 2017)
  - Safety:
    - Both glyburide and metformin cross placental barriers and have been found in umbilical cord serum concentrations (SMFM, 2018).
    - Metformin has a higher rate of supplemental insulin use compared to glyburide (Corcoy et al, 2018).

Discussion

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

- Glyburide:
  - Overall, lack of statistically significant data.
  - However, there are multiple reviews illustrating higher rates of macrosomia and neonatal hypoglycemia associated with GDM treated glyburide vs insulin or metformin.
  - Glyburide crosses placental barrier and reaches concentration of up to 70% of maternal concentrations (SMFM, 2018).
  - Lack of studies assessing long-term effects of in-utero glyburide use.
- Metformin:
  - Overall, lack of statistically significant data.
  - Some evidence of lower rates of neonatal hypoglycemia and macrosomia when compared to both insulin and glyburide.
- Insulin via MDI/CSII:
  - Overall, lack of statistically significant data, as well as studies assessing GDM management with CSII.
  - No difference in rates of macrosomia or neonatal glycemia between MDI/CSII.

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

- Both metformin and glyburide cross placental barriers.
  - Serum cord concentration of metformin is equivalent to maternal serum concentrations of metformin (SMFM, 2018).
  - Serum cord concentrations of glyburide are 70% of maternal concentrations (SMFM, 2018)
- 2 year follow-up of children from GDM mothers treated with metformin had less intraabdominal fat and more subcutaneous fat causing question if metformin use in-utero changes neonatal fat distribution changes (SMFM, 2018).
- Higher rates of supplemental insulin needed in metformin managed GDM treatment groups.
- Overall lack of studies assessing long-term effects of in-utero metformin or glyburide use.
- Lack of statistically significant data assessing safety and efficacy of CSII use for GDM management.
- Lack of studies comparing GDM treated with MDI versus CSII.

Applicability to Clinical Practice

- Overall broad conclusion: more research needs to be conducted evaluating the management of GDM beyond diet/exercise modifications.
- CSII may be an option for women who have prior experience with a pump, history of GDM, or for those highly motivated to learn how to use a pump.
  - Pump therapy education is a deterrent to the use of CSII for those newly diagnosed with GDM.
  - MDI is faster to learn and may help achieve euglycemia more quickly than GSII .
- Both Metformin and Glyburide cross the placental barrier
  - Current research has shown lower rates of neonatal hypoglycemia and macrosomia with metformin, although there is a lack of statistically significant data.
  - Minimal research assessing long-term effects of glyburide or metformin on fetus, infant, or child.
- 2018 ACOG guidelines continue to recommend insulin as first-line therapy for GDM if diet/exercise fail to control hyperglycemia (Caughey & Turrentine, 2018).
  - ACOG further recommends that if insulin is not appropriate for the patient, or is too costly for the patient, metformin should be considered the next option for treatment (Caughey & Turrentine, 2018).
- Ultimately, treatment option, beyond diet/exercise modifications, needs to be a shared decision between patient and their provider.

References

Brown, J., Martis, R., Hughes, B., Rowan, J., & Crowther, CA. (2017). Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. *Cochrane Database of Systematic Reviews, 1*. http://doi.org/10.1002/14651858.CD011967.pub2.

Castorino, K., Paband, R., Zisser, H., & Jovanovic, L. (2012). Insulin pumps in pregnancy: using technology to achieve normoglycemia in women with diabetes. *Diabetes and Pregnancy, 12*, 53-59. http://doi.org/10.1007/s11892-011-0242-7.

Caughey, A., & Turrentine, M. (2018). Gestational diabetes mellitus: ACOG practice bulletin. *Obstetrics and Gynecology, 131*(2), e49-e69. http:doi.org/10.1097/AOG.0000000000002501.

Corcoy, R., Balsells, M., Garcia-Patterson, A., Shmueli, A., & Hadar, E. (2018). Pharmacology for hyperglycemia in pregnancy- do oral agents have a place? *Diabetes Research and Clinical Practice*, 1-8. http://doi.org/10.1016/j.diabres.2018.04.015.

Coustan, D. & Barbour, L. (2018). Insulin vs glyburide for gestational diabetes. *American Medical Association*, *319*(17), 1769-1770.

Farrar, D., Tuffnell, DJ., West, J., & West, HM. (2016). Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes (review). *Cochrane Database of Systemic Reviews, 6*. http://doi.org/10.1002/14651858.CD005543.pub3.

Kesavadez, J. (2016). Insulin pump therapy in pregnancy. *Journal of Pakistan Medical Associates, 66*[11(suppl 1)], s39-s44.

Kitwittee, P., Limwattananon, S., Limwattananon, C., Waleekachonlert, O., Ratanachotpanich, T., Phimphilai, M., Nguyen, T., & Pongchaiyakul, C. (2015). Metformin for the treatment of gestational diabetes: an updated meta-analysis. *Diabetes Research and Clinical Practice, 109*, 521-532. http://dx.doi.org/10.1016/j.diabres.2015.05.017.

Malek, R. & Davis, S. (2016). Pharmacokinetics, efficacy and safety of glyburide for treatment of gestational diabetes mellitus. *Expert Opinion on Drug Metabolism & Toxicology, 12*(6), 691-699. http:://doi.org/10.1080/17425255.2016.1187131.

Mirzamoradi, M., Heidar, Z., Faalpoor, Z., Naeiji, Z., & Jamali, R. (2014). Comparison of glyburide and insulin in women with gestational diabetes mellitus and associated perinatal outcomes: a randomized clinical trial. *Acta Medica Iranica*, *53*(2) 97-103. Retrieved from URL: http://acta.tums.ac.ir/index.php/acta/article/view/2929.

Poomalar, G. (2015). Changing trends in management of gestational diabetes mellitus. *World Journal of Diabetes*, *6*(2), 284-295. http://doi.org/10.4239/wjd.v6.i2.284.

Society for Maternal-Fetal Medicine Publications Committee. (2018). SMFM statement: pharmacological treatment of gestational diabetes. *Society for Maternal-Fetal Medicine*, B2-B4. http://dx.doi.org/10.1016/j.ajog.2018.01.041.

Su, D. & Wang, X. (2014). Metformin vs insulin in the management of gestational diabetes: a systemic review and meta-analysis. *Diabetes Research and Clinical Practice*, *104*, 353-357. http://doi.org/10.1016/j.diabres.2013.12.056.

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