

# Pre-pregnancy care for women with diabetes mellitus

**T**his article reviews the importance of pre-pregnancy care for women with diabetes and describes how best to deliver this service in clinical practice.

## Background: diabetes and pregnancy

While the majority of pregnancies have a positive outcome for mother and baby, pregnancy is associated with an elevated risk in the setting of pre-existing diabetes. Multiple studies reveal poor pregnancy outcomes for women with diabetes including a five-fold increased risk of stillbirth and a congenital malformation rate twice that of the background population (Macintosh et al, 2006; Dunne et al, 2009). In particular, cardiac and CNS anomalies are more common in offspring of women with diabetes and tend to be associated with increased mortality and long-term morbidity.

The rate of caesarean sections for these women is 67% compared to 22% in the background population, and rates of macrosomia are approximately 21% compared to 11% in the general population (Macintosh et al, 2006). Miscarriage, pre-eclampsia and preterm labour are also more common in women with pre-existing diabetes (National Institute for Health and Care Excellence, 2015).

Over recent years, a rise in the incidence of type 2 diabetes in pregnancy has been observed. This is associated with an increase in obesity rates and maternal age. Women with

type 2 diabetes experience similar adverse outcomes to those with type 1 diabetes and are less likely to access specialist care. As they are more frequently from ethnic minorities and socially disadvantaged backgrounds, women with type 2 diabetes are a particularly vulnerable group (Confidential Enquiries into Maternal and Child Health, 2007; Murphy et al, 2010). On a more positive note there is a move towards improving outcomes for these women. The provision of structured, clinical care programmes providing coordinated care to women with diabetes is associated with significant outcome improvements (Murphy et al, 2011; Egan et al, 2016). One such programme is pre-pregnancy care and this will be the focus of this review.

## Rationale for pre-pregnancy care

Fetal organogenesis takes place in the first trimester of pregnancy, often before the woman knows she is pregnant. Research has demonstrated a clear association between poor glycaemic control in early pregnancy and adverse pregnancy outcomes. One population-based study revealed a four-fold increase in spontaneous abortion and a nine-fold increase in major congenital malformations in women with a glycated haemoglobin concentration above 7.5% at booking (Temple et al, 2002). It stands to reason that intervention before the pregnancy is necessary to ensure adequate and stable glycaemic control throughout the critical early stage.

Pre-pregnancy care addresses this issue and aims to optimize all aspects of diabetes-related health before embarking on pregnancy. It may be defined as targeted support and additional clinical care offered to women planning pregnancy (Murphy et al, 2010).

## Delivery of pre-pregnancy care

While individual pre-pregnancy care programmes may vary in terms of delivery details, the core components are similar (Table 1). Typically women attending for pre-pregnancy care are reviewed at 1–3-monthly intervals in a dedicated clinic

run by a multidisciplinary team involving a diabetologist, diabetes nurse or midwife specialist and dietitian (Egan et al, 2015). An average of 4.5 outpatient visits is required before pregnancy (Egan et al, 2016). These clinics should be accessible to all women with diabetes and a variety of referral pathways should exist including self-referral or via the patient's endocrinologist or GP. There should be no waiting list for attendance at a pre-pregnancy care clinic.

At the clinic, the importance of avoiding an unplanned pregnancy should be explained and contraception advised until treatment goals are achieved. The choice of contraception should be made on an individual basis. A diagnosis of diabetes does not exclude the use of any particular contraceptive including the oral contraceptive pill (National Institute for Health and Care Excellence, 2015). Women with diabetes who are planning to become pregnant should aim to keep their glycosylated haemoglobin (HbA<sub>1c</sub>) level below 48 mmol/mol (6.5%), if this is achievable without causing problematic hypoglycaemia (National Institute for Health and Care Excellence, 2015).

**Table 1. Checklist for initial pre-pregnancy care consultation**

Discuss timeline for pregnancy planning and advise on contraception
Discuss positive ways to reduce risk of adverse pregnancy outcomes
Review glucose and glycosylated haemoglobin (HbA <sub>1c</sub> ) targets
Hyper- and hypoglycaemia education
Full medication review
Individualized dietary advice and/or weight loss
Retinal and renal screening
Baseline blood testing including thyroid function, coeliac screen, HbA <sub>1c</sub> +/- vitamin B <sub>12</sub> and vitamin D
Commence folic acid 5 mg once daily

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In order to achieve this goal, regular home glucose monitoring must take place. Women should take four to seven home glucose levels per day and these should be a mixture of pre- and post-prandial measurements. In general, fasting glucose levels of 4–7 mmol/litre should be targeted. As the risk of hypoglycaemia increases with tighter glycaemic targets, women and family members require education regarding hypoglycaemia management including the use of glucagon. In addition, women with type 1 diabetes should be instructed on the importance of ketones and should test for ketones if they are hyperglycaemic or become unwell.

While the target HbA<sub>1c</sub> may seem like an unrealistic goal for some patients, women should be reassured that any reduction in HbA<sub>1c</sub> towards the target is likely to reduce the risk of congenital malformations. Many women reach their glycaemic goals on multiple daily injection therapy, but newer technologies may be considered on a case-by-case basis. Insulin pump therapy can improve glucose control, reduce the risk of severe hypoglycaemia and improve quality of life. Nowadays, pump therapy may be combined with real-time continuous glucose monitoring and this may further improve efficacy (Egan et al, 2015). Currently, insulin pump therapy and continuous glucose monitoring are typically reserved for women with type 1 diabetes.

At the first clinical encounter, a full medication review should take place. In relation to insulin, clinical studies support the safety of the rapid-acting insulin analogues aspart and lispro. The National Institute for Health and Care Excellence guidance states that isophane insulin should be the first choice for long-acting insulin during pregnancy. However, the authors recommend that women who are well established on long-acting insulin analogues including detemir or glargine should be continued on these insulins. Detemir in particular is approved for use in pregnancy and a study indicates that it does not cross the human placenta (Suffecool et al, 2015). Metformin therapy is considered safe in pregnancy and may be used alone or in combination with insulin in the preconception period. All other oral blood glucose-lowering agents including sulphonylureas, glucagon-like-peptide-1 agonists, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors

should be discontinued (National Institute for Health and Care Excellence, 2015).

Other medications commonly used in diabetes care include statins, angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers. These medications are not considered safe in pregnancy and should be discontinued. On the other hand, satisfactory blood pressure control is of utmost importance, and if necessary alternative antihypertensives deemed safe in pregnancy should be instituted to achieve a target blood pressure of <130/80 mmHg. Each antihypertensive should be considered individually based on the risk–benefit estimate. Beta-blockers, predominantly labetalol, may be used with caution in pregnancy and calcium-channel blockers such as nifedipine are commonly used. Methyldopa is another agent frequently used in this setting but postural dizziness is a frequent side effect (Egan et al, 2015).

Women attending pre-pregnancy care require a full assessment of diabetes complications. Retinal evaluation is required for every patient and where necessary, treatment and stabilization should occur before embarking on pregnancy. Owing to the risk of progressive eye disease, it may be necessary to defer rapid optimization of glycaemic control until after retinal treatment is completed (National Institute for Health and Care Excellence, 2015).

Renal assessment should include measurement of the urinary albumin:creatinine ratio and if greater than 30 mg/mmol, referral to a nephrologist should be considered before proceeding with pregnancy. Similarly, if the estimated glomerular filtration rate is <45 ml/min/1.73 m<sup>2</sup>, specialist referral should be contemplated (National Institute for Health and Care Excellence, 2015). Evaluation for macrovascular complications including heart disease should be considered on a case-by-case basis following risk evaluation. In particular older women, those with longstanding diabetes and those with additional morbidities may benefit from screening for coronary artery disease before pregnancy.

Thyroid status must be established in each patient because of the association between diabetes and thyroid dysfunction. Both hyperthyroidism and hypothyroidism may reduce fertility, increase risk of pregnancy loss and impair fetal development if untreated.

It is reasonable to check vitamin B<sub>12</sub> levels and replace if insufficient. This is particularly important in those women treated with metformin. Although the mechanism is not entirely clear, metformin users have a higher prevalence of vitamin B<sub>12</sub> deficiency compared to the background population (Reinstatler et al, 2012).

Vitamin D deficiency (serum level <37.5 nmol/litre) is common in northern Europe, especially in obese women and those with pigmented skin. Although the issue is under much debate, vitamin D deficiency in pregnancy has been associated with multiple adverse outcomes such as pre-eclampsia and low birthweight infants (Royal College of Obstetricians and Gynaecologists, 2014). Until further information is available, the authors recommend screening at-risk women and treating vitamin D deficiency.

Type 1 diabetes is associated with coeliac disease and while the optimal screening frequency for asymptomatic patients is not clear, the authors believe women with type 1 diabetes should be screened at the initial pre-pregnancy care visit.

Women with diabetes should take folic acid 5 mg daily beginning 3 months before withdrawing contraceptive measures or otherwise trying to conceive. While there is no definite evidence that this increased dose is of benefit, several advisory groups have made this recommendation based on a theoretical benefit in reducing the increased risk of neural tube defects (Blumer et al, 2013; Egan et al, 2015; National Institute for Health and Care Excellence, 2015). Women should be offered individualized dietary advice and weight reduction preconception should be recommended to those who are overweight or obese. A diabetes dietician should be available to review all women attending pre-pregnancy care. Obesity is associated with increased pregnancy risk independent of a diabetes diagnosis and women should be counseled in relation to this issue.

### Benefits associated with pre-pregnancy care

There is now over 30 years of clinical experience with pre-pregnancy care. Steel et al (1982) described 5 years experience of a pre-pregnancy clinic for patients with insulin-dependent diabetes in Edinburgh with evidence of lower HbA<sub>1c</sub> concentrations in the first trimester and fewer congenital abnormalities among attendees.

**KEY POINTS**

- Pre-pregnancy care is as essential as antenatal care for women with diabetes.
- Attendance is associated with improved pregnancy preparation and a significant reduction in adverse pregnancy outcomes.
- Care should be delivered in a structured manner.
- Women require review by a multidisciplinary team every 1–3 months.
- Pre-pregnancy care should be accessible to women with all types of pre-existing diabetes.

In 2010, Murphy and colleagues implemented and evaluated a regional pre-pregnancy care programme for women with type 1 and type 2 diabetes. They found that women with pre-pregnancy care presented earlier for antenatal care, were more likely to take preconception folic acid 5 mg and had lower HbA<sub>1c</sub> levels before and during pregnancy. In addition, those who attended had fewer adverse pregnancy outcomes (1.3% vs 7.8%). They concluded that pre-pregnancy care had benefits beyond glycaemic control and was a stronger predictor of pregnancy outcome than maternal obesity, ethnicity or social disadvantage (Murphy et al, 2010).

Earlier this year, the Atlantic Diabetes in Pregnancy research group evaluated a similar pre-pregnancy care programme involving a number of clinical sites in the West of Ireland. This group also observed improved pregnancy preparation among attendees with higher rates of folic acid use, and lower rates of smoking and use of potentially teratogenic medications. Attendees had lower HbA<sub>1c</sub> levels throughout pregnancy and offspring had lower rates of congenital malformations (0.8% vs 5.2%) and rates of admission to neonatal intensive care units (44.3% vs 62%). A cost analysis of the programme revealed that the difference in complication costs between those who did and did not receive pre-pregnancy care was €2578.00 while the average cost of pre-pregnancy care delivery is €449.00 per pregnancy (Egan et al, 2016). These findings demonstrate that pre-pregnancy care is both clinically effective and cost-saving in nature.

**Challenges**

The greatest challenge associated with pre-pregnancy care is getting the care to those who need it most. Despite the clear

benefits, only a minority of women with diabetes in the UK and worldwide attend pre-pregnancy care. This was highlighted by the Confidential Enquiry into Maternal and Child Health (2007) which revealed that just 17% of maternity units in the UK offered pre-pregnancy care and only 10% women with diabetes attended.

Women report a number of barriers to attending pre-pregnancy care including lack of information, child care difficulties and work commitments (O’Higgins et al, 2014). While a regionalized approach to care has been shown to improve on these figures, the overall uptake in the most recently published study was still less than ideal at 36%. This was despite an effort to overcome certain barriers and focus on the positive aspects of pregnancy and childbearing. In particular, those with type 2 diabetes, ethnic minorities and those with poor glycaemic control were less likely to attend (Egan et al, 2016). The authors believe that a norm needs to be established that situates pre-pregnancy care as something every women with diabetes will do. It is hoped that the positive clinical and economic associations with pre-pregnancy care will stimulate health-care providers to design and implement programmes at a local level. These programmes should evaluate various recruitment strategies to incorporate those women who are less likely to attend.

**Conclusions**

Pre-pregnancy care for women with diabetes may be considered as essential as antenatal care and is effective in reducing adverse pregnancy outcomes. Care should be delivered in a specialized setting by a multidisciplinary team with a focus on intensive glycaemic control, diabetes education and optimization of health before embarking on pregnancy. **BJHM**

*Conflict of interest: none.*

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**TOP TIPS**

- Reassure women that any improvement towards the target glycosylated haemoglobin level is beneficial.
- Don’t forget high dose folic acid 5 mg once daily.
- Update the patient on hypoglycaemia management.
- Regularly review diabetes complication status.

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