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Review – Sir William Osler Medicine Masterclass

REVIEW – SIR WILLIAM OSLER MEDICINE MASTERCLASS

The management of type 1 and type 2 diabetes in pregnancy

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Introduction

Although pregnancy is typically a joyous event, it can pose significant risk to the mother and infant in the setting of type 1 or type 2 diabetes, also referred to as pregestational diabetes. Studies from UK and Ireland reveal poor outcomes for women with diabetes in pregnancy including a congenital malformation rate twice that of the background population, a 5-fold increased risk of stillbirth and a 3-fold increased risk of perinatal mortality and caesarean delivery.^{1–3} A further, emerging challenge is the increasing prevalence of type 2 diabetes in pregnancy associated with the concurrent rise in obesity. These women are more commonly from ethnic minorities and although predominantly cared for in community settings with minimal access to specialist care, they experience similar adverse outcomes to those with type 1 diabetes and are a particularly vulnerable group.^{4,5} Unfortunately, we have not achieved the target of the Saint Vincent declaration which in 1989 called for outcomes equal to that of the non-diabetic pregnancy within 5 years.⁶ On a more positive note, structured clinical care programs providing coordinated, evidence-based care to these women before, during and after pregnancy have demonstrated improved clinical outcomes.^{4,7} This article focuses on optimal management of women with type 1 and type 2 diabetes during this important time. Unless otherwise specified the information provided relates to both type 1 and type 2 diabetes. Gestational diabetes, typically a transient abnormality of glucose intolerance during pregnancy is not discussed.

Prepregnancy care: an opportunity not to be missed

The risk of certain adverse outcomes including malformations and perinatal mortality is related to poor glycaemic control in

early pregnancy.⁸ Intervention before the pregnancy is necessary to ensure optimal glycaemic control throughout the time of conception and this critical early stage. The value of a 'prepregnancy' clinic was first demonstrated almost 30 years ago and it is now accepted practice that preconception counselling is provided to all women with diabetes who are considering pregnancy.^{9,10} Typically women attending a centre for prepregnancy care are reviewed at 1–3 monthly intervals. The importance of avoiding an unplanned pregnancy should be explained and contraception advised until treatment goals are achieved.

A full medication review should take place and any medications unsuitable for pregnancy such as angiotensin converting enzyme inhibitors or statins should be discontinued.⁴ With the exception of metformin, all hypoglycaemic agents should be discontinued. If necessary, smoking and alcohol cessation advice should be provided. Retinal evaluation should take place and if therapy is required, pregnancy deferred until its completion. Satisfactory blood pressure control is necessary (<130/80 mmHg) and if there is evidence of renal dysfunction, nephrology review is recommended.⁹ Thyroid status must be assessed and managed at this time. Hypothyroidism may reduce fertility, increase the risk of miscarriage and impair foetal brain development if untreated.⁹ All women require a dietician review and those with a body mass index (BMI) above 27 kg/m² should be offered advice on how to lose weight. Prior to discontinuing contraception, folic acid 5 mg once daily is advised until 12 weeks gestation.³ Although there is no evidence of a clinical benefit for this higher dose, several advisory groups have made this recommendation based on a theoretical benefit in reducing the increased risk of neural tube defects associated with diabetes mellitus in pregnancy.^{2,3,9}

Women on insulin should be treated with a multiple daily injection (MDI) regimen or continuous subcutaneous insulin infusion (CSII) in preference to split-dose, premixed insulin.⁹ The rapid-acting insulin analogues aspart and lispro are safe and commonly used in pregnancy.^{3,11} Newer, long-acting analogues also appear safe for use in pregnancy and have begun to replace the traditionally used isophane insulin in clinical practice.¹² Detemir in particular, is approved for use in pregnancy and a recent study indicates that it does not cross the human placenta.¹³ Regular capillary blood glucose monitoring must take place and both pre- and postprandial levels are required. The 2015 draft National Institute for Health and Care Excellence (NICE) guidelines advise women with diabetes who are planning to become pregnant to maintain their HbA1c below 6.5% (48 mmol/mol) as this is associated with a reduction in congenital anomalies to close to that seen in the background population.³ The major limitation to tight glycaemic targets is hypoglycaemia and instruction on its management including use of glucagon should be provided to the patient and/or family members. Women with type 1 diabetes should have the ability to test for ketones (urinary or capillary) should they become unwell or hyperglycaemic.

Attendance at prepregnancy care is associated with a reduction in congenital anomalies, perinatal mortality and maternal HbA1c in the first trimester of pregnancy.¹⁴ These reductions are applicable to women with both type 1 and type 2 diabetes. Unfortunately, attendance at prepregnancy care is not universal and therein lies a challenge in getting advice to those who need it in an acceptable and understandable form. Of concern is the Confidential Enquiry into Maternal and Child Health survey which revealed that only 17% maternity services in the United Kingdom actually provided structured multidisciplinary preconception care.⁵ Murphy *et al.* demonstrated that a regionalized approach to preconception counselling and prepregnancy care improved pregnancy preparation and reduced risk of adverse pregnancy outcomes; however, women with type 1 diabetes were still more likely to have had documented preconception counselling (54 vs. 32% with type 2 diabetes). Despite improved counselling only 27% women attended prepregnancy care clinics with significantly more women with type 1 diabetes represented (30 vs. 20%). Socioeconomic status appears to be a major determinant as women who attended prepregnancy care were more likely to be white and less likely to live in a deprived area, smoke cigarettes and to be overweight or obese.⁴ Although women with type 1 diabetes are more likely to have suboptimal preconception control, attendance at prepregnancy care programs is particularly poor among women with type 2 diabetes.^{4,5} Cited barriers to engaging with preconception care include negative experiences with health professionals, lack of information and work commitments.^{15,16}

Antenatal care

When the woman becomes pregnant, immediate contact with a joint diabetes and antenatal clinic should be facilitated. This concept of a combined clinic allows the diabetes physician to be involved in a meaningful way as the pregnancy progresses.¹⁷ Although these clinics may differ in terms of structure, it is important that women are reviewed every 1–2 weeks by the diabetes team and a system for diabetes consultation (e.g. telephone helpline) is available on demand. Capillary blood glucose levels are monitored before and either 1 or 2 h after the start of each meal, before bed and if necessary overnight. Targets must be individualized and safe, however a fasting glucose of

<5.3 mmol/l and 1-h post prandial of <7.8 mmol/l are reasonable goals. HbA1c does not reliably reflect changes in mean blood glucose in pregnancy, particularly in the second and third trimesters, but higher levels (HbA1c >6.0–6.5%) may still be used as marker of poor glycaemic control and a pregnancy which is at increased risk of poor outcome.¹⁸ Hypoglycaemia is a common problem in the first trimester and is often associated with a diminished awareness. The situation changes by ~16 weeks and increasing insulin resistance requires regular uptitration of insulin to achieve euglycaemia with prepregnancy insulin doses often doubling by 30 weeks gestation.¹⁷ Recurrent hypoglycaemia affects women with type 1 diabetes more frequently than those with type 2, likely related to the fact that women with type 1 diabetes have longer diabetes duration, more hypoglycaemia unawareness and that not all women with type 2 diabetes require insulin therapy.⁵ The importance of ketone testing and hypoglycaemic management should be reemphasized during the pregnancy. If there is a suspicion or diagnosis of diabetic ketoacidosis during pregnancy, this must be treated as an emergency and the woman admitted to a critical care area with immediate specialist review.³

Excessive weight gain during pregnancy is now established as an independent risk factor for adverse pregnancy outcomes.¹⁹ We advocate the use of 2009 Institute of Medicine recommendations to advise on appropriate gestational weight gain as per BMI at booking visit and the provision of additional support to facilitate lifestyle changes to assist adherence (Table 1).²⁰ In general, physical activity should be encouraged and while some dietary modifications are necessary to prevent large increases in blood glucose, a balanced diet is advised overall. Pregnant women with diabetes should be referred to a dietician specializing in pregnancy. Sugars and simple carbohydrates should be eliminated with ideal carbohydrate sources including fresh vegetables, some fruits and whole grains.²¹ There is no definitive evidence for the optimal proportion of carbohydrate in the diet of women with diabetes and more research is needed into the relationship between maternal dietary intake both in terms of gestational weight gain and postprandial glucose control in these women.⁹ Furthermore, there are no randomized trials evaluating the effects of a modified diet for those women with diabetic nephropathy in pregnancy.⁴

Progression of diabetic retinopathy during pregnancy is well described in both type 1 and type 2 diabetes. Various contributing factors are identified including pre-existing retinopathy, increasing duration of diabetes and higher blood pressure in early pregnancy.²² Although associations between rapid declines in HbA1c during pregnancy and deterioration in retinopathy status have been identified, the presence of retinopathy should not be considered a contraindication to rapid optimization of glycaemic control if necessary. Instead, the authors advise identification and close monitoring of those women at high risk of deterioration. NICE recommend retinal assessment by digital imaging following the first antenatal appointment and again at 28 weeks if the first assessment is normal. If any diabetic retinopathy is present, an additional retinal assessment should be performed at 16–20 weeks.³

If unknown, renal status should be established at the booking visit. Nephrology review is necessary if serum creatinine is abnormal (120 µmol/l or more) or if total protein excretion exceeds 2 g/day. Renal function is closely linked with blood pressure and the latter must be monitored closely during pregnancy. Specialist care is essential as aggressive management of hypertension often requires multiple agents and is associated with improved pregnancy outcomes.²³ Calcium

Table 1. Institute of medicine guidelines for gestational weight gain

Pregestational BMI category	BMI, kg/m ²	Recommended total weight gain, kg	Recommended mean weight gain (kg/wk): Trimesters 2 and 3
Underweight	<18.5	12.5–18.0	0.51 (0.44–0.58)
Normal weight	18.5–24.9	11.5–16.0	0.42 (0.35–0.50)
Overweight	25.0–29.9	7.0–11.5	0.28 (0.23–0.33)
Obese	≥30.0	5.0–9.0	0.22 (0.17–0.27)

channel blockers such as nifedipine are commonly used while beta blockers such as labetalol may be used with caution. Methyldopa also has proven safety during embryogenesis and is also suitable, although it is commonly associated with maternal side effects of postural dizziness.¹⁷

Women with diabetes in pregnancy require additional foetal monitoring. As many women with diabetes have menstrual irregularities making dating based on last menstrual period less accurate, viability of pregnancy and gestational age should be confirmed on ultrasound scan at 7–9 weeks.³ A four-chamber view of the foetal heart and outflow tracts must be offered at 18–20 weeks with referral to a specialist centre if necessary. Monitoring of foetal growth and amniotic fluid volume is advised every 4 weeks from 28–36 weeks. When a macrosomic foetus is diagnosed on ultrasound, a specialist decision regarding the optimal method and timing of delivery is necessary. If a woman is treated with insulin and steroids are required for foetal lung maturation, additional insulin is necessary. This is typically administered intravenously and infusion rates adjusted according to the glucose level on an hourly basis. Each centre should have a clear protocol in this regard.

Labour and delivery

This is an exciting time for the woman and her family and it is important that clear protocols are in place in the delivery unit to ensure the process runs smoothly. Home births are not advised. Women with diabetes-related complications (particularly autonomic neuropathy) may benefit from an anaesthetic consultation in the third trimester to ensure the birth plan is appropriate. Pregnant women with diabetes who have a normally grown foetus should be offered elective birth through induction of labour or by elective caesarean section (if indicated) between 37 weeks +0 days and 38 weeks +6 days of pregnancy.³ The presence of pregestational diabetes alone is not an indication for caesarean delivery. As maternal hyperglycaemia during labour and delivery is associated with neonatal hypoglycaemia and foetal distress, tight glycaemic control is necessary.³ This is traditionally achieved using intravenous insulin and dextrose infusions to maintain maternal blood glucose levels at 4–7 mmol/l, although CSII is increasingly used.

All neonates born to mothers with diabetes in pregnancy require review by a neonatologist on delivery. The maternity unit must have the facility to provide advanced neonatal care on demand at all times should the need arise. Unless there is a complication, neonates should go to the postnatal ward with their mother on delivery. Feeding should take place as soon as possible after birth and at regular intervals thereafter. Blood glucose testing should be carried out routinely in babies of women with diabetes at 2–4 h after birth to exclude neonatal hypoglycaemia. This should take place earlier if there are clinical signs of

Table 2. Key points

General:

- Pre-existing diabetes is associated with an increased risk of adverse pregnancy outcomes
- Engagement with a prepregnancy care program is essential.
- Antenatal care should take place in a joint diabetes and antenatal clinic.

Type 1 diabetes:

- Increased risk of hypoglycaemia (particularly first trimester).
- All women should have the ability to test for ketones.

Type 2 diabetes:

- Less likely to engage with prepregnancy care and receive appropriate retinal screening.
- Weight loss pre- and postpregnancy should be facilitated as necessary.
- Other than metformin, oral and injectable hypoglycaemic agents are contraindicated.

hypoglycaemia such as severe irritability or seizure-like activity. If blood glucose values are below 2.0 mmol/l on two consecutive readings despite feeding or if there are abnormal clinical signs, additional measures such as intravenous dextrose or tube feeding may be necessary.³ Other neonatal complications occurring more frequently in offspring of mothers with diabetes include respiratory distress, jaundice and hypocalcaemia.

Postpartum care

Typically women revert to their prepregnancy insulin doses post delivery; however, a further reduction of ~25% may be necessary if breastfeeding is established. Breastfeeding should be encouraged when possible as it may facilitate postpartum weight loss along with its well-established nutritional and immunological benefits for the infant. Women should be advised regarding the need to monitor glucose levels carefully while breastfeeding and additional carbohydrate snacks are often required to avoid hypoglycaemia. Metformin is deemed to be safe while breastfeeding but it must be noted that there is not a marketing authorization for this indication in UK.³ Glibenclamide (glyburide) is also used in clinical practice in the management of diabetes while lactating and while there is strong evidence for its safety, information on its excretion in breast milk is limited. This information should be explained to the mother before initiating treatment. Other oral or injectable hypoglycaemic agents are contraindicated while breastfeeding.

The importance of planning further pregnancies and the use of contraception in intervening periods should be reviewed. Women with diabetes can use oral contraceptives provided there are no standard contraindications to their use. Women's choice of contraception should be based on their own preferences and risk factors.³ Women with type 2 diabetes are less likely to receive postnatal contraceptive advice than those with type 1 and this may be due to language difficulties and perceived differences in cultural attitudes.⁵ If appropriate, women should be supported to achieve interpregnancy weight loss in order to reduce obesity-related pregnancy complications in subsequent pregnancies. Finally, as postpartum thyroiditis is more common in women with diabetes, screening thyroid function tests should take place at 3 and 6 months postpartum.⁹

Emerging technologies for optimal glucose control

A randomized controlled trial (RCT) in 322 type 1 diabetes pregnancies, demonstrated that even in an optimal RCT setting

(excluding women with HbA1c >8%), two out of three infants had at least one diabetes-related complication.²⁴ These data suggest that MDI injections, even using new generation insulin analogues, are inadequate for optimal neonatal health outcomes. The 2012–13 National Pregnancy in Diabetes Audit showed that only 5% of women with type 1 diabetes achieve the NICE glucose control target of HbA1c <6.1% and <25% achieve a booking HbA1c <7%.²⁵ The sustained lack of improvement in maternal glucose control and perinatal outcomes, particularly in type 1 diabetes pregnancy has prompted increased focus on the role of new technologies to optimize glycaemic control before and during pregnancy.

Outside pregnancy, insulin pump therapy (CSII) can improve glucose control, reduce risk of severe hypoglycaemia and improve quality of life with ~20% pregnant women using CSII across the UK.^{25,26} Despite the theoretical advantages of CSII, there is currently little evidence supporting routine use of CSII in pregnancy. A meta-analysis of six studies (107 CSII vs. 106 MDI) showed comparable glucose control and pregnancy outcome.²⁷ These studies were conducted over 20 years ago, with very small sample sizes (18 women per arm) and lacked power to detect differences in infant outcomes. Results from observational series of CSII versus MDI (mostly retrospective with selection biases) are conflicting, with some but not all, suggesting lower HbA1c levels. Most suggest that CSII is safe but inadequate for optimal maternal/foetal outcomes.^{28,29} Some suggest that for optimal efficacy, CSII works best when combined with real-time continuous glucose monitoring (CGM).

The 2015 draft NICE guidelines advise considering CGM for pregnant women who have problematic severe hypoglycaemia (with or without impaired awareness of hypoglycaemia) or women with unstable blood glucose levels or to gain information about variability in blood glucose.³ The CGM devices available include traditional retrospective/professional (Medtronic Ipro2) and real-time CMG (Dexcom G4, Medtronic Enlite 2, Navigator 2). A recent innovation is the FreeStyle Libre Flash Glucose Monitoring System which represents an intermediate step between finger-stick glucose testing and real-time CGM. It can be worn for up to 14 days and does not require finger-stick tests for calibration, which could replace finger-stick glucose testing for women on MDI.

The future for diabetes technology looks optimistic. Ongoing trials (GlucoMOMS and CONCEPTT) will determine the clinical impact of retrospective and real-time CGM in type 1 diabetes pregnancy. Others are investigating the role of closed-loop insulin delivery, combining real-time CGM with CSII using a computer algorithm, with preliminary feasibility studies suggesting that this could provide consistently safe effective glucose control for many women with type 1 diabetes.³⁰

Summary

Pregestational diabetes is a common medical complication of pregnancy and preconception planning is an essential component of care for affected women of childbearing age. Once pregnant, structured care in a multidisciplinary team setting is necessary to ensure optimal outcomes. Although significant progress has been made, these women and their offspring remain to have a significantly elevated risk of multiple adverse complications. Structured programmes using information technology and enabling access to novel technologies may facilitate our goal of ensuring an outcome closer to that of a pregnancy unaffected by diabetes.

Conflict of interest: None declared.

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