Type 2 diabetes in pregnancy: importance of optimized care before, during and after pregnancy

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Summary: Women with Type 2 diabetes (T2DM) are an increasingly important part of the practice of obstetric medicine. The rising rates of obesity and advanced maternal age have resulted in a surge in the number of pregnant women with T2DM. The hyperglycaemia and associated conditions of the metabolic syndrome lead to poor obstetric outcome and impact on the long-term health of the mother and offspring. It is essential that women and care-givers recognize the seriousness of T2DM in pregnancy and strive to improve prepregnancy care, obstetric outcome and the long-term health of both the mother and child.

Keywords: diabetes, prepregnancy, glycaemic control

INTRODUCTION

Historically, women with type 1 diabetes (T1DM) have been the major concern for obstetricians and physicians caring for pregnant women with pregestational diabetes. The current epidemic of type 2 diabetes (T2DM) has created an imperative to recognize the seriousness of this illness for both the mother and the child. T2DM is part of the metabolic syndrome which includes hyperinsulinaemia with insulin resistance, abdominal obesity, dyslipidaemia, hypertension, premature atherosclerosis, polycystic ovary disease (PCOS) and a proinflammatory state. Pregnant women with T2DM are generally older, more likely to have children at home and originate from non-Caucasian ethnic groups than women with T1DM. The high prevalence of T2DM in immigrant and socioeconomically disadvantaged women, and its association with obesity and hypertension, may contribute to the poor obstetric outcomes in this population.^{1–4} T2DM is often perceived as being less severe than T1DM by patients and care-givers, resulting in less intensive care and education. In pregnancy, this belief must change in order to improve outcomes in these women and their children.

T2DM rates are increasing, especially in women of childbearing age. In the USA, there has been a 70% increase in the prevalence of diabetes in individuals aged 30–39 years when compared with the overall increase of 33%.⁵ There are large regional variances in the rate of T2DM, in part, due to the ethnic diversity and socioeconomic circumstances of the population. It is thus difficult to extrapolate other population's data to one's own circumstance. In a large USA population-based study, the proportion of women with T2DM increased from

26% of all pregestational diabetes mellitus in 1980 to 65% in 1988.⁶ In the UK, T2DM accounts for 13–45% of the women with diabetes in pregnancy and has increased six-fold in some areas.^{1,7}

Women with T2DM often have other components of the metabolic syndrome including obesity, hypertension, dyslipidaemia and potentially cardiovascular disease. According to the NHANES data from 1999 to 2002, 54.5% of women aged 20–39 years are overweight (BMI > 25), 29.1% are obese (BMI > 30) and 5.6% are extremely obese (BMI > 40). The prevalence of obesity is particularly high among non-Hispanic black women who have a 46.6% incidence of BMI > 30, compared with 38% for Mexican-American and 31% non-Hispanic white women.⁸ Based on self-reported data, the prevalence of women entering pregnancy with a BMI > 25 increased from 25% in 1991 to 35% in 2001, with 5% of women starting a pregnancy with a BMI > 40.⁹ Obesity itself is increasingly recognized as a serious contributor to poor obstetric outcome.¹⁰ It is important to recognize the need for glycaemic control and understand the impact of associated conditions of insulin resistance on pregnancy outcome. Despite many general advances in diabetes care, there continue to be lost opportunities for optimizing pregnancy outcomes in women with T2DM.

PREPREGNANCY CARE

Low rates of preconception counselling and care

Since glucose is a teratogen, prepregnancy control of hyperglycaemia is imperative. Case-control studies have demonstrated that preconception counselling lowers the risk of congenital anomalies and is a critical component for the care of all women with diabetes.¹¹ Unfortunately, many pregnancies are unplanned (but not necessarily unwanted). Delaying pre-conceptual counselling until just prior to a planned pregnancy will result in many women being deprived of the opportunity

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to ensure ideal glycaemic control prior to conception. Women with T2DM were less likely to have had a prepregnancy haemoglobin A_{1c}, an eye examination or appropriate folic acid supplementation than women with T1DM or the general population. In the UK only 25% of women with T2DM had documented prepregnancy counselling compared with 35% in the general population and 38% of women with T1DM.¹ Possible contributors to lower rates of preconception counselling in women with T2DM may be age, a history of infertility, a socially disadvantaged background, or language and cultural barriers. Both care-givers and patients may assume that T2DM is a 'milder' form of diabetes needing less intense monitoring since it can be treated with oral agents. It is important to emphasize the need for a partnership between the patient and care-givers prior to pregnancy, early diagnosis of pregnancy and early antenatal care to optimize outcomes.¹²

Preconception care should include revisiting self-care gaps, optimizing glycaemic control, assessing and stabilizing complications, diagnosing and treating associated conditions, recommendations for folic acid supplementation and assessing pharmacological choices. Counselling should include recommendations regarding optimal timing for conception, clear objectives for glycaemic control and the importance of effective contraception until these goals are realized. A supportive, positive relationship increases the likelihood of achieving target glycaemic levels prior to pregnancy.

Congenital anomalies and T2DM

By the time most women know they are pregnant and seek medical care, the majority of organogenesis is complete. Thus, the opportunity to reduce the rate of congenital anomalies occurs prior to pregnancy. Glucose is a well-known teratogen but there may also be other mechanisms for increased congenital anomalies in women with T2DM. When comparing congenital anomaly rates in infants of mothers with T1DM versus T2DM, some authors have found similar congenital anomaly rates, with both increased compared with the non-diabetic population.¹³ Other investigators have noted a greater increased anomaly rate in infants of women with T2DM despite similar glycaemic control.¹⁴ Factors that may contribute to the increased rate independent of glucose control include obesity, lower rates of folate supplementation and use of multiple medications. Several recent reports have highlighted the increased risk of neural tube defects (NTDs) and possibly other congenital anomalies in overweight/obese women.^{15,16} One study concluded that for every unit increase in BMI, the risk of NTD increased 7%.¹⁶ Increased BMI is also associated with lower serum folate levels despite adequate supplementation, resulting in less amount of folate reaching the embryo.^{16,17} Women with BMI > 30 kg/m² need to take an additional 350 µg of folate per day to achieve the same serum levels as non-obese women.^{18,19}

Optimizing glycaemic control – oral agents versus insulin

Women who achieve glycaemic control prior to pregnancy are less likely to have an infant with a congenital anomaly. Although there is no definitive evidence that oral hypoglycaemic agents cause fetal anomalies, the increase in insulin resistance associated with pregnancy results in maintaining

glycaemic control with oral agents alone unlikely (see below). Given the time required to optimize control with insulin, it is better to establish an insulin regimen prior to pregnancy to avoid fluctuations in the first trimester when glycaemic control is critical for organogenesis. Some women still prefer to continue oral agents until they are pregnant. Women with polycystic ovary syndrome, for example, which is associated with insulin resistance and T2DM, may require insulin sensitizers (e.g. metformin) for ovulation induction and this is generally continued until pregnancy is achieved.

Optimizing-associated conditions

Many women with T2DM will also require treatment for their hypertension and dyslipidaemia. Chronic hypertension occurs in approximately 13–19% of women with T2DM.^{20,21} Given the current clinical practice guidelines in diabetes care, many of these women will be taking an angiotensin-converting enzyme-inhibitor (ACE-I) which is of concern in pregnancy. In a cohort of 29,507 infants (209 exposed to ACE-I), first trimester exposure was associated with a 3.7-fold (95% CI 1.89–7.30) increase in cardiovascular anomalies and 4.39-fold (95% CI 1.37–14.02) increase in central nervous system anomalies and overall 2.7-fold increase in the (95% CI 1.72–4.27) risk of major anomalies.²² In the second and third trimester, exposure is associated with ACE-I fetopathy which includes oligohydramnios, growth restriction, renal failure and hypocalvaria. Despite these known risks, one retrospective cohort study, from 1986 to 2003 of 262,179 pregnancies in women on Medicaid during pregnancy, showed an alarming increase in ACE-I exposure.²³ Exposures in the first trimester increased from 8.4/10,000 pregnancies in 1986–1988 to 54.4/10,000 pregnancies in 2003 (RR 5.44; 95% CI 3.16–9.36) and in the second/third trimester, increased from 6.1/10,000 to 17.6/10,000 (RR 2.88; 95% CI 1.45–5.75). This increase in exposure was likely secondary to expanded indications for use of ACE-Is as first-line treatment in hypertension, increase in maternal age and increase in rates of T2DM. This increase underscores the need for widespread education and preconception counselling.

Women with T2DM may be on a lipid-lowering agent to reduce cardiovascular risk, which will most commonly be a statin. The data on teratogenicity of statins is conflicting and primarily based on animal studies since the human data is limited by small numbers.²⁴ Use of statin therapy increased from 0.03% of the pregnant population in 1996 to 0.11% in 2005 according to a USA HMO study of 118,935 deliveries.²⁵ Women over 40 years were most likely to receive statins (0.56%). Statin use at the time of conception should not result in complications, but should ideally be stopped prior to pregnancy.

Women with T2DM may also have evidence of microvascular complications despite a relatively short duration of known diabetes. There is very limited data, obtained from small cohort studies, on the incidence of diabetic nephropathy and retinopathy. Women with T2DM may be less likely to have retinal and renal assessments before and during pregnancy than women with T1DM.¹ The prevalence of retinopathy in women with T2DM varies widely between studies ranging from <1%²¹ to 32%, similar to rates in T1DM.^{26,27} The wide variation in the prevalence may relate imperfect or delayed ascertainment. The presence and degree of diabetic retinopathy are both associated with the duration of diabetes and glycaemic

control. Many studies have shown some worsening of retinopathy over the course of a pregnancy, however, most of the data is from T1DM. The risk of progression is dependent on duration of diabetes, degree of retinopathy, previous laser therapy and glycaemic control.^{28,29} In the non-pregnant state, the progression of diabetic nephropathy is slowed through tight glycaemic control, treatment with ACE-Is and tight blood pressure control. The need to discontinue ACE inhibition during pregnancy, together with the physiological increase in glomerular filtration rate during pregnancy, contribute to the frequently observed increase in microalbuminuria.

CARE DURING PREGNANCY

Obstetrical outcomes

The likelihood of an adverse outcome of pregnancy is as great from T2DM as from T1DM, and much greater than the general population. Although many studies have looked at obstetric risk, the comparison group and characteristics of each study group make it difficult to generalize these results to all populations. It is difficult to determine how much of the increased risk of an adverse outcome is due to hyperglycaemia *per se* compared with the associated conditions of obesity and hypertension.

Pregnancy loss, early and late are increased in T2DM relative to the general population. Although early losses appear related to glycaemic control (e.g. lethal congenital anomalies), late losses are likely multifactorial. Some,^{14,20,30,31} but not all,^{32,33} studies have shown increased perinatal mortality in T2DM versus T1DM pregnancies. In an Italian study, a higher stillbirth and neonatal mortality rate occurred in T2DM versus T1DM (1.9% versus 1.06% and 1.9% versus 0.21%, respectively); however, congenital malformation rates were higher in T1DM (5.9% versus 2.0%).³² This increased rate of late losses in T2DM compared with T1DM was confirmed in a 20-year prospective study from New Zealand.²⁷ The associated conditions of obesity, hypertension, ethnicity and disadvantaged socioeconomic status seen in women with T2DM likely plays a role in the increased risk of stillbirth and may differ across populations.

Macrosomia rates are increased among diabetic pregnancies. Excess fetal growth is believed to be due in part to fetal hyperinsulinaemia in response to maternal hyperglycaemia. Other factors, such as prepregnancy maternal weight, gestational weight gain, parity, ethnicity and other genetic factors, may also affect birthweight.³⁴ The impact of maternal obesity on birthweight has been well documented.³⁵ The increase in large for gestational age (LGA) births seen in the past decade may be directly related to increase in maternal weight and reduction in maternal smoking.³⁶ There is a two-fold increase risk (95% CI 1.4–3.0) and 2.4-fold (95% CI 1.5–3.8) risk of delivering a macrosomic infant (>4500 g) for women with a BMI 30–34.9 and >35, respectively.³⁷

Concern about the risk of stillbirth, and complications from macrosomia, result in high induction rates. The risk of operative delivery is increased significantly in women with T2DM compared with the non-diabetic population, especially when complicated by maternal obesity.³⁸ Obesity increases the risk of bleeding, wound infection, dehiscence and venous thromboembolic events following caesarean section.³⁹

Pregnancy-associated hypertension, including preeclampsia, is more common in women with T2DM than the general

population, which may be related to its association with obesity, insulin resistance and chronic hypertension.⁴⁰ The preeclampsia rates reported vary between studies (based on different population characteristics and definitions of the disorder) but range from 7% to 13%^{20,30} with gestational hypertension occurring in similar numbers.

Achieving glycaemic control in women with T2DM

The profound insulin resistance associated with pregnancy makes it unlikely that women will maintain glycaemic control with diet/exercise or oral hypoglycaemic agents throughout pregnancy. For women who are still on oral agents when they achieve pregnancy, it is important to continue them in the first trimester until insulin can be initiated, otherwise severe hyperglycaemia may occur during organogenesis.

Metformin has been used successfully in pregnancy with no definitive evidence of increased teratogenicity or adverse obstetric or neonatal outcome. The majority of metformin studies are in small cohorts of women with PCOS⁴¹ and women with gestational diabetes mellitus (GDM),⁴² and not T2DM. Metformin freely crosses the placenta, reaching concentrations that are higher than maternal levels.^{43,44} Some observational studies of small numbers of women have suggested worse outcomes in women with T2DM who continue metformin.^{45,46} It is possible that poor glycaemic control and other maternal co-morbidities account for these differences.⁴⁷ Although in theory metformin may be a beneficial adjunct in women requiring large amounts of insulin in later pregnancy, there is insufficient long-term data to support this given the known fetal exposure. Until ongoing studies are completed, the use of metformin during pregnancy other than for ovulation induction in women with PCOS is not supported by current evidence.

Second-generation sulphonylureas, in particular glyburide (known as glibenclamide in some countries), do not appear to accumulate in fetal circulation either owing to failure to cross the placenta or through active transport from the fetus to the mother.^{48,49} Although glyburide has been demonstrated to be effective and safe in the treatment of GDM,^{49–51} the insulin resistance associated with pregestational T2DM is rarely controlled adequately with these agents. Thiazolidinediones are now commonly used for the treatment of T2DM. Like metformin, they may induce ovulation in women with PCOS and thus increase pregnancy rates in previously infertile women.⁵² Data on safety in pregnancy is scant. Rosiglitazone is detected in fetal tissue, especially after 10 weeks gestation, however, the effect of this on fetal development is unknown.⁵³ There is no data on the safety of meglitinides, e.g. repaglinide in pregnancy.

Since oral hypoglycaemic agents are unlikely to maintain adequate glycaemic control and there is insufficient safety data, their use for glycaemic control in women who wish to become pregnant should be avoided. For women who do conceive on oral agents, they should not be discontinued until insulin therapy is initiated as hyperglycaemia is potentially much more dangerous than any of the currently available oral therapies used to treat diabetes.

Insulin therapy, thus, remains to be the accepted standard of care for women with pregestational diabetes requiring pharmacological treatment. Most regimens involve the use of a basal intermediate or long-acting insulin combined with prandial

(bolus) rapid-acting insulin. This provides adequate control for meals and flexibility for variable factors such as exercise. Insulin analogues, developed to enable better glycaemic control with less hypoglycaemia, are increasingly used in the care of non-pregnant diabetic patients. Limited studies in pregnancy demonstrate that short-acting lispro insulin does not cross the placenta, does not cause anti-insulin antibody production and is associated with fewer hypoglycaemic reactions than regular insulin with similar perinatal outcomes.⁵⁴ There is considerably less data available for aspart insulin. It has been shown to effectively control postprandial glucose excursions in GDM and provide comparable outcomes in women with T2DM.^{55,56}

Glargine insulin, the first available long-acting analogue has a 24-hour duration of action, which makes it an excellent basal insulin. In animal studies, no embryotoxic effects have been demonstrated.⁵⁷ It does have theoretical risks in pregnancy because of its known activation of insulin-like growth factor 1 (IGF-1) receptors and mitogenic potency, however, small cohort studies have not demonstrated any concerns.⁵⁸ For women well-controlled on glargine prior to pregnancy it may be difficult to return to intermediate-acting insulins. Despite this, currently, glargine cannot be recommended in pregnancy. There are no published reports of detemir use in pregnancy to date.

Nutrition and exercise are important components of the treatment of T2DM in pregnancy both for glycaemic control and reducing poor obstetric outcomes. The current guidelines for gestational weight gain are likely excessive, especially for obese women with T2DM. Limited or no weight gain has been associated with better obstetric outcome for women with a BMI > 30.⁵⁹ In order to reduce glycaemic excursions, most recommend limiting carbohydrate intake with avoidance of simple carbohydrates and distribution of food throughout the day.⁶⁰ Dietary counselling should be individualized and provided by a dietician. A recent trial in non-diabetic obese women demonstrated that individual dietary counselling was successful in limiting weight gain and improving glucose metabolism.⁶¹ Exercise is safe for most women and should be continued in pregnancy. The benefit of exercise to reduce insulin resistance in GDM has been demonstrated, however, data is lacking in T2DM.⁶²

POSTPARTUM CARE

The postpartum care of mothers with diabetes should include individual counselling on contraception, breastfeeding, healthy weight goals, nutrition, exercise, medical management of diabetes and future pregnancy planning. Although the postpartum period is a difficult time for women to commit to lifestyle changes, in particular exercise, there is opportunity to impact on the family's health through educating the mother on lifestyle choices.

Breastfeeding should be encouraged for all women. However, it may be even more important for women with T2DM given the evidence that breastfeeding may be beneficial in reducing the risk of childhood obesity and insulin resistance.^{63,64} Multiple variables influence a woman's intention and persistence with breastfeeding. Women with T2DM may be less likely to breastfeed due to obesity or desire to restart oral hypoglycaemic drugs with concerns of safety in lactation.

Obesity is associated with lower intention to initiate breastfeeding, lower rates of putting the baby to the breast in the

first two hours of life and delayed arrival of milk, which may be related to lower prolactin levels. Potential mechanical difficulties with infant latching, increased pregnancy complications including operative delivery and body image/discomfort with breastfeeding/exposure in public may also play a role.⁶⁴ It is interesting that the differences in breastfeeding between obese and non-obese women were not found in populations with high breastfeeding initiation rates (Russia and Denmark) and not found in black women in the USA.⁶⁵⁻⁶⁷

There has been reluctance to reintroduce oral agents during the breastfeeding period due to early reports of high breast milk concentrations of first generation sulphonylureas and lack of safety data. However, a recent paper showed that glyburide and glipizide do not enter the breast milk and are likely safe in lactating mothers.⁶⁸ In three studies of small sample size, metformin was detected in breast milk with a milk-to-plasma ratio of 0.35-0.71. Infant exposure was calculated at approximately 0.28-0.65% of the maternal dose, with very low or undetectable serum levels in the infant.⁶⁹⁻⁷¹ Thus, the amount of metformin in breast milk is likely clinically insignificant but an open discussion of the uncertainties with the woman is necessary before prescribing it to the lactating patient. There is no data to guide discussions for safety of thiazolidinediones or meglitinides during lactation.

If ACE-Is were used before pregnancy, they can be safely restarted during breastfeeding although some practitioners prefer to wait until lactation is stopped.⁷² There is no human data regarding statins and lactation, however, studies in rats do show transfer to breast milk and, thus, until further safety data is available these agents should not be restarted during breastfeeding.⁷³

There is an increasing concern about the impact of *in utero* hyperglycaemia on the long-term risk of obesity and T2DM in the offspring.^{74,75} Childhood obesity and abnormal glucose tolerance is increased in individuals exposed to hyperglycaemia *in utero*, even in normal weight neonates, however, most of this data originates from high-risk populations. It is important that these children be identified as high-risk so that preventive strategies may be introduced to the family, including proper nutrition, weight management and exercise.

CONCLUSION

Women with T2DM prior to pregnancy present a unique opportunity for care-givers to make a significant impact not only during the pregnancy, but for the life of the mother and child. There is an urgent need to reinforce the seriousness of T2DM in women of childbearing age and to their care-providers. Close collaboration between primary care-providers, obstetricians, obstetric internists, endocrinologists, paediatricians and the patient, will be critical to the success of any interventions. Serious adverse outcomes can be reduced through preconception glycaemic control, folate ingestion and optimization of management for chronic complications. Care during pregnancy should be as rigorous as that provided for women with T1DM, including multidisciplinary specialized clinics and close surveillance. The postpartum period should be used to encourage breastfeeding and seen as an opportunity to make long-lasting changes in nutrition, exercise and medical management that will improve the woman's lifetime risk from her diabetes and promote healthy behaviours in her family.

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(Accepted 16 June 2008)