Managing type 1 diabetes mellitus in pregnancy—from planning to breastfeeding

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Abstract | Type 1 diabetes mellitus in pregnant women increases the risk of adverse outcomes for mother and offspring. Careful preconception counselling and screening is important, with particular focus on glycaemic control, indications for antihypertensive therapy, screening for diabetic nephropathy, diabetic retinopathy and thyroid dysfunction, as well as review of other medications. Supplementation with folic acid should be initiated before conception in order to minimize the risk of fetal malformations. Obtaining and maintaining tight control of blood glucose and blood pressure before and during pregnancy is crucial for optimizing outcomes; however, the risk of severe hypoglycaemia during pregnancy is a major obstacle. Although pregnancy does not result in deterioration of kidney function in women with diabetic nephropathy and normal serum creatinine levels, pregnancy complications such as pre-eclampsia and preterm delivery are more frequent in these women than in women with T1DM and normal kidney function. Rapid-acting insulin analogues are considered safe to use in pregnancy and studies on long-acting insulin analogues have provided reassuring results. Immediately after delivery the insulin requirement declines to approximately 60% of the prepregnancy dose, and remains 10% lower than before pregnancy during breastfeeding.

Ringholm, L. *et al. Nat. Rev. Endocrinol.* **8**, 659–667 (2012); published online 11 September 2012; doi:10.1038/nrendo.2012.154

Introduction

Diabetes mellitus is associated with an increased risk of adverse outcomes for pregnant mothers and their infants.[1–11] Although adverse pregnancy outcomes are also common in pregestational type 2 diabetes mellitus and gestational diabetes mellitus, this Review will focus on pregestational type 1 diabetes mellitus (T1DM). Large observational studies of pregnant women with T1DM have demonstrated an increased risk of adverse pregnancy outcomes, including fetal and neonatal death (occurring between 22 gestational weeks and 28 days after delivery), congenital malformations, preterm delivery, macrosomia, pre-eclampsia, a need for caesarean section and maternal mortality.[1–11] In data from the Confidential Enquiry into Maternal and Child Health (CEMACH) in the UK, diabetes mellitus was associated with a significantly increased risk of death for the child during pregnancy or soon after delivery, compared with national rates in the general population.[3,8] These figures are consistent with observations of a 4–5-fold increase in perinatal death[2,5,8,10] and a 4–6-fold increase in stillbirths in women with diabetes mellitus compared with the general population.[2,8,10] In an Italian multicentre study of pregnant women, pregestational diabetes mellitus—particularly T1DM—was associated with high rates of stillbirths, neonatal mortality and congenital malformations.[12] Unplanned pregnancies and non-optimal glycaemic control could partly explain these high rates of maternal and neonatal complications.[12]

A Swedish study of T1DM pregnancies found that although several perinatal outcomes seemed to have improved over the years, the prevalence of macrosomia has increased significantly.[13] Macrosomia can cause major problems during labour, such as labour dystocia, emergency caesarean delivery, instrument delivery by forceps or ventouse, shoulder dystocia and laceration of the birth canal. Moreover, macrosomia is associated with increased neonatal morbidity as well as a long-term increased risk of obesity and metabolic disorders.[14–17] Other studies have reported a high prevalence of macrosomia.[9,18] Pregnant women with T1DM probably have better metabolic control now than in the past,[19] and it is, therefore, surprising that the prevalence of macrosomia is increasing. This increase might be explained by the fact that pregnant women with diabetes mellitus are now more often obese, which is similar to pregnant women without diabetes mellitus,[20] and also that the use of rapid-acting analogues has led to a more liberal intake of sweets and other short-acting carbohydrates than previously.

Obtaining and maintaining strict glycaemic control before and during pregnancy is crucial to optimize maternal and fetal outcomes. In addition, early and intensive antihypertensive therapy could improve outcomes. This Review explores the importance of optimal glycaemic control and antihypertensive therapy, from pregnancy planning to the breastfeeding period, in women with T1DM.

Competing interests
P. Damm and E. R. Mathiesen declare associations with the following company: Novo Nordisk. See the article online for details of the relationships. L. Ringholm and L. Kelstrup declare no competing interests.

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Key points

- Tight maternal glycaemic and blood pressure control is crucial, and hypoglycaemia must be avoided during pregnancy
- Insulin analogues can be used before and during pregnancy
- Folic acid supplementation should be initiated before conception and continued to the end of the first trimester
- Maternal screening for retinopathy and nephropathy should be carried out
- Close surveillance of fetus and newborn baby is important

Box 1 | Recommendations for pregnancy planning

- Use of safe contraception in the planning phase
- Achieve an HbA_{1c} level as near to normal levels as possible
- Supplementation with folic acid
- Appropriate antihypertensive therapy
- Treatment of possible thyroid dysfunction
- Revision of other medical treatment (such as cholesterol-lowering agents)
- Monitoring and treating late diabetic complications (for example, nephropathy and retinopathy)
- Reduce risk of severe hypoglycaemia

Preconception management

Counselling

Use of contraception is an important issue to address with women of child-bearing age who have pregestational diabetes mellitus because an unplanned pregnancy could have a serious adverse effect on the health of the mother and child.[20] Therefore, careful counselling of the woman (and her partner) about the potential effects to herself and to any offspring is essential to prepare the couple to make a well-considered decision about pregnancy. Measures should be taken to reduce the risk of congenital malformations, and an up-to-date assessment of the woman's diabetes status should be made, including measurement of HbA_{1c} level, serum creatinine level, blood pressure, proteinuria, evaluation of the risk of hypoglycaemia, thyroid function and the degree of diabetic retinopathy to estimate the risk of complications during pregnancy (Box 1).

Medication should be reviewed, because up to 41% of women of child-bearing age with pregestational diabetes mellitus take potentially teratogenic medications.[21] Cholesterol-lowering agents are often given to patients with diabetes mellitus but should be discontinued before or at the time pregnancy is confirmed.[22] Low-dose aspirin might reduce the risk of cardiovascular complications, and could also reduce the risk of pre-eclampsia.[22] Use of antidepressant drugs during pregnancy should be discussed with a psychiatrist.

Glycaemic control

Intensive glycaemic control before and during pregnancy gives considerable health benefits to pregnant women with diabetes mellitus and their offspring. This therapy should ideally be managed as a collaborative effort between obstetricians, endocrinologists, dieticians and nurse educators before and during pregnancy.

A study of women with T1DM compared the effect of having preconception counselling with no preconception counselling on diabetes mellitus care and adverse pregnancy outcomes.[23] The rate of congenital malformations was about threefold lower in the group attending preconception counselling than the control group (1.8% versus 6.1%, respectively). Although there is no evidence from randomised, controlled trials to support a beneficial effect of preconception counselling on diabetes mellitus care and pregnancy outcomes,[24] observational studies[23,25] and clinical experience clearly support the notion that preconception counselling is important.

Unfortunately, few women with T1DM attend preconception counselling sessions, and poor glycaemic control remains common in these women when they are pregnant,[3,25] possibly because many women do not have access to preconception counselling. In many countries, such as Denmark and the UK, control of diabetes mellitus is organized in local centres and women of child-bearing age who have diabetes mellitus are not always offered counselling about pregnancy planning and safe contraceptive methods. Although this advice is important to improve the outcomes of pregnancy in women with T1DM, many clinicians might be reluctant to address these issues during busy clinics. In the CEMACH study only 35% of women with pregestational diabetes mellitus received preconception counselling, 37% had a measurement of HbA_{1c} level within the 6 month period before pregnancy and less than 39% were taking folic acid before conception.[3] Overall, the risk of an adverse outcome is halved with each percentage reduction in HbA_{1c} level achieved before pregnancy.[26] This information could be a useful motivating factor to achieve glycaemic goals, and to reassure patients that any improvement of blood glucose regulation is genuinely helpful, irrespective of the final value achieved.

Near normoglycaemia should be the target when planning pregnancy to prevent adverse outcome of the pregnancy and to improve the health of the newborn baby, particularly to avoid congenital malformations. According to guidelines of the International Diabetes Federation (IDF), the goal is a prepregnancy HbA_{1c} level of <7.0%.[27] The British National Institute for Health and Clinical Excellence (NICE) guidelines recommend even lower HbA_{1c} limits of <6.1% if this is safely achievable,[28] but the risk and frequency of severe hypoglycaemia should be considered if such tight glycaemic control is obtained in early pregnancy.[29] The combination of insulin treatment, diet and self-monitoring of glucose levels is the cornerstone of treatment optimization. Furthermore, the risk of episodes of severe hypoglycaemia should be taken into account when tailoring the individual's treatment regimen.

The best predictors of severe hypoglycaemia in pregnancy are the presence of at least one episode of severe hypoglycaemia the year before pregnancy and/or self-estimated reduced hypoglycaemia awarness.[30] Evaluating the number of episodes of severe hypoglycaemia the year before pregnancy and assessing each woman's self-estimated hypoglycaemia awareness are, therefore, important to estimate the individual risk of severe hypoglycaemia during pregnancy.[30] Supplementation with folic acid before pregnancy and for up to 12 gestational

weeks might reduce the incidence of congenital malformations in pregnant women with T1DM.[31] There is no consensus on the dose of folic acid; at least 400 μg per day is recommended in Denmark but in Canada and the USA the recommendation is up to 5 mg per day.[32]

Antihypertensive therapy

Prepregnancy treatment with angiotensin-converting enzyme (ACE) inhibitors combined with strict metabolic control for at least 6 months (resulting in low levels of urinary albumin excretion) was associated with successful pregnancy outcomes in 24 women with diabetic nephropathy.[33] ACE inhibitor treatment was discontinued immediately after the positive pregnancy test and only four out of 24 women had preterm deliveries. Severe disability or late intrauterine death was seen in two cases.[33] In a study of the offspring of 209 women who were taking ACE inhibitors during fetal organogenesis, the relative risk of congenital malformations was 2.7 times higher than in women who were not taking antihypertensive agents.[34] However, another study showed a very low risk of malformations in infants of women with T1DM after treatment with an angiotensin II antagonist during the first trimester.[35] Furthermore, ACE inhibitors are not more likely to induce congenitial malformations than other antihypertensive agents.[36] Nonetheless, blockers of the renin–angiotensin system are not generally recommended during pregnancy owing to the possible increased risk of congenital malformations[34] and a high risk of fetal renal dysfunction when used in late pregnancy.[37,38]

As part of preconception counselling, treatment with ACE inhibitors or angiotensin II antagonists should be stopped[34,38] and replaced by antihypertensive agents that are considered to be safe in pregnancy, such as methyldopa, β-blockers (for example labetalol) or calcium antagonists. For patients with severe diabetic nephropathy requiring continuous treatment to block the renin–angiotensin system, or if the women becomes pregnant unexpectedly, a change to other antihypertensive agents can take place when pregnancy is confirmed.[33] The use of diuretics throughout pregnancy is controversial owing to concerns about reduced plasma volume and uteroplacental perfusion,[39] but in our clinical experience, it is often useful to continue diuretics in stable doses during pregnancy in women with diabetic nephropathy.[40,41]

Diabetic retinopathy

Screening for diabetic retinopathy is of utmost importance. Women with moderate or severe retinopathy have the highest risk of progression to sight-threatening diabetic retinopathy (that is, active proliferative diabetic retinopathy or major diabetic macular oedema).[42] Patients with severe diabetic retinopathy should be advised to postpone conception until these conditions are properly treated and have remained stable for at least 6 months.

Thyroid function

Thyroid dysfunction is common in women with diabetes mellitus[43] and subclinical hypothyroidism could lead to cerebral dysfunction of the offspring.[44] Assessing TSH and appropriate treatment of any hyperthyroidism or hypothyroidism is, therefore, recommended before and during pregnancy.[45] Thyroid function should be normalized before pregnancy.

Box 2 | Recommendations during pregnancy

- Maintain preprandial glucose levels of 3.5–5.9 mmol/l
- Maintain postprandial glucose levels of 3.5–7.8 mmol/l
- Avoid severe hypoglycaemia
- Aim for HbA_{1c} <6% in second part of pregnancy
- Supplementation with folic acid during the first 12 weeks
- Appropriate antihypertensive treatment given to obtain blood pressure <135/85 mmHg
- Treatment of possible thyroid dysfunction
- Revision of other medical treatment (such as cholesterol-lowering agents)
- Eye examination for signs of retinopathy and treatment given if necessary
- Close obstetric surveillance

Severe T1DM complications in pregnancy

The presence of active proliferative retinopathy, severe diabetic nephropathy with glomerular filtration rate reduced to ≤30%, severe autonomic neuropathy or severe coronary heart disease could suggest a seriously increased maternal risk.[46] In such circumstances, avoiding pregnancy should be recommended. If a patient is already pregnant, termination of pregnancy might occasionally be advisable to prevent severe fetal and maternal morbidity.

Pregnancy care

Glycaemic control

The goal of insulin therapy for women with T1DM during pregnancy is to attain glucose profiles similar to those of pregnant women without T1DM and to limit postprandial glucose fluctuations (Box 2). NICE guidelines suggest the following goals for home glucose measurements: fasting glucose values of 3.5–5.9 mmol/l and 1 h postprandial values of <7.8 mmol/l.[29] The American Diabetes Association (ADA) guidelines are similar, recommending fasting glucose values of 3.4–5.5 mmol/l and 1h postprandial values of 5.5–7.1 mmol/l.[47] The challenge is to achieve a level of blood glucose sufficient to prevent adverse pregnancy outcome but to avoid hypoglycaemia. However, there is no consensus on the best method of monitoring blood glucose levels to ensure that they are kept within appropriate limits.

Simulating the glucose profiles of pregnant women without diabetes mellitus requires intensive monitoring of blood glucose levels up to 10 times per day to achieve good glycaemic control.[48] During pregnancy, insulin requirements usually increase continuously from 16–37 weeks, although there are wide individual variations.[49] Notably, in women receiving glucocorticoid treatment for premature fetal lung maturation, insulin requirements are 40–50% higher for up to 1 week after initiation of glucocorticoid treatment.[50] A prompt increase of insulin dose (which can be established with an algorithm, for example)[50] after glucocorticoid treatment is initiated leads to improved glycaemic control.

Continuous glucose monitoring could be a supplementary tool to intermittent self-monitoring of plasma glucose levels for selected patients with T1DM, particularly in women with hypoglycaemia unawareness.[46,51,52] General use of real-time continuous glucose monitoring was not supported by the findings of a study of unselected pregnant women with T1DM (A. L. Secher, unpublished work).

HbA_{1c} levels are lower in healthy pregnant women than in healthy nonpregnant women,[53,54] probably owing to a decrease in fasting blood glucose levels[55] and decreased erythrocyte lifespan in pregnancy.[56] A decline of the upper normal level of HbA_{1c} from 6.3% to 5.7% in early pregnancy and to 5.6% in the third trimester of pregnancy was demonstrated in healthy women without pregestational diabetes mellitus.[54] The results of another study showed a similar pattern,[53] although they observed a small increase in HbA_{1c} level in the third trimester.

In pregnant women with T1DM, HbA_{1c} level should be monitored every 2–4 weeks and the target should be close to the late pregnancy upper normal value of 5.6%.[54] The ADA recommends a target HbA_{1c} level of <6% in the second and third trimester.[47] HbA_{1c} level changes rapidly during pregnancy and is a useful clinical monitoring tool.[47] However, the HbA_{1c} value cannot be relied on alone because plasma glucose measurements or continuous glucose monitoring can disclose wide variations in plasma glucose levels that might not otherwise be recognised.[57]

Soluble rapid-acting and fast-acting insulin is useful for multiple-dose regimens, insulin pumps and continuous infusion during labour or medical emergencies.[58] Long-acting insulin is usually administered once or twice daily and can be useful for bedtime dosing to suppress increased nocturnal endogenous glucose production.[58]

The rapid-acting insulin analogues, insulin aspart and insulin lispro, are accepted for use in pregnancy by the FDA[59,60] and by the European Medicines Agency (EMA).[61,62] These analogues are at least as well-tolerated and effective as fast-acting human insulin, allowing better postprandial glucose control, reduction of HbA_{1c} level during the first trimester and show a trend towards reduced risk of severe hypoglycaemia and fewer preterm deliveries compared with regular human insulin.[7,18,63] In a large, randomized study of insulin detemir and neutral protamine Hagedorn (NPH) insulin, the fasting plasma glucose level was significantly lower in the detemir group, and the pregnancy outcome was similar in both groups.[64] In March 2012, the use of detemir in pregnancy was approved by the FDA[65] and the EMA states that the use of detemir and glargine in pregnancy can be considered if the potential benefits outweigh possible disadvantages, according to clinical judgment. The available observational data on the use of the long-acting insulin analogue glargine in pregnancy have not shown any adverse effects and similar outcomes are seen across studies.[64,66–68]

An alternative method of insulin administration is continuous subcutaneous insulin infusion (by an insulin pump), which can lead to improved glycaemic control in nonpregnant patients with diabetes mellitus, and a reduced likelihood of severe hypoglycaemia.[69] However, this approach has proved to be disappointing in pregnant women. Cohort studies and randomized, controlled trials have reported only minor maternal and fetal benefits, if any, compared with those of conventional therapy.[70]

Hypoglycaemia

Severe hypoglycaemia, which is defined by the ADA as the need for help from another person to administer oral carbohydrates, or to inject glucagon or glucose to restore blood glucose level,[71] is the main obstacle to good glycaemic control, limiting the extent to which glycaemic control can be optimized during pregnancy.[72] Road traffic accidents[73] and death[74] due to severe hypoglycaemia and hypoglycaemic coma[75] are problems for pregnant women with T1DM. Severe hypoglycaemia occurs most frequently in the first trimester, during which the incidence is five-times higher than in the year preceding pregnancy.[30] Several studies have shown a peak of severe hypoglycaemic events between 8 and 16 weeks (Figure 1).[30,72,73]

The risk of hypoglycaemia during pregnancy in women with T1DM could be increased because the fetus continues to draw glucose across the placenta from the maternal bloodstream during periods of fasting and, accordingly, the risk of hypoglycaemia is highest between meals and during sleep.[30] Risk factors for these episodes include a history of severe hypoglycaemia before pregnancy, impaired hypoglycaemia awareness, longer duration of diabetes mellitus, HbA_{1c} level ≤6.5% in early pregnancy and a higher total daily insulin dose.[30,75,76] Preconception counselling has not been shown to have a beneficial effect on the rate of severe hypoglycaemia during pregnancy.[23,76] Experimental data from studies of animal models link hypoglycaemia early in pregnancy with congenital abnormalities[77,78] and growth retardation.[77–79] However, at present the evidence from human studies suggests that maternal hypoglycaemia has no short-term or long-term adverse effect on the fetus.[72,73,80]

Preventive measures to reduce the risk of severe hypoglycaemia during pregnancy include early identification of high-risk patients, particularly women with self-estimated impaired hypoglycaemia awareness and/or a history of severe hypoglycaemia the year preceding pregnancy. Insulin dose should be reduced by approximately 10% at 8–16 weeks and supplementary insulin should be used with caution in early pregnancy. In our centre, we encourage women to perform frequent blood glucose monitoring throughout their pregnancy, including in the period 0200–0400 h and bedtime plasma glucose levels should not be <6.0 mmol/l.[81]

The use of rapid-acting and long-acting insulin analogues might also reduce the risk of severe hypoglycaemia.[63,64,66–68,82–84] A case report suggests that continuous glucose monitoring is useful for preventing severe hypoglycaemia in pregnant women with hypoglycaemia unawareness.[52] An ongoing randomized study at our centre in Copenhagen to investigate the effect of real-time, continuous, subcutaneous glucose monitoring on

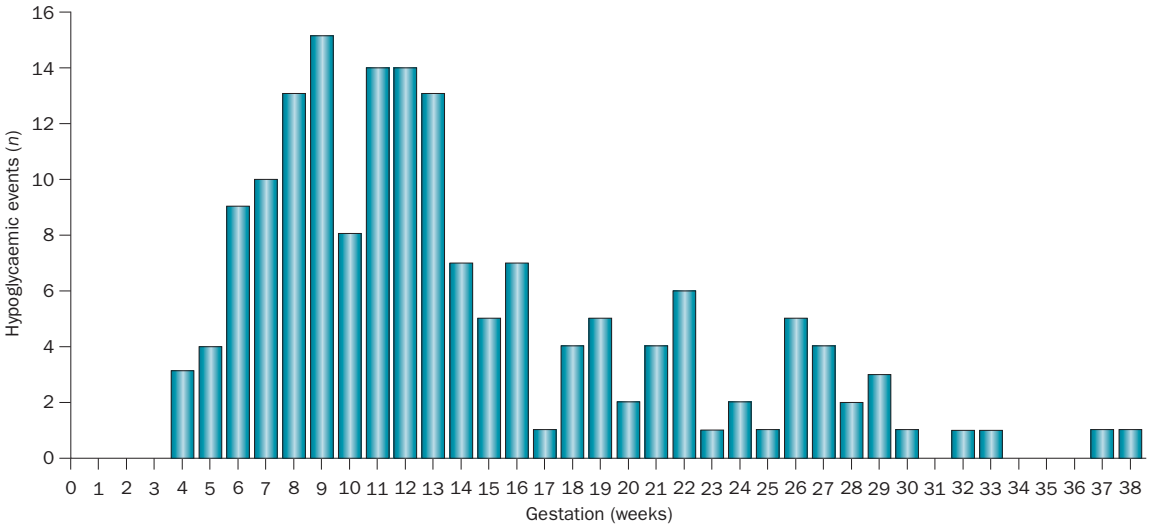

Figure 1 | Hypoglycaemic events in pregnancy. The number of severe hypoglycaemic events during pregnancy in 108 women with type 1 diabetes mellitus are shown during each week of gestation. The first event usually occurs within the first 20 weeks; 80% of all events happen before 20 weeks, particularly around 9 weeks. Permission obtained from the American Diabetes Association © Nielsen, L. R. *et al*. *Diabetes Care* **31**, 9–14 (2008).

pregnancy outcomes, including severe hypoglycaemia, includes 123 pregnant women with T1DM.[85] The results are expected in autumn 2012.

Diet and exercise

Patients should be encouraged to optimize both diet and physical activity as far as possible during pregnancy. Exercise patterns should include at least 30 min per day of physical activity and be modified to accommodate the physiological and anatomic changes that occur over the duration of gestation. Information from studies in healthy women indicates that leisure-time physical activity before and/or during pregnancy reduces the rate of pre-eclampsia and preterm delivery, and improves physical fitness and emotional wellbeing.[86]

Minor dietary modifications are required during pregnancy to cover the energy cost to the mother. The overall aim in designing a diet for pregnant women with T1DM is to avoid single large meals and foods with a high content of simple carbohydrates. A small amount of carbohydrate at breakfast, around 10–20 g (which corresponds to 10% of the daily carbohydrate intake), is advisable in order to control postprandial blood glucose in the period after waking.[87] Teaching carbohydrate counting to all pregnant women with T1DM might be useful to match the injected rapid-acting insulin to the amount of carbohydrate intake.[88]

Hypertension and diabetic nephropathy

Gestational hypertension or pre-eclampsia are common and potentially serious complications of pregnancy, occurring in 11–20% of women with T1DM compared with ~5% of women without T1DM.[89–91] Several observational studies have linked the development of gestational hypertension or pre-eclampsia with hyperinsulinaemia and insulin resistance.[92–95] Hypertension in T1DM is often associated with diabetic nephropathy and sodium retention, and the presence of nephropathy increases the risk of hypertension during pregnancy.[96,97] Microalbuminuria (urinary albumin excretion 30–299 mg per 24 h) or overt diabetic nephropathy (urinary albumin excretion ≥300 mg per 24 h) in early pregnancy is associated with markedly increased risks of preterm delivery, mainly owing to pre-eclampsia (Figure 2).[40,98] An observational study has demonstrated that early and intensive antihypertensive treatment in pregnant women with T1DM and microalbuminuria or diabetic nephropathy improved pregnancy outcomes irrespective of the presence of hypertension.[41] Antihypertensive therapy with agents considered to be safe in pregnancy, such as methyldopa, labetalol or calcium antagonists, should be used when indicated unless urinary albumin excretion spontaneously declines to values near the normal range.[40]

Careful monitoring and control of blood pressure and urinary albumin excretion before and during pregnancy is necessary. A blood pressure target of <135/85 mmHg and a urinary albumin excretion target of <300 mg per 24 h have been suggested, and in our clinical experience using this strategy has resulted in a marked reduction in the prevalence of pre-eclampsia and preterm delivery.[40,41]

The rate of decline in glomerular filtration rate was comparable in a cohort of women with diabetic nephropathy who either had or had not been pregnant in the observation period of up to 16 years.[99] However, in women with severely reduced kidney function, progression to end stage renal failure during or shortly after pregnancy has been observed.[100] The risk of potentially irreversible kidney damage during pregnancy is low in women with diabetic nephropathy who have normal or slightly elevated serum creatinine levels (<124 μmol/l).[100]

Diabetic retinopathy

Long-term optimal glycaemic control decreases the risk of diabetic retinopathy progression. However, seemingly paradoxically, intensification of insulin therapy with an abrupt improvement in glycaemic control has

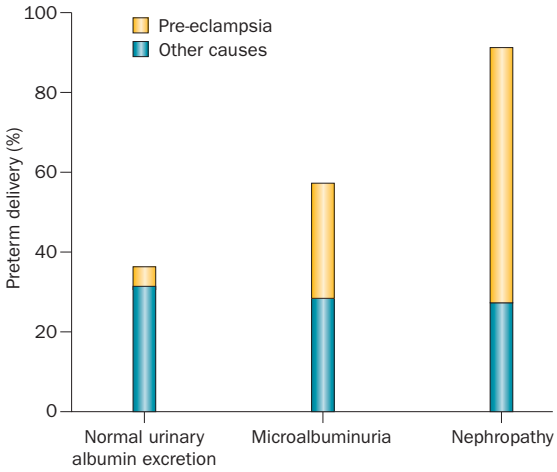

Figure 2 | Preterm delivery related to urinary albumin excretion in type 1 diabetes mellitus. Rates of preterm delivery (<37 gestational weeks) in relation to urinary albumin excretion in early pregnancy in women with type 1 diabetes mellitus. Yellow bars, preterm delivery associated with pre-eclampsia; blue bars, preterm delivery due to other causes. Permission obtained from the American Diabetes Association © Ekbom, P. *et al*. *Diabetes Care* **24**, 1739–1744 (2001).

been associated with a temporary worsening of diabetic retinopathy.[101–103]

Pregnancy-induced deterioration of diabetic retinopathy can occur in T1DM.[42,104] Poor glycaemic control and hypertension in early pregnancy increase the risk of progression.[42] Therefore, careful retinal examination in early and late pregnancy is necessary. Additional laser treatment can be given before or during pregnancy.

Thyroid function

Particular care should be taken to avoid maternal hypothyroidism in early pregnancy because of the risk of fetal cerebral dysfunction.[44] For women with established hypothyroidism, an increase of levothyroxine dose by approximately 50% after conception is common.[43,105] In hyperthyroidism, the minimal dose of antithyroid medication that can achieve euthyroidism should be used to minimize the risk of fetal hypothyroidism.[105]

Obstetric surveillance

Pregnant women with T1DM should be examined frequently with ultrasonography. In the first half of pregnancy the purpose is particularly to identify fetal malformations. Later, observation of fetal growth is important to diagnose excessive fetal growth (macrosomia), but also to detect intrauterine growth restriction, which is most often seen in women with diabetic nephropathy, chronic hypertension or pre-eclampsia. Growth-restricted and macrosomic fetuses have an increased risk of stillbirth. Many centres use antenatal nonstress testing once or twice per week, as well as daily kick-counting (maternal registration of fetal movements) from 32–34 weeks in an attempt to monitor the wellbeing of the fetus, owing to the generally increased risk of stillbirth in diabetic pregnancy.[106]

The timing and mode of delivery should be planned taking all aspects of maternal and fetal health into account. When vaginal delivery is planned, labour is often induced at 38–40 weeks to prevent late serious adverse outcomes (such as stillbirth, macrosomia and pre-eclampsia). In most centres more than 50% of births to women with T1DM are delivered by caesarean section.[107]

T1DM management during delivery

Tight glycaemic control during delivery is necessary to sustain sufficient fetal oxygen supply. Additionally, plasma glucose values >7 mmol/l increase the risk of neonatal hypoglycaemia. The goal for glucose values was, therefore, set at 4–7 mmol/l in the NICE guidelines.[29] This level can be achieved with very low-doses of rapid-acting or fast-acting insulin given subcutaneously during delivery, by intravenous insulin or by other regimens (Box 3).[108]

Labour has a glucose-lowering effect and reduces insulin requirements in women with T1DM, but it could necessitate an increase in glucose substrate in order to prevent maternal hypoglycaemia and ketosis, and an intravenous glucose infusion is given during labour, for example 2.55 mg/kg.[108] The same regimen should be followed for delivery by caesarean section and intravenous glucose infusion should be prepared for the surgical trauma, which leads to increasing demand for glucose. Additionally, the patient would be in a fasting state before and during the procedure.

Neonatal management and breastfeeding

The newborn baby has an increased risk of neonatal morbidities such as neonatal hypoglycaemia, respiratory distress and jaundice. Early oral feeding every 3 h during the first 24 h can be given to avoid neonatal hypoglycaemia. Close observation of the newborn baby is necessary and can usually take place in a specialized maternity ward.[109] Breastfeeding provides benefits for mother and offspring and is strongly encouraged for women with T1DM.[110] At our centre, the proportion of women with T1DM who breastfeed 4 months after delivery is similar to that of women without T1DM.[111] However, other studies have shown that women with T1DM are less likely to breastfeed their children or to breastfeed for a shorter period of time than women without T1DM.[112,113] For example, in a multicentre study, the finding that women with T1DM were likely to breastfeed for a shorter period of time compared with women without T1DM was explained by higher rates of caesarean section, earlier delivery, younger maternal age and shorter duration of education.[114] After adjusting for these confounders, no difference in the duration of breastfeeding among women with and without T1DM was found.[114] The clinical implication of this study is that health-care professionals should focus on encouraging breastfeeding in women with T1DM.

Immediately after delivery the mother's need for insulin declines to approximately 60% of the prepregnancy dose, owing to lack of placental hormonal influence. There is a concomitant increased risk of severe maternal hypoglycaemia because of fluctuating glucose levels during breastfeeding and excessive insulin dose. Insulin requirements gradually increase over the next weeks. In women who are breastfeeding, the insulin-dose requirement is

still around 10% lower than prior to pregnancy, with wide individual variations.[111,115]

Short-acting ACE inhibitors, such as captopril and enalapril, are considered to be safe choices of antihypertensive medication during breastfeeding.[116,117] β-blockers that have a high degree of protein binding[116,118] and calcium channel antagonists[116] also seem to be safe. Methyldopa is safe during breastfeeding,[116,119] but, unlike during pregnancy, methyldopa is not the first choice of antihypertensive therapy during lactation because of adverse effects such as fatigue and exacerbation of postpartum depressive states. Diuretics can potentially suppress lactation and are not recommended unless the patient has already been treated with diuretics before and during pregnancy.[116] Angiotensin II antagonists are not recommended because of insufficient data from studies of breastfeeding.[117] Our approach is to prescribe a short-acting ACE inhibitor if continued antihypertensive therapy is indicated in lactating women with T1DM.

In women with hypothyroidism, the dose of levothyroxine should be reduced to the dose taken before pregnancy once the patient has delivered,[105] and levothyroxine is considered to be safe during breastfeeding. Propylthiouracil and thiamazole are regarded safe for women with hyperthyroidism during breastfeeding, if administered in low to moderate doses.[105]

Box 3 | Recommendations during and after delivery

- Maintain plasma glucose levels of 4–7 mmol/l during delivery
- Close obstetric surveillance during labour and delivery
- Close observation of the newborn baby for morbidity including hypoglycaemia
- Monitor maternal insulin requirement, which declines to approximately 60% of the prepregnancy dose immediately after delivery
- ACE inhibitors captopril and enalapril are considered safe during lactation
- Thyroid dysfunction can be treated during lactation

Conclusions

Tight glycaemic control before and during pregnancy is crucial in order to prevent adverse pregnancy outcomes, although the benefits of tight glycaemic control should be balanced against the increased risk of hypoglycaemia. Rapid-acting insulin analogues are considered to be safe in pregnancy, and insulin pumps and long-acting analogues are widely used. Supplementation with folic acid could reduce the risk of congenital malformations.

Diabetes mellitus and development of hypertension are closely related and the effect of antihypertensive therapy on the risk of pregnancy-related complications should be considered. Early and intensive antihypertensive therapy during pregnancy is of utmost importance in women with microalbuminuria or diabetic nephropathy. The goal of antihypertensive therapy should include setting blood pressure targets and urinary albumin excretion levels within lower ranges than normally considered in pregnant women without diabetes mellitus. Screening for diabetic retinopathy and thyroid dysfunction should be performed before and during pregnancy.

The ultimate goal of the management of pregnant women with T1DM is to obtain similar pregnancy outcomes as those obtained in the population without T1DM. The use of the ADA, IDF and NICE guidelines has resulted in improved pregnancy outcomes in many centres with special interests and experience of managing T1DM; however, the goal of similar outcomes in women with and without T1DM has not been reached in these centres or in other centres, mainly owing to suboptimal glycaemic control, which results in a high prevalence of preterm delivery or macrosomia. The goal of glycaemic control in women with T1DM should, therefore, be to maintain glucose values within normal ranges at all times. Although having T1DM is compatible with breastfeeding, a focus on reducing insulin doses immediately after delivery and constant evaluation of other medications during breastfeeding is needed.

Review criteria

A literature search in the MEDLINE database was carried out in February 2012 to identify papers written in the English language. The search terms used were "pregnancy" and "diabetes" or "type 1 diabetes" and were combined with "hypoglycaemia" or "hypoglycemia", "pre-conception counseling", "postpartum care", "antihypertensive therapy", "microalbuminuria", "nephropathy", "retinopathy, "glycemic control", "breastfeeding", "lactation", "thyroid". This Review also draws on other reference sources, such as guidelines and textbook chapters, as stated when relevant.

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Author contributions

L. Ringholm contributed to researching and discussing content, writing the manuscript and editing the article before submission. E. R. Mathiesen, L. Kelstrup and P. Damm contributed substantially to discussions of the content and reviewing and/or editing of the manuscript before submission.