

Gestational Diabetes: Do We Have to Use Insulin?

Kim A. Boggess, MD

Saturday, February 18, 2017


8:00 a.m. – 8:45 a.m.

Gestational diabetes (GDM) is a common complication of pregnancy that increases maternal and infant risk. GDM is associated with infant macrosomia, shoulder dystocia and birth trauma, and stillbirth. Women with GDM are at increased risk for cesarean section and gestational hypertension/preeclampsia. Achieving maternal glycemic control is the key to optimizing infant and maternal outcomes. When diet and lifestyle changes fail to achieve maternal euglycemia, pharmacotherapy is used, with insulin considered the mainstay of GDM treatment. However, oral hypoglycemic agents such as glyburide and metformin have emerged as potential alternatives to insulin for GDM pharmacotherapy. Early studies of oral agents for GDM treatment demonstrated that glyburide and metformin were comparable to insulin with regard to infant birth weight. More recent data suggest that metformin may be preferred to glyburide. Long term maternal and infant outcome data, and large studies examining safety, are lacking.

References:

1. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015;350:h102.
2. Berggren EK, Boggess KA. Oral agents for the management of gestational diabetes. *Clin Obstet Gynecol* 2013;56(4):827-36.
3. Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK, Jr., Jonsson Funk M. Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000-2011. *Obstet Gynecol* 2014;123(6):1177-84.
4. Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK, Jr., Jonsson Funk M. Association of Adverse Pregnancy Outcomes With Glyburide vs Insulin in Women With Gestational Diabetes. *JAMA Pediatr* 2015;169(5):452-8.
5. Caritis SN, Hebert MF. A pharmacologic approach to the use of glyburide in pregnancy. *Obstet Gynecol* 2013;121(6):1309-12.
6. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982;144(7):768-73.
7. Chmait R, Dinise T, Moore T. Prospective observational study to establish predictors of glyburide success in women with gestational diabetes mellitus. *J Perinatol* 2004;24(10):617-22.
8. Conway DL, Gonzales O, Skiver D. Use of glyburide for the treatment of gestational diabetes: the San Antonio experience. *J Matern Fetal Neonatal Med* 2004;15(1):51-5.
9. 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(24):2477-86.
10. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2013;8(5):e64585.
11. Holt RI. Glyburide for gestational diabetes: time for a pause for thought. *JAMA Pediatr* 2015;169(5):427-8.
12. Ijas H, Vaarasmaki M, Morin-Papunen L, Keravuo R, Ebeling T, Saarela T, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG* 2011;118(7):880-5.
13. Kahn BF, Davies JK, Lynch AM, Reynolds RM, Barbour LA. Predictors of glyburide failure in the treatment of gestational diabetes. *Obstet Gynecol* 2006;107(6):1303-9.

14. Kremer CJ, Duff P. Glyburide for the treatment of gestational diabetes. *Am J Obstet Gynecol* 2004;190(5):1438-9.
15. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361(14):1339-48.
16. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343(16):1134-8.
17. McGrath RT, Glastras SJ, Hocking S, Fulcher GR. Use of metformin earlier in pregnancy predicts supplemental insulin therapy in women with gestational diabetes. *Diabetes Res Clin Pract* 2016;116:96-9.
18. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. *Obstet Gynecol* 2010;115(1):55-9.
19. Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstet Gynecol* 2009;113(1):193-205.
20. Poolsup N, Suksomboon N, Amin M. Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: a meta-analysis. *PLoS One* 2014;9(10):e109985.
21. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358(19):2003-15.
22. Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. *J Perinat Med* 2012;40(3):225-8.
23. Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet* 2010;111(1):37-40.
24. Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2014;104(3):353-7.
25. Terti K, Ekblad U, Koskinen P, Vahlberg T, Ronnema T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab* 2013;15(3):246-51.
26. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Int J Gynaecol Obstet* 2002;78(1):69-77.
27. Yogeve Y, Melamed N, Chen R, Nassie D, Pardo J, Hod M. Glyburide in gestational diabetes--prediction of treatment failure. *J Matern Fetal Neonatal Med* 2011;24(6):842-6.





Gestational Diabetes: Is Insulin Necessary?


Kim A. Boggess MD
University of North Carolina at Chapel Hill
Dept. of Ob/Gyn
Division of Maternal Fetal Medicine

Learning Objectives

- To understand rationale and choices for pharmacologic treatment of gestational diabetes (GDM)
- To identify knowledge gaps regarding use of oral hypoglycemic agents for GDM treatment





Gestational Diabetes



- 3-5 % of pregnant women
- 'Abnormal GTT which is diagnosed or first recognized during gestation'
- Screening for all pregnant women at 24-28 weeks
- 1 or 2 step method for diagnosis

Gestational Diabetes



- Insulin resistance
- Diminished insulin secretory response
 - Usually normal fasting response
 - Postprandial hyperglycemia
 - Increased time to reach 'pre-prandial' glucose levels

GDM Diagnostic Criteria

- 1 step: 75 gm GTT
- 2-step: 50 gm GTT (> 135 gm/dl) then 100 gm GTT

	75-g oral GTT		EASD	IADPSG	100-g oral GTT		
	WHO	WHO			Osull	NDDG	CC
	Venous WB mmol/l (mg/dl)	Venous plasma mmol/l (mg/dl)	Venous plasma mmol/l (mg/dl)	Venous plasma mmol/l (mg/dl)	Venous WB mmol/l (mg/dl)	Venous plasma mmol/l (mg/dl)	Venous plasma mmol/l (mg/dl)
Fasting	≥ 6.1 (110)	≥ 7.0 (126)	≥ 6.0 (108)	≥ 5.1 (92)	≥ 5.0 (90)	≥ 5.8 (105)	≥ 5.3 (95)
1h				≥ 10.0 (180)	≥ 9.1 (164)	≥ 10.6 (190)	≥ 10.0 (180)
2h	≥ 6.7 (121)	≥ 7.8 (140)	≥ 9.0 (162)	≥ 8.5 (153)	≥ 8.0 (144)	≥ 9.2 (165)	≥ 8.6 (155)
3h					≥ 6.9 (124)	≥ 8.1 (145)	≥ 7.8 (140)

GDM – What's the big deal?



BIG DEAL

GDM Risks

- Macrosomia, LGA
- Shoulder dystocia, birth injury
- Cesarean delivery
- Stillbirth
- Preeclampsia/GHTN

Black Diabetes Care 2013
Casey Obstet Gynecol 1997
Langer Amer J Obstet Gynecol 1994

GDM Management



- Maintaining euglycemia is key to optimizing outcomes
- Surveillance with fasting and postprandial capillary blood glucose
- Diet and insulin mainstay of treatment

GDM Management



- Target capillary blood glucose level
 - Fasting 60 - 90 mg/dl
 - 1 hr PP \leq 140 mg/dl
 - 2 hr PP \leq 120 mg/dl
- 1 hr PP may be better predictor of glycemic control, infant birth weight
- Continuous glucose monitoring under study

Nicholson Evid Rep Technol Assess 2008

GDM Management



- 50% successfully treated with:
 - Dietary modification
 - 2000 -2200 cal/day
 - Complex, high fiber carbs
 - Distributed 10 - 20% BF, 20 - 30% lunch, 30 - 40% dinner, 30% snacks
 - Exercise
 - 3 - 4x/weekly, 20 - 30 min

GDM Management



- Historical debate about utility of aggressive treatment
- Pharmacotherapy when diet and lifestyle changes fail to achieve euglycemia
- ACOG and ADA endorse use of oral agents

Effect of GDM Treatment



- ACHOIS trial
 - RCT of insulin vs. usual care
 - ~1000 women 24-34 weeks
- Serious complications
RR 0.33 (0.14-0.75)
- Secondary outcomes
Birth weight -145 g (-219, -70)
LGA 0.62 (0.47-0.81)
> 4000 g 0.47 (0.34-0.64)

Crowther NEJM 2005



Effect of GDM Treatment

- ACHOIS trial
 - RCT of insulin vs. usual care
 - ~1000 women 24-34 weeks
- Serious complications
RR 0.33 (0.14-0.75)
- Secondary outcomes
 - Birth weight -145 g (-219, -70)
 - LGA 0.62 (0.47-0.81)
 - > 4000 g 0.47 (0.34-0.64)

Crowther NEJM 2005



Effect of GDM Treatment

- ACHOIS trial
 - RCT of insulin vs. usual care
 - ~1000 women 24-34 weeks
- Serious complications
RR 0.33 (0.14-0.75)
- Secondary outcomes
 - Birth weight -145 g (-219, -70)
 - LGA 0.62 (0.47-0.81)
 - > 4000 g 0.47 (0.34-0.64)

Crowther NEJM 2005



Effect of GDM Treatment

- MFMU GDM trial
 - RCT of insulin vs. usual care
 - ~950 women 24-31 weeks
- Composite outcome – no difference
RR 0.87 (0.72-1.07)
- Secondary outcomes
 - Birth weight 3302 vs. 3408 g
 - LGA 0.49 (0.32-0.76)
 - > 4000 g 0.41 (0.26-0.66)

Landon NEJM 2009



Effect of GDM Treatment

- MFMU GDM trial
 - RCT of insulin vs. usual care
 - ~950 women 24-31 weeks
- Composite outcome – no difference
RR 0.87 (0.72-1.07)
- Secondary outcomes
 - Birth weight 3302 vs. 3408 g
 - LGA 0.49 (0.32-0.76)
 - > 4000 g 0.41 (0.26-0.66)

Landon NEJM 2009



Effect of GDM Treatment

- MFMU GDM trial
 - RCT of insulin vs. usual care
 - ~950 women 24-31 weeks
- Composite outcome – no difference
RR 0.87 (0.72-1.07)
- Secondary outcomes
 - Birth weight 3302 vs. 3408 g
 - LGA 0.49 (0.32-0.76)
 - > 4000 g 0.41 (0.26-0.66)

Landon NEJM 2009



Effect of GDM Treatment

- Systematic review/meta-analysis of diet and insulin showed treatment reduced
 - Macrosomia and LGA
 - Shoulder dystocia
 - Preeclampsia/CHTN

Horvath BMJ 2010

What is Best Treatment?



- Insulin mainstay until 2000
- Rational for oral hypoglycemic agents
 - Convenience
 - Less discomfort
 - More acceptable
 - Fewer supplies, less cost

GDM Pharmacotherapy



- Oral agents
 - Glyburide-sulfonylurea
 - Metformin-biguanide
 - Others

Glyburide



- 2nd generation sulfonylurea
- Stimulates insulin secretion, decreases hepatic clearance
- Metabolized in liver
- Onset 1 hr, peak 3-4 hrs, ½ life 8-10 hrs
- Primary adverse effect: hypoglycemia

Glyburide vs. Insulin in GDM

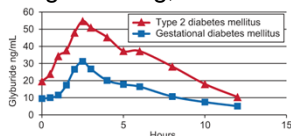


- RCT 11-33 weeks n=404
- 1^o outcome – glycemic control
 - Comparable outcomes
 - Lower incidence of maternal hypoglycemia
 - Good compliance, less costly

Langer et al NEJM 2000

Glyburide in Pregnancy

- Begin 2.5 mg, max 20 mg; QD, BID, or TID



- Fetal level 70% of maternal level

Caritis Obstet Gynecol 2013
Hebert Clin Pharmacol Therap 2009

Glyburide 'Failure' in GDM



Author/year	N	Failure rate (%)	Macrosomia (%)	Predictors
Chmait 2004	69	19	17	Earlier dx Higher BG
Conway 2004	75	16	11	Earlier tx Higher OGTT
Kremer 2004	73	19	19	
Kahn 2006	95	19	7	Earlier dx
Yogev 2011	124	25	6.5	Higher GWG GTT > 200



Glyburide in GDM

- Marketscan database of >110,000 women
 - 2000-2011: glyburide use increased from 7 to 64%
 - Compared to insulin, glyburide higher risk for
 - NICU admission (RR 1.41; 95% CI 1.23-1.62)
 - RDS (RR 1.63; 95% CI, 1.23-2.15),
 - Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
 - Birth injury (RR 1.35; 95% CI, 1.00-1.82)
 - LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015



Glyburide in GDM

- Marketscan database of >110,000 women
 - 2000-2011: glyburide use increased from 7 to 64%
 - Compared to insulin, glyburide higher risk for
 - NICU admission (RR 1.41; 95% CI 1.23-1.62)
 - RDS (RR 1.63; 95% CI, 1.23-2.15),
 - Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
 - Birth injury (RR 1.35; 95% CI, 1.00-1.82)
 - LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015



Glyburide in GDM

- Marketscan database of >110,000 women
 - 2000-2011: glyburide use increased from 7 to 64%
 - Compared to insulin, glyburide higher risk for
 - NICU admission (RR 1.41; 95% CI 1.23-1.62)
 - RDS (RR 1.63; 95% CI, 1.23-2.15),
 - Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
 - Birth injury (RR 1.35; 95% CI, 1.00-1.82)
 - LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015



Glyburide in GDM

- Marketscan database of >110,000 women
 - 2000-2011: glyburide use increased from 7 to 64%
 - Compared to insulin, glyburide higher risk for
 - NICU admission (RR 1.41; 95% CI 1.23-1.62)
 - RDS (RR 1.63; 95% CI, 1.23-2.15),
 - Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
 - Birth injury (RR 1.35; 95% CI, 1.00-1.82)
 - LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015



Glyburide in GDM

- Marketscan database of >110,000 women
 - 2000-2011: glyburide use increased from 7 to 64%
 - Compared to insulin, glyburide higher risk for
 - NICU admission (RR 1.41; 95% CI 1.23-1.62)
 - RDS (RR 1.63; 95% CI, 1.23-2.15),
 - Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
 - Birth injury (RR 1.35; 95% CI, 1.00-1.82)
 - LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015

In Summary...

**THERE IS NOTHING
CERTAIN, BUT THE
UNCERTAIN**

Proverb

Metformin in GDM



- Biguanide, from French lilac
 - Reduces gluconeogenesis in the liver
 - Limits glucose absorption in the gut
 - Increases insulin receptor sensitivity
- Does not increase insulin production
 - Less likely than insulin to cause hypoglycemia
 - Favorable weight effects
- Dosing start at 500 mg BID increase to 1000 mg BID

Metformin in GDM



- GI upset (diarrhea, nausea, vomiting)
- Lactic acidosis ~ 1/10-30,000
- Crosses the placenta
- Fetal levels exceed maternal levels
- Small amount in breast milk
- Not a teratogen

Metformin in GDM



- RCT of metformin vs. insulin N=733
- No difference in 1° composite outcome
 - Less neo hypoglycemia (3 vs 8%, p=.008)
 - LGA rate comparable (18 vs. 19%)
 - Less weight gain (0.4 vs. 2.0 kg, p<.001)
 - Metformin preferred by women

Rowan NEJM 2008

Metformin in GDM



- RCT of metformin vs. insulin N=733
- No difference in 1° composite outcome
 - Less neo hypoglycemia (3 vs 8%, p=.008)
 - LGA rate comparable (18 vs. 19%)
 - Less weight gain (0.4 vs. 2.0 kg, p<.001)
 - Metformin preferred by women

Rowan NEJM 2008

Metformin in GDM



- RCT of metformin vs. insulin N=733
- No difference in 1° composite outcome
 - Less neo hypoglycemia (3 vs 8%, p=.008)
 - LGA rate comparable (18 vs. 19%)
 - Less weight gain (0.4 vs. 2.0 kg, p<.001)
 - Metformin preferred by women

Rowan NEJM 2008

Metformin in GDM



- Systematic review/meta-analysis of metformin in GDM and T2DM
- 16 RCT, N=2165
- Metformin lower risk of
 - Neo hypoglycemia (RR 0.63, 0.45-0.87)
 - LGA rate (RR 0.56, 0.37-0.85)
- No long term data

Butalia Diabet Med 2017

Metformin vs. Insulin



- Systematic review/meta analysis
- 6 RCT, 1420 subjects
- No differences in primary outcomes
- Less maternal weight gain
– (-1.49 kg, -2.66-0.31)
- ? Increase in PTB
– (RR 1.56, 1.06-2.30)

Su Wang Diabetes Res Clin Prac 2014

Metformin vs. Insulin



- Systematic review/meta analysis
- 6 RCT, 1420 subjects
- No differences in primary outcome
- Less maternal weight gain
– (-1.49 kg, -2.66-0.31)
- ? Increase in PTB
– (RR 1.56, 1.06-2.30)

Su Wang Diabetes Res Clin Prac 2014

Metformin vs. Insulin



- Systematic review/meta analysis
- 6 RCT, 1420 subjects
- No differences in primary outcomes
- Less maternal weight gain
– (-1.49 kg, -2.66-0.31)
- ? Increase in PTB
– (RR 1.56, 1.06-2.30)

Su Wang Diabetes Res Clin Prac 2014

Glyburide vs. Metformin



Author /Year	N	Failure (%)	BW (g)	Neo hypogly (%)
Moore 2010	74 glyburide	13	3330±334	0
	75 metformin	35	3103±600	1
Silva 2012	96 glyburide	29	3387±512	14
	104 metformin	21	3193±521	11

What Do We Know (or Think)?

- Treatment of GDM improves outcomes
- Choice of oral agent versus insulin
- Choice of glyburide versus metformin



www.tmoelott.com

"I'm making a decision! Stop confusing me with facts!"

Which Agent?



- Systematic review/meta-analysis
- 2509 subjects, 15 studies
- As monotherapy, glyburide inferior to both insulin and metformin
- Metformin (plus insulin when required) slightly better than insulin

Balsells BMJ 2015

Which Agent?



BIRTHWEIGHT DIFFERENCES

Glibenamide vs Insulin N=798	108.5 (35.9, 181.2)	Favors insulin
Metformin vs Insulin N=1362	-31.4 (-86.5, 23.64)	Favors metformin
Metformin vs. Glibenamide N=349	-209 (-314.4, -103.6)	Favors metformin

Are There Other Options?

- Older sulfonylureas (tolbutamide, chlorpropamide) not used due to fetal hyperinsulinemia and neonatal hypoglycemia
- Acarbose (alpha glucosidase inhibitor) only 2 small studies
- Thiazolidinediones, meglitinides, DPP-4 inhibitors considered experimental
- Inositol

Summary



- Glycemic control reduces perinatal morbidity
- When diet and lifestyle fail pharmacologic therapy indicated
- Oral agents reasonable alternative to insulin; metformin preferred to glyburide
- Long term outcome data lacking

