UNC SCHOOL OF MEDICINE

Diabetes in Pregnancy References:

1) Gestational diabetes mellitus. Practice Bulletin No. 137. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2013; 122:406-16
2) Gestational diabetes mellitus. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e49–64.
3) Pregestational diabetes mellitus. ACOG Practice Bulletin No. 60. American College of Obstetricians and Gynecologists. Obstet Gynecol 2005 (reaffirmed 2014); 105:675-85.
4) Blumer I, Hadar E, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 98: 4227–4249, 2013)
5) American Diabetes Association. Management of Diabetes in Pregnancy. Diabetes Care 2016;39(Suppl. 1): S94–S98
6) Diabetes in pregnancy: management from preconception to the postnatal period NICE guideline Published: 25 February 2015.
7) Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352:2477–86
8) Mark B. Landon, M.D.1, Catherine Y. Spong, M.D.2, Elizabeth Thom, Ph.D.3, Marshall W. Carpenter, M.D.4, et al, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes. N Engl J Med. 2009 October 1; 361(14): 1339–138

RCT expectant treatment vs insulin tx for GDM diagnosed by 3 hour GCT and 'majority' of self testing values > 95 fasting and > 120 at 2 hours PP. 'Although treatment of mild gestational diabetes mellitus did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders.'

No difference in composite of stillbirth or perinatal death and neonatal complications, including hyperbilirubinemia, hypoglycemia, hyperinsulinemia, and birth trauma. Among treatment group, lower: mean birth weight (3302 vs. 3408 g), neonatal fat mass (427 vs. 464 g), the frequency of large-for gestational-age infants (7.1% vs. 14.5%), birth weight greater than 4000 g (5.9% vs. 14.3%), shoulder dystocia (1.5% vs. 4.0%), and cesarean delivery (26.9% vs. 33.8%)

9) Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med. 2000;343:1134–1138.
10) Langer, O, et al. Insulin and glyburide therapy: Dosage, severity level of gestational diabetes, and pregnancy outcome. AJOG. 2005:192; 134-139.

Most require glyburide dose of >= 10 mg q day to achieve control.'Achieving the established level of glycemic control, not the mode of pharmacologic therapy, is the key to improving outcome in GDM.'

11) Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–2015.

Patients randomized to metformin who required insulin noted with significantly higher current BMI (36 vs 33), positive family history of DM, higher FBS on GCT (109 vs 95), prior GDM (33% vs 19%). No differences in outcome between those continued on metformin vs metformin + additional insulin.

12) Berggerin, E MD, MSCR and Boggess, K. Oral Agents for the Management of Gestational Diabetes. Clinical Obstetrics and Gynecology. 2013:56:827-836.

Although insulin remains the only Federal Drug Administration-approved agent to treat GDM,oral hypoglycemic agents are an attractive and increasingly common alternative. Research suggests that glyburide and metformin can each effectively manage hyperglycemia in pregnancy.

Summary of OHA vs insulin in GDM requiring medical therapy:

13) Wanda Nicholson, MD, MPH, MBA, Obstetrician, Gynecologist, Epidemiologist [a,b,c,*], Kesha Baptiste-Roberts, PhD, Epidemiologist. Oral hypoglycaemic agents during pregnancy: The evidence for effectiveness and safety. Best Practice & Research Clinical Obstetrics and Gynaecology 25 (2011) 51–63

Key findings for glyburide compared with insulin
- Average maternal FBG and 2-h postprandial glucose levels as well as the proportion of women undergoing caesarean delivery did not differ significantly between the insulin and glyburide groups. However, three of the four studies presented had limited power, due to small sample sizes, to detect significant differences in these outcomes.
- Adverse maternal outcomes, such as maternal hypoglycaemia, were difficult to assess because of inconsistencies in the definition of this outcome across studies. Only one study evaluated the proportion of women developing pre-eclampsia; hence, it is difficult to draw any conclusions regarding this outcome.
- Insulin may be associated with an average 95-g lower infant birth weight when compared with glyburide, but this difference was not statistically significant and was unlikely to have substantial clinical relevance, given the small difference in infant size.
- Few congenital malformations or anomalies were reported in either treatment group.

Key findings for metformin compared with insulin
- FBG levels did not differ between the metformin and insulin groups.
- The larger RCT reported a higher proportion of infants with an episode of hypoglycaemia with insulin compared with metformin; the smaller trial reported no differences, but had limited statistical power to detect meaningful differences.
- No differences in the proportion of infants with a congenital anomaly between treatment groups were reported in the larger RCT by Rowan et al. Data on congenital anomalies were not collected in the smaller trial.

Key findings for metformin compared with glyburide
- FBG levels did not differ between treatment groups;
- almost one-third of participants receiving metformin in the study by Moore et al. required insulin;
- no data were available on episodes of maternal hypoglycaemia; and
- Moore reported that infants were, on average, 200 g heavier in the glyburide group compared with the metformin group, which is statistically significant and clinically relevant.

Practice points
_ Gestational diabetes is increasing in prevalence, paralleling the trends in obesity and sedentary lifestyles worldwide.
_ Although limited, obstetrician–gynaecologists and primary care providers have evidence to support the use of glyburide and metformin as well as insulin in the management of GDM.
_ While there are no long-term safety data on infants whose mothers were treated with glyburide or metformin, short-term neonatal complications, such as hypoglycaemia, are few in number and do not differ substantially between treatment groups.
_ When counselling their patients, providers can report that the proportion of infants with congenital malformations does not differ with the use of oral diabetes medication compared with insulin.
_ There are no substantial differences in maternal glucose control (FBG and 2-h postprandial) with the use of oral diabetes medications compared with insulin, but women often prefer and are more compliant with oral medications.

14) Nachum Z, et al. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. BMJ 1999;319:1223–7

In women with gestational diabetes the four times daily regimen resulted in a lower rate of overall neonatal morbidity than the twice daily regimen (relative risk 0.59, 0.38 to 0.92), and the relative risk for hyperbilirubinaemia and

hypoglycaemia was lower (0.51, 0.29 to 0.91 and 0.12, 0.02 to 0.97 respectively). The relative risk of hypoglycaemia in newborn infants to mothers with pregestational diabetes was 0.1(0.04 to 0.74). Giving insulin four times rather than twice daily in pregnancy improved glycaemic control and perinatal outcome without further risking the mother.

15) Spong, et al. Timing of Indicated Late-Preterm and Early-Term Birth. Obstet Gynecol. 2011 Aug; 118(2 Pt 1): 323–333.

Diabetes – pregestational well controlled	*LPTB/ETB not recommended*
• *Diabetes – pregestational with vascular disease*	*37–39 weeks*
• *Diabetes – pregestational, poorly controlled*	*34–39 weeks (individualized to situation)*
Diabetes – gestational well controlled on diet	*LPTB/ETB not recommended*
• *Diabetes – gestational well controlled on medication*	*LPTB/ETB not recommended*
• *Diabetes – gestational poorly controlled on medication*	*34–39 weeks (individualized to situation)*

16) Physical activity and exercise during pregnancy and the postpartum period. Committee Opinion No. 650. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e135–42

An exercise program that leads to an eventual goal of moderate-intensity exercise for at least 20–30 minutes per day on most or all days of the week should be developed with the patient and adjusted as medically indicated

17) Wilson, RD, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. J Obstet Gynaecol Can. 2015 Jun;37(6):534-52.

Women with personal history of pre-pregnancy diabetes are considered MODERATE RISK for ONTD and recommend 1 mg daily folic acid supplementation 3 months prior to conception

18) Shields, L and Tsay, GS. Editors, California Diabetes and Pregnancy Program Sweet Success Guidelines for Care. Developed with California Department of Public Health; Maternal, Child and Adolescent Health Division; revised edition, July, 2012. Guidelines for Care, California Diabetes and Pregnancy Program,2012. p 48

19) Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. Endocr Pract. 2009 Apr;15(3):187-93.

Note:

California Sweet Success Guidelines (2012) – management of hypoglycemia (17)

Table 10. PRINCIPALS FOR THE PREVENTION AND TREATMENT OF HYPOGLYCEMIA (40, 41, 42)
❖ Balance activity and food with insulin.
❖ With the initiation of OGLA or insulin, educate regarding signs and symptoms of hypoglycemia.
❖ With the use of OGLA or insulin instruct to always carry quick acting carbohydrate snacks and glucose tabs.
❖ Glucagon education must be provided to the significant others of all women who have type 1 diabetes. Ensure patient has one or two current glucagon kits.
❖ Glucose targets may be raised for women with hypoglycemia unawareness.
❖ If hypoglycemia occurs follow the Rule of 15 (40) described below: ❖ Treat with 15 grams of carbohydrate ❖ Re-check blood glucose in 15 minutes ❖ Expect to see a rise of 15 mg/dL in 15 minutes
If blood glucose > 50 < 70 + symptoms: ❖ Give 8 oz of non-fat milk. Recheck blood glucose in 15 minutes ❖ Repeat milk if still < 70 + symptoms ❖ Repeat blood glucose every 15 minutes until blood glucose is > 70 x 2 ❖ Use 1/2 sandwich if there is a milk allergy
If blood glucose < 50 + Symptoms: ❖ Give 4 oz juice (4 (4mg) glucose tabs with water). ❖ Recheck blood glucose in 15 minutes. If > 50 + symptoms, give 8 oz of non-fat milk, otherwise repeat juice or tabs. ❖ Repeat blood glucose check every 15 minutes until blood glucose > 70 x 2. Have snack or next meal.
If found unconscious: ❖ Call 911. ❖ Give GLUCAGON 1 mg SC immediately. ❖ May be given IM but will take longer to act.