



## Obesity and Type 2 Diabetes: Is Your Patient Ready for Pregnancy?



**Erin Keely, MD, FRCPC**

Presented at the University of Ottawa's Annual Update in Endocrinology and Diabetes, November 2008.

Type 2 diabetes mellitus (T2DM) and obesity are becoming increasingly common in pregnancy. In the US, 55% of women of childbearing age are overweight and 30% are obese.<sup>1</sup> T2DM is now as common as Type 1 diabetes (T1DM) in pregnancy in many populations.

It is essential that women with T2DM and obesity plan their pregnancies carefully to reduce their risk of poor outcomes (Table 1). Unfortunately this only occurs in about half of women. Women with T2DM have less pregnancy optimization than women with T1DM.

This may be because women and their caregivers do not recognize the seriousness of T2DM in pregnancy or perhaps because of the associated obesity, lower expectation of fertility secondary to polycystic ovarian syndrome and demographic variables such as recent immigration, non-Caucasian ethnic background and older age.<sup>2</sup> Treatment with metformin or a glitazone increase the likelihood of pregnancy in women with associated polycystic ovary disease (PCOD).

*In the US, 55% of women of childbearing age are overweight and 30% are obese.*

### Meet Sheila

Sheila is a 32-year-old accountant that has had Type 2 diabetes for the past 5 years.

#### Physical

- She is a G1T0P0A1L0 with a history of oligomenorrhea and hirsutism since menarche
- She is on metformin 500 mg b.i.d. and glyburide 10 mg b.i.d. Her glucose control is poor with a hemoglobin A1c of 0.086
- She has no known retinopathy or nephropathy
- She is hypertensive with a BP of 132/85 mmHg on ramipril 10 mg o.d.
- Her BMI is 36 kg/m<sup>2</sup>
- She has a new partner and is not on an OC

### Components of preconception care

There are several important components of preconception care and counselling that should occur (Table 2). A supportive, positive relationship increases the likelihood of achieving target glycemic levels prior to pregnancy.

### Weight loss prior to pregnancy

For obese women, weight loss may restore ovulation and improve pregnancy outcomes. However, it is often unrealistic to hold off on pregnancy until an ideal body weight is achieved.



**Table 1**

**Risks in pregnancy from Type 2 diabetes and obesity**

- First trimester loss
- Congenital anomalies
- Worsening hypertension/pre-eclampsia
- Late pregnancy loss/stillbirth
- Macrosomia and shoulder dystocia
- Increased likelihood of caesarean section
- Surgical complications including blood loss, infection, thrombosis
- Decreased breastfeeding rates
- Long-term maternal and childhood obesity

**Table 2**

**Important components of preconception care**

- Insure adequate (1mg to 5 mg) folic acid
- Optimize glucose control, aim for hemoglobin A1c < 0.07
- Discontinue/replace medications known to be teratogens or unknown risk
- Assess for complications and need for intervention
- Enhance self-management through consultation with multidisciplinary team
- Encourage smoking cessation
- Encourage alcohol abstinence
- Encourage weight loss, consider bariatric surgery in morbidly obese

The safety of medical therapy for weight loss in pregnancy is not known. Bariatric surgery has been associated with improved obstetrical outcomes, however, unique nutritional needs must be addressed.

## *Reduce the risk of congenital anomalies*

By the time a woman knows she is pregnant and seeks medical advice, the majority of organogenesis is complete. Glucose is a teratogen. Normalizing glucose levels, folate replacement and the discontinuation of medications associated

## *FAQ*

### *Should oral agents be continued in pregnancy?*

There is some evidence that metformin may reduce first trimester loss in women with polycystic ovary disease. Given the lack of robust safety data and that metformin crosses the placenta, most clinicians would stop metformin at the time of conception. When used for ovulation induction, insulin should be used for glucose control.

with teratogenesis must occur prior to pregnancy to make a difference. Overweight women have a two fold higher risk of anomalies with obese women having a three and a half fold risk of neural tube defects and two fold risk of cardiac anomalies.<sup>3</sup> Obese women are less likely to eat folate-containing foods and have lower serum folate levels with the same oral intake. Thus, women with T2DM and/or a BMI > 35 should be counselled to take 5 mg of folate.<sup>4</sup>

*Women with T2DM have less pre-pregnancy optimization than women with T1DM.*

## *Change to insulin or continue oral agents*

Although oral agents are unlikely teratogenic, they are not recommended for glycemic control in pregnancy. Though glyburide and most recently metformin appear safe in the treatment of gestational diabetes, it is unlikely that women with T2DM can maintain glycemic control without

**FAQ*****What should I use to treat her hypertension?***

ACE inhibitors and ARBs should be discontinued prior to pregnancy. Labetalol, methyldopa or nifedipine are the preferred agents.  $\beta$ -blockers, except for atenolol, may also be used.

insulin given the dramatic increase in insulin resistance in pregnancy. To avoid poor blood glucose levels while switching to insulin during organogenesis, it is best to find a suitable insulin regimen prior to pregnancy.

***F***or obese women, weight loss may restore ovulation and improve pregnancy outcomes.

If the woman conceives on oral agents, they should not be stopped until insulin can be safely initiated. If metformin is being used for ovulation induction, then it should be continued until conception. For women with previous first trimester losses, there may be some benefit in continuing until 12 weeks.

Insulin regimens should be individualized, but most women will do best on multiple daily doses adjusted to carbohydrate intake and glucose levels. There is limited data on the safety of the newer insulin analogues during pregnancy. Insulin does not cross the placenta, however, the newer insulin analogues have been manipulated to alter their action profile and thus in theory could cross the placenta. Glargine

**FAQ*****Is it safe for a woman to conceive on oral hypoglycemic agents?***

There is no evidence that oral agents are teratogenic. However, it is best to initiate insulin prior to pregnancy to find an effective regimen before organogenesis. Metformin may be used for ovulation induction in women with polycystic ovary disease.

has a theoretical concern, in that it has more mitogenic potential in cell cultures. Because of this it is generally avoided, however, if it is the best insulin for glycemic control for an individual patient it may be best to use it.

***Optimize treatment of hypertension—discontinue or replace ACE inhibitors/ARBs***

Women with T2DM and obesity often also have hypertension. Although second and third trimester exposure to ACE inhibitors is well known to be associated with fetopathy (oligohydramnios, growth restriction, renal failure), recent evidence suggests increased risk of congenital anomalies with first trimester exposure.<sup>5</sup> Despite this known risk, more women are getting pregnant on ACE inhibitors, likely due to increasing awareness of their benefits for people with T2DM.<sup>6</sup>

Women with hypertension should be changed to a safe medication for pregnancy notably labetalol, methyldopa or nifedipine.<sup>7</sup> Thiazide diuretics, although not known to be teratogenic, limit the increase in plasma volume associated with pregnancy and should be avoided.



## *Treatment of lipid disorders prior to pregnancy*

Women with T2DM will often be prescribed a lipid lowering medication to reduce CV risk. Fibrates and statins do appear to cross the placenta. There is limited and conflicting evidence on the safety of statins.<sup>8</sup> Although there is no definitive evidence of harm, there is also no clear evidence of benefit. Thus, only women with severe hypertriglyceridemia, where pancreatitis is a concern, should be treated pharmacologically.

### *Summary*

T2DM is just as serious as T1DM in pregnancy. There is an urgent need for caregivers to reinforce the importance of pregnancy planning with women with T2DM and obesity.<sup>9</sup> Serious adverse outcomes can be avoided through pre-conception glycemic control, folate ingestion and optimization of associated conditions.

**cme**

**Dr. Keely** is a Professor, Department of Medicine and Obstetrics/Gynecology, University of Ottawa; and Chief, Division of Endocrinology and Metabolism, The Ottawa Hospital, Ottawa, Ontario.

## Take-home message

- Type 2 diabetes is at least as serious as Type 1 diabetes in pregnancy
- Women with Type 2 diabetes may be less likely to seek prepregnancy counselling
- Treatment of Type 2 diabetes with insulin sensitizers may increase ovulation rates and thus pregnancy, in women with PCOD
- Organogenesis is almost complete by the time the woman knows she is pregnant
- Glucose is a teratogen. A target HbA1c prior to pregnancy should be  $\leq 7.0\%$
- Insulin should be initiated prior to pregnancy when possible
- Obese women need more folic acid than lean women
- ACE inhibitors and ARBs should be stopped prior to pregnancy

### References

1. Hedley AA, Ogden CL, Johnson CL, et al: Prevalence of Overweight and Obesity Among US Children, Adolescents and Adults, 1999-2002. *JAMA* 2004; 291(23):2847-50.
2. Confidential Enquiry into Maternal and Child Health: Pregnancy in Women with Type 1 and Type 2 diabetes in 2002-03, England, Wales and Northern Ireland. London: CEMACH; 2005. Accessed: <http://www.cemach.org.uk/getattachment/8940bb02-7d42-4067-9aed-92bbeed144ea/Pregnancy-in-women-with-type-1-and-type-2-diabetes.aspx>
3. Watkins ML, Rasmussen SA, Honein MA, et al: Maternal Obesity and Risk for Birth Defects. *Pediatrics* 2003; 111(5 Part2):1152-8.
4. Wilson RD, Johnson JA, Wyatt P, 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 Gynaecol Can* 2007; 29(12):1003-26.
5. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al: Major Congenital Malformations After First-Trimester Exposure to ACE Inhibitors. *N Engl J Med* 2006; 354(23):2443-51.
6. Bowen ME, Ray WA, Arbogast PG, et al: Increasing Exposure to Angiotensin-Converting Enzyme Inhibitors in Pregnancy. *Am J Obstet Gynecol* 2008; 198(3):291
7. Podymow T, August P: Update on the Use of Antihypertensive Drugs in Pregnancy. *Hypertension* 2008; 51(4):960-9.
8. Kazmin A, Garcia-Bournissen F, Koren G: Risks of Statin Use During Pregnancy : A Systematic Review. *J Obstet Gynaecol Can* 2007; 29(11):906-8.
9. Roland JM, Murphy HR, Ball V, et al: The Pregnancies of Women With Type 2 Diabetes: Poor Outcomes But Opportunities for Improvement. *Diab Med* 2005; 22(12):1774-7.