

## Diabetes in Pregnancy and Gestational Diabetes Mellitus (GDM)

### What are the complications of diabetes in pregnancy?<sup>1,2,3</sup>

- Tight glucose control is critical in the first 42 days of pregnancy (organogenesis).
- Poor glycemic control is associated with adverse pregnancy outcomes including perinatal mortality, and congenital malformations. (1<sup>st</sup> trimester concerns re: birth defects, 3<sup>rd</sup> trimester concerns re: fetal growth and development, metabolic complications).
- All pregnant women should be screened for GDM between 24-28 weeks gestation.
- Maternal:** pre-eclampsia, retinopathy, nephropathy, hypertensive disorders, caesarian deliveries, increased rates of DM post partum (20% within 9 years).
- Offspring:** macrosomia and associated birth trauma, NICU admissions, still births, metabolic disturbances, feeding problems, respiratory disturbances, infant/childhood obesity and glucose intolerance.

Pregnancy Outcome	Pre-Existing Diabetes *	Gestational Diabetes *
<b>Maternal Morbidity/Mortality</b>	<b>7.9%</b> (2.6%)	<b>3.1%</b> (2.6%)
Pre-eclampsia	<b>13.8%</b> (4.4%)	<b>6.7%</b> (4.4%)
Caesarian Delivery	<b>33.3%</b> (11.3%)	<b>17.6%</b> (11.3%)
<b>Infant Morbidity/Mortality</b>	<b>13.6%</b> (3.1%)	<b>3.2%</b> (2.3%)
Macrosomia	<b>35%</b> (10.4%)	<b>15.9%</b> (10.4%)
Hypoglycemia	<b>47.8%</b> (1.6%)	<b>19.1%</b> (1.6%)
Still births	<b>1.6%</b> (0.6%)	<b>0.3%</b> (0.3%)
Admission to NICU	<b>10.4%</b> (2.1%)	<b>2.4%</b> (1.7%)

\*Numbers in parentheses indicate rate of outcome in pregnancy without diabetes

### What are the glycemic targets for diabetes in pregnancy?<sup>1</sup>

- Pre-existing diabetes and gestational diabetes:

	Glycemic targets
Pre-pregnancy: A1c (%)	≤ 7.0
Once pregnant:	
FBG & preprandial BG (mmol/L)	3.8-5.2
1-hour postprandial BG (mmol/L)	5.5-7.7
2-hour postprandial BG (mmol/L)	5.0-6.6
A1c (%)	≤6.0 (normal)

### What treatments are recommended for diabetes in pregnancy and gestational diabetes?<sup>1,4</sup>

- Optimal glycemic control prior to conception is essential with pre-existing diabetes.
- In GDM, nutrition therapy and light exercise (e.g. walk after meals) are initial treatment. If glycemic targets are not met within 2 weeks, initiate insulin.
- Use intensive insulin therapy – multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusions. No particular insulin regimen has been shown to be more effective in pregnant women requiring insulin therapy.
- Self-monitoring of blood glucose: preprandial & postprandial at least 4 times per day, with occasional nighttime monitoring.
- Care should be taken to avoid hypoglycemia as a result of striving to achieve glycemic targets. Risk of hypoglycemia is increased in Type 1 DM during the first trimester.

### Which insulins are safe to use in pregnancy?<sup>1,4,5,6,7,8</sup>

- Regular human** and **NPH** insulin are the most studied and have the most safety experience. A number of clinical trials evaluating some of the new insulins have been published. **Lispro** or **Aspart** have less experience, but appear to be as safe as regular human insulin. They may be preferred by patients needing the convenience of mealtime dosing.
- Women on long-acting insulin analogues, i.e. **glargine** or **detemir**, may be switched to NPH preferably prior to conception.
- There is insufficient evidence to routinely recommend **glargine** or **detemir** in pregnancy, but may be an option in women who cannot tolerate NPH because of nocturnal hypoglycemia. Theoretical risks would suggest that patients should avoid glargine use in pregnancy; however, a meta-analysis comparing glargine (n=331) to NPH (n=371) use during pregnancy found no statistically significant differences in adverse fetal outcomes.<sup>17</sup>

### Can oral hypoglycemic agents be used in pregnancy?<sup>1,8,9,10,11,12,13,14,15</sup>

- Historically, oral agents for diabetes were not recommended during pregnancy. Patients should generally be switched to insulin therapy and titrated to achieve acceptable glucose control before conception. However, **metformin** and **glyburide** may be continued in T2DM, or initiated in GDM females who are non-adherent to or refuse insulin. Glyburide does not cross the placenta, and neither agent appears to be teratogenic nor is excreted into breast milk. Metformin and glyburide are similar to insulin in terms of maternal and fetal outcomes. Insulin may be added to metformin if needed to achieve targets.
- Update Jan 2010: small Latina study suggests glyburide more likely to produce glycemic control than metformin.<sup>12</sup>

**What are other important considerations in the management of diabetes in pregnancy?<sup>1, 8,16</sup>**

**Pre-conception & Early Pregnancy**

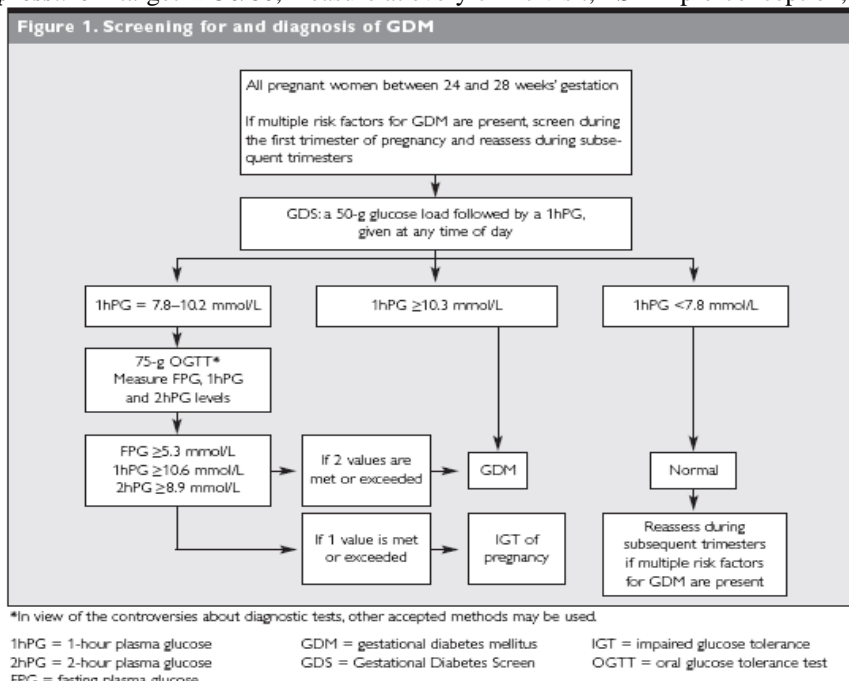
- Folic acid 5mg/d supplementation is recommended 3 months pre-conception to prevent neural tube defects and for the first 12 weeks post conception. Thereafter, supplement with 0.4-1 mg/day.
- **Statins** should be discontinued prior to conception due to the risk of teratogenicity.
- New evidence suggests that **ACE inhibitors and ARBs** during the 1<sup>st</sup> trimester may not increase the risk of fetal toxicity more than other antihypertensives. Hypertension itself may contribute to fetal toxicity.<sup>18</sup> These medications are still contraindicated during 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. **If your patient is on an ACE inhibitor or ARB prior to conception:**
  - **For the treatment of hypertension**, discuss the above with the patient and jointly decide to either switch to an alternative antihypertensive prior to conception, or wait until pregnancy is confirmed & then switch.
  - **For the prevention/treatment of proteinuria**, continue the ACE inhibitor or ARB until conception occurs. Once pregnancy is confirmed, switch to a safer alternative and resume the ACE inhibitor or ABR post-partum.
- Insulin requirements are typically decreased in the first trimester (may increase risk of hypoglycemia if significant nausea/vomiting) and increase in 2<sup>nd</sup> and 3<sup>rd</sup> trimester.
- Decreased nutritional intake may increase the risk of diabetic ketoacidosis; ketone monitoring is warranted to ensure mother and baby's nutritional needs are being met.

**Late Pregnancy, Delivery and Post-Partum**

- Insulin **may** not be required on the day of delivery and up to 24-48 hours post partum.
- Insulin requirements may increase if antenatal steroids used in preterm labour.
- Maternal hyperglycemia at delivery increases risk of neonatal hypoglycemia.
- Women who have had GDM should be re-evaluated between 6 weeks – 6 months of delivery with a 75g oral glucose tolerance test (OGTT) and be counseled on a healthy lifestyle.

**SCREENING Considerations:**

- **Ophthalmologic exam** – pre-conception, 1<sup>st</sup> trimester, PRN pregnancy & 1<sup>st</sup> year post partum; **nephropathy** – pre-conception; **blood pressure** – target <130/80, measure at every clinic visit; **TSH** – pre-conception, or early pregnancy.<sup>8</sup>



1. Canadian Diabetes Association Clinical Practice Guidelines 2008. Accessed online: <http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf>
2. Shand AW, et al. Outcomes of pregnancies in women with pre-gestational diabetes mellitus & gestational diabetes mellitus: a population based study in New South Wales Australia, 1998-2002. Diabet Med 2008;25:708-715
3. Feig DS, Zinaman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ 2008;179:229-34
4. Pharmacists Letter July 2008. Pregnancy and Diabetes
5. Budgen S, MacNair K. Insulin analogues. Upskilling document prepared for COMPUS. August 29, 2008.
6. Hod M et al. Fetal & perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. Am J Obstet Gynecol 2008; 198:186.e1-186.e7.
7. Jovanovic L, Pettitt DJ. Treatment with insulin and its analogs in pregnancies complicated by diabetes. Diabetes Care 2007; 30:S220-5
8. Kitzmiller JL, Block JM, Brown FM, et al. Managing pre-existing diabetes for pregnancy. Diabetes Care 2008;31:1060-1079
9. Moretti ME, Rezvani M, Koren G. Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. Ann Pharmacother 2008;42:483-490
10. Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 200;343:1134-8
11. Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003-15
12. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010.Jan;115(1):55-9.
13. Rowan JA et al. MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med.2008 May 8;358(19):2003-15.
14. Rowan JA et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care. 2011 Oct;34(10):2279-84.
15. Dhulkotia JS et al. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Nov;203(5):457.e1-9.
16. Wilson RD, et al. Pre-conceptional vitamin/folic acid supplementation 2007: The use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynecol 2007; 29:1003-1013
17. Pollex E. et al. Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. Annals of Pharmacotherapy 2011;45:9-16.
18. Li DK et al. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011 Oct 18;343.