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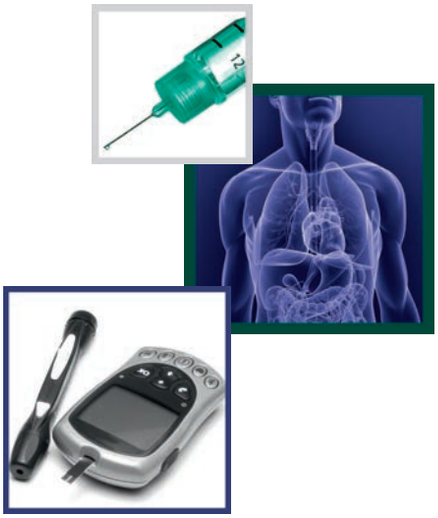

Managing pregnancy in women with Type 1 diabetes

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Practice Points

- Pre-pregnancy counseling is paramount in the optimal management of pregnancy in Type 1 diabetes.
- Good glycemic control before and during pregnancy reduces the risk of fetal and maternal complications.
- Screening for retinopathy, nephropathy, vascular and/or thromboembolic risk factors with appropriate management before and during pregnancy is important.
- Tight glycemic control using frequent glucose monitoring, appropriate dietary modification and intensive insulin regimens, balancing the risk of hypoglycemia to the mother with fetal complications of hyperglycemia, remains the mainstay of management.
- Ultrasound scan evaluation is important primarily to detect structural anomalies (with detailed four-chamber cardiac views) and later to monitor the fetal growth trajectory.
- Closely monitored labor with neonatology input is required in 30–40% infants; therefore, delivery should be done in a center equipped with a specialist multidisciplinary team.

SUMMARY Pregnancy in women with Type 1 diabetes is associated with an increased risk of complications for both the woman and her offspring. The risks can be effectively ameliorated when women are managed by experienced, multidisciplinary obstetric diabetes teams, emphasizing pre-pregnancy planning with tight glycemic control before and during pregnancy, and close monitoring during labor, delivery and postpartum. This review describes the issues particular to Type 1 diabetes pregnancy and how best to manage these pregnancies to minimize negative outcomes. There is also a brief description of recent developments in the field and current research on novel therapies.

Before the discovery of insulin in 1921, Type 1 diabetes (T1D) was associated with a dramatically reduced life expectancy and was, apart from in rare cases, incompatible with pregnancy. The introduction of insulin led to more frequent pregnancies in women with diabetes. By the 1940s, the maternal mortality rate was estimated at 10–17%, with live birth rates of just 55% [1]. While great progress has been made, there is still a two- to three-fold increased risk of congenital

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anomaly, a threefold increased risk of neonatal mortality and a fivefold increased risk of stillbirth in the offspring of women with diabetes [2]. These disappointing UK data are corroborated by a large scale nationwide Swedish study (n = 5089 T1D pregnancies), demonstrating similar increases in congenital malformation and perinatal mortality with an eightfold increase in macrosomia [3]. A recent Finnish cohort showed no improvement in the rate of preterm delivery or macrosomia between 1989 and 2008 [4].

Macrosomia remains the most frequent complication, and is accompanied by increased rates of neonatal hypoglycemia, respiratory distress, intracranial hemorrhage, hyperbilirubinemia and the need for neonatal intensive care [5,6]. Advances in medical care for pregnant women with T1D must be focused on reducing the persistently high rates of neonatal morbidity, in particular macrosomia, hypoglycemia and preterm delivery. T1D is also associated with long-term problems for the offspring, including increased incidence of obesity, insulin resistance and diabetes, presumably due to intrauterine fetal programming [7,8].

Maternal outcomes

The risks for women with T1D are dependent on the duration of diabetes and presence of complications. Compared with women with T1D and no nephropathy, microalbuminuria (30–300 mg albumin/24 h) alone is associated with a threefold increased risk of pre-eclampsia and a twofold increased risk both of early preterm delivery (<34 weeks) and of low birth weight [9]. When creatinine is elevated (>200 µmol/l) diabetic nephropathy can progress to end-stage renal failure [10]. The DCCT and EURODIAB studies showed that in the longer term, women with mild nephropathy do not have progressive decline in their renal function, which often returns to pre-pregnancy status [11,12]. Data from Denmark demonstrates that improved outcomes for women with diabetic nephropathy can be achieved when strict targets for blood pressure and metabolic control are instituted [13]. Pre-eclampsia is not only associated with nephropathy but also with elevated HbA1c in early pregnancy. There was a threefold higher incidence of pre-eclampsia when HbA1c was ≥8% (76 mmol/mol) in one study [14], and a reduction in HbA1c during early pregnancy resulted in almost halving the risk of pre-eclampsia in a Finnish cohort [15].

Diabetic retinopathy further complicates pregnancy in women with T1D. Data from the FinnDiane study demonstrated that women who develop pre-eclampsia or pregnancy-induced hypertension are at higher risk of developing diabetic retinopathy after 16 years of follow-up (26 and 24%, respectively, vs 6% for normotensive pregnancies) [16]. The DCCT suggested that both pregnancy and rapid improvements in glycemic control were associated with short-term deterioration of retinopathy, but showed no significant long-term decline [12]. Progression to proliferative retinopathy can occur and is more likely if significant retinopathy is present at baseline [17]. Retinopathy may continue postpartum, so close postnatal ophthalmologic follow-up is essential for these women [12,18]. Pregnancy should be delayed until proliferative retinopathy has stabilized, using photocoagulation if necessary [17], with data demonstrating this is associated with a reduced risk of progression [19].

Diabetic neuropathy does not seem to progress in pregnancy [11]. However, autonomic neuropathy manifesting as gastroparesis can be associated with significant morbidity, weight loss and hospital admission for intravenous nutrition and warrants specialist management [20].

Macrovascular disease is increasing amongst women of childbearing age, and is particularly relevant to women with T1D, who have an increased risk of cardiovascular events (hazard ratio of 7.7 for major cardiovascular events compared with background population) [21]. Pregnancy increases the rate of acute myocardial infarction three- to four-fold in all women, with or without diabetes [22,23]. The trend toward increasing maternal age further exacerbates this problem. As acute myocardial infarction in pregnancy is associated with high maternal (11%) and fetal mortality (9%) [24], unstable cardiovascular disease is a contraindication to pregnancy [25].

Pre-pregnancy counseling

Women with diabetes of childbearing age should be counseled about the risks of unplanned pregnancy with advice regarding safe effective forms of contraception until pregnancy is desired. As for all women, the combined oral contraceptive pill is associated with an up to fivefold increased risk of thromboembolic events [26] and potentially increased stroke and myocardial infarction rates [27]. It should, therefore, be used with caution in women with diabetes who are over 40 years old (over 35 years for cigarette smokers),

for whom intrauterine devices may be preferable. The progesterone-only pill has higher failure rates and depot progestogens, such as medroxyprogesterone, have adverse effects on lipid metabolism [28]. Progestogen-releasing intrauterine devices are safe, effective (>99.9% efficacy) [29] and have no negative impact on metabolic and/or thromboembolic risks [30].

Pre-pregnancy & antenatal care

Pre-pregnancy care has been shown to significantly improve glycemic control [31]. However, there is an inevitable selection bias favoring educated, socioeconomically privileged women with higher self-efficacy and diabetes self-management skills. Pre-pregnancy care consists of careful explanation of the risks associated with pregnancy, and the stratification of these risks according to glycemic control **(Table 1)** [32,33]. As neural tube disorders are more common in T1D pregnancy [34], women are advised to take 5 mg folic acid from before conception until 12 weeks gestation. Rubella antibody titer should be measured with repeat vaccination for nonimmune women. All women with T1D should have retinal screening performed prior to conception and/or at the booking visit. Autoimmune thyroid disease is more common in T1D, therefore, thyroid function tests and thyroid peroxidase antibody titers should be assayed. Blood pressure is measured at all visits and urinary albumin:creatinine ratio (mg/mmol) measured at intervals to screen for pregnancy-induced hypertension and pre-eclampsia. Ultrasounds are performed to confirm pregnancy, with a detailed four-chamber cardiac anomaly scan at 18–20 weeks gestation. Thereafter, the ultrasound schedule typically includes scans at 28, 32 and 36 weeks gestation to monitor fetal growth (as recommended by NICE guidelines) [35], although clinical measures are still used in some regions.

Structured education, dietary & lifestyle advice

Structured diabetes education programs to encourage daily self-adjustment of insulin doses, while not validated during pregnancy are considered beneficial [36]. Where available, structured education programs, such as Dose Adjustment for Normal Eating, should be offered as soon as possible to diabetic women who are planning to become pregnant [35]. All should have individualized dietary advice from appropriately trained dieticians to ensure adequate nutritional requirements are met, and to adjust the macronutrient meal content to minimize postprandial glycemic excursions. Recommended caloric intake depends on pre-pregnancy BMI, with weight gain of 5.5–10 kg for overweight women and up to 12.5–17.5 kg for normal weight women considered optimal [37]. The UK NICE guidelines suggest restricting caloric intake to 25 kcal/kg/day in women with BMI >27 kg/m^2 (~50% of T1D). There is insufficient evidence to show that weight loss is safe in T1D pregnancy, although gestational weight gain of ≤5 kg was associated with reduced perinatal morbidity in obese women with Type 2 diabetes [38].

All pregnant women are advised to take 30 min of moderately vigorous exercise on most days [20]. Moderately intense exercise may ameliorate glycemic excursions after meals and reduce glycemic variability [39].

Medical antenatal advice

Titration of insulin doses is closely monitored with tighter glycemic control targets and more emphasis on postprandial glucose levels compared with outside of pregnancy. Typically, women will be seen every 2–4 weeks by a multidisciplinary obstetric diabetes team (endocrinologist, obstetrician, diabetes nurse specialist and dietician). Angiotensin converting enzyme inhibitors, angiotensin receptor blockers and statins are discontinued once the woman stops using contraception. Antihypertensives that are generally considered acceptable include labetolol, nifedipine and methyldopa. Stringent blood pressure control is recommended and has been shown to improve pregnancy outcomes for women with diabetic nephropathy [13]

Insulin analogs, including glargine, detemir, aspart and lispro, are commonly used before and during pregnancy, with all but glargine approved for use in pregnancy by the US FDA. The basal insulin analogs appear safe, if not definitively superior to neutral protamine hagedorn insulin [40,41]. One large randomized controlled trial demonstrated reduced fasting maternal glucose levels with insulin detemir without an increase in nocturnal hypoglycemia [42]. Data for insulin aspart suggest reduced glycemic excursions compared with soluble insulin [43]. Many practitioners will continue basal analogs, while others switch to neutral protamine hagedorn or insulin pump therapy in pregnancy.

Table 1. Common complications for offspring of Type 1 diabetes pregnancy.

Trimester	Complications	Description
First trimester	Congenital malformations	Cardiac defects are the most common abnormalities (ventricular septal defect, transposition of great vessels, tetralogy of Fallot, pulmonary valve stenosis and atrioventricular septal defects) Abnormalities of CNS (intracranial anomalies and spinal defects), limb abnormalities, facial clefts, esophageal atresia, duodenal atresia and diaphragmatic hernia Syndromes (monogenic or unknown) occur, as well as multiple anomalies Sacral agenesis uncommon but pathognomonic of diabetes
Second and third trimester	Fetal growth acceleration	Fetal hyperinsulinemia leads to accelerated fetal growth
	Intrauterine growth restriction	In long-standing diabetes and established cardiovascular or renal disease
	Fetal programming	Adverse intrauterine environment has a lasting effect on fetal pancreatic islets and β-cell development, increasing the risk of diabetes in adult life
	Stillbirth	Poor glycemic control resulting in deranged metabolic environment of hypoxia, acidosis and placental insufficiency
Neonatal	Neonatal hypoglycemia	Transient neonatal hypoglycemia contributes to neonatal morbidity. Most common in preterm and macrosomic infants
	Large for gestational age	Macrosomic infants may get shoulder dystocia, brachial plexus injuries and metabolic complications, including hyperbilirubinemia and hypocalcemia
	Neonatal mortality	Primarily due to congenital malformation and prematurity
	Other neonatal morbidities	Respiratory distress: excess fetal insulin interferes with fetal lung maturity Cardiac complications: transient hypertrophic cardiomyopathy and/or congestive cardiac failure

Glycemic targets

The recommended glycemic targets in pregnancy are considerably tighter than outside of pregnancy **(Table 2)** [20]. To safely achieve these, frequent self-monitoring of blood glucose is necessary, before each meal, 1 h after meals and before bed. A minimum of four insulin injections per day are necessary, along with correctional boluses when postprandial values are outside targets, or extra snacks are taken. Although insulin pump therapy can improve glycemic control while reducing severe hypoglycemia outside of pregnancy, there are no adequately powered randomized controlled trials of insulin pump versus multiple daily injections during pregnancy [44,45].

Insulin requirements vary as pregnancy progresses, most likely due to physiological changes in hormones, including cortisol, leptin, adiponectin, prolactin, progesterone, human placental lactogen and placental growth hormone [46,47]. In early pregnancy, hypoglycemia unawareness increases, despite reduced insulin requirements [48]. As episodes of severe hypoglycemia increase fivefold in early pregnancy [49], care must be taken to detect and if possible counteract hypoglycemic awareness by meticulous hypoglycemia avoidance. Severe hypoglycemia causes substantial maternal morbidity and is the leading cause of maternal mortality in T1D pregnancy [50]. Restricting the carbohydrate content of meals can help to avoid large boluses of insulin and/or postmeal corrections, with earlier premeal insulin administration also useful [51]. During later pregnancy, insulin doses may increase two- to three-fold as the first trimester focus on reducing hypoglyemia shifts towards tightening glycemic control to reduce fetal pancreatic hyperinsulinemia (fetal insulin secretion begins at 14–16 weeks gestation).

Continuous glucose monitoring in pregnancy

The use of continuous glucose monitoring (CGM) is increasing but whether or not it will assist more women to safely achieve optimal glucose control and infant outcomes is debated. The authors' own CGM data suggest that during the first trimester, women with T1D spend 46%

(10.4 h/day) of the time in target (glucose levels between 3.5–7.8 mmol/l), rising to only 56% (13.6 h/day) in the third trimester [52]. When used as an educational tool, intermittent retrospective CGM is associated with a 0.5% reduction in HbA1c and reduced rates of macrosomia [53]. By contrast, a Danish study recently showed no improvement in maternal glycemic and/or infant outcomes with intermittent use of newer real-time CGM in pregnancy [54]. Real-time CGM may also be effective [55] if used continuously before and during pregnancy with a large international multicenter trial comparing CGM with capillary glucose testing currently underway [101].

Peripartum care

The potential for peripartum complications means that delivery should be supervised by a specialist diabetes obstetric team. Delivery is usually planned for 38 weeks gestation to reduce the risk of stillbirth and as there is evidence that earlier induction of delivery is associated with a reduced incidence of cesarean section [56]. Cesarean section rates are increased for several reasons, due to the induction of labor at 38 weeks not progressing satisfactorily, and as it is the usual mode of delivery when the fetal weight is estimated at 4 kg or more. Optimization of glycemic control in the weeks up to delivery and during labor is important to reduce the risk of neonatal hypoglycemia. It is recommended that intravenous insulin is used once active labor starts (cervix dilated by 3 cm and/or rupture of membranes) to achieve near normal capillary blood glucose values [35,57]. As with other high-risk pregnancies, cardiotocography should be used to monitor the progression of labor and detect fetal distress. Fetal distress during labor results in a two- to threefold increase in interventions [3], the level of erythropoietin in the amnion in week 36–37 has been shown to be associated with fetal hypoxia, and can be used to predict fetal distress [58].

Respiratory distress syndrome is more common in T1D offspring, possibly due to the counteracting effect of insulin on surfactant production, contributing to reduced clearance of pulmonary fluid, respiratory distress and/or transient tachypnea. Glucocorticoids mimic the normal surge of stress hormones in the fetus once labor starts, this is absent in cesarean-section delivery further contributing to the increased rates of respiratory distress in these neonates [59]. The efficacy of glucocorticoids to reduce neonatal respiratory distress in neonates born before 32 weeks is well established [60], and their use in preterm labor between 24 and 34 weeks is widely accepted practice [61]. Recent data suggest steroids should be given in all pregnancies with suspected fetal lung immaturity (e.g., T1D pregnancies with suboptimal glycemic control) and/or when labor is induced regardless of gestational age [62,63]. This is based upon work demonstrating conversion of amniotic fluid indices of fetal lung maturity (surfactant:albumin ratio) from an immature to a mature result after treatment with steroids [62]. This change in practice is of particular importance in T1D as steroid-induced insulin resistance exacerbates maternal hyperglycemia. However, this can be effectively addressed by careful titration of insulin doses in the 24–48 h following glucocorticoid administration.

Neonatal outcomes

Congenital malformations remain significantly more common in the offspring of women with T1D [2,3,64] and the risk correlates with HbA1c in the first trimester [31]. In a large UK registry of over 40,000 pregnancies, there was a linear increase of 1.3 in the odds ratio of congenital malformations occurring per 1% (11 mmol/mol) rise in periconceptual HbA1c above 6.3% (45 mmol/mol), giving a rate of one in 33 at HbA1c of 6.5% (45 mmol/mol), and one in ten at HbA1c of 9.5% (80 mmol/mol) [33]. Data from the East Anglia region of the UK, suggest a 50% reduction in congenital malformation, stillbirth and neonatal death per 1% lowering in HbA1c [31]. Stillbirth is also increased fivefold above the background population rates, neonatal mortality is threefold higher, and both are associated with suboptimal glycemic control at conception [31].

Neonatal hypoglycemia results from pancreatic β-cell hyperplasia in the neonate in response

Table 2. International guidelines on glycemic targets for pregnancy.

Guidelines	HbA1c target	Glucose targets (mmol/l)			Ref.
		Premeal/ fasting	Peak postprandial	Mean daily glucose	
American Diabetes Association	<6.0% <42 mmol/mol	3.3–5.5	5.6–7.2	<6.1	[20]
NICE	<6.1% <43 mmol/mol	3.5–5.9	<7.8	–	[35]
Australasian Diabetes in Pregnancy Society	<7% <53 mmol/mol	4.0–5.5	<8.0	–	[77]

to increased glucose transport from the maternal circulation. This can be counteracted by strict glycemic control in the weeks up to delivery [20]. Glucose levels should be monitored in all T1D offspring. Blood glucose <2.6 mmol/l more than 2 h after delivery should be treated enterally (breast milk or formula feed) and sometimes warrants nasogastric tube feeding or intravenous dextrose, according to neonatal wellbeing.

Macrosomia (birth weight >90th centile for sex and gestational age) is not only associated with an increased risk of birth injuries but can also result in organomegaly and most seriously myocardiac hypertrophy. Intrauterine growth restriction is also increased in T1D pregnancies, and is associated with stillbirth [65]. Other common complications for offspring of T1D pregnancy are listed in **Table 1**.

There is growing evidence that the intrauterine milieu has significant impact on fetal programming and a consequent increased incidence of obesity, insulin resistance and Type 2 diabetes later in life [66]. Further study is necessary to elucidate the relative impact of intrauterine versus postnatal environments. Breastfeeding is encouraged, with benefits including postpartum weight reduction, reduced risk of cardiovascular disease, and ovarian and breast cancer in the mothers [67], and it appears to improve lipid profiles [68] and reduce the incidence of T2D in their offspring [69]. Breast-feeding women should be advised to further reduce insulin doses and/or take additional carbohydrate snacks (~50 g extra carbohydrate per day).

Conclusion & future perspective

The increased risks associated with pregnancy in T1D remain unacceptably high. Vast improvements in terms of maternal and fetal mortality and morbidity have been made in the past century but there is still work to be carried out. Although the majority of T1D pregnancies have a positive outcome, the persistence of the increased incidence of negative outcomes, in particular stillbirth and congenital malformations, highlights the critical importance of appropriate counseling for women with T1D of reproductive age and improved availability of pre-pregnancy care. Future developments and research underway involve efforts to modulate the immune system to reverse T1D, a search for new renewable sources of β-cells for transplantation [70–72], drugs to induce regeneration of the native β-cells [73] and closed-loop technology [74]. The latter is the only one as yet with a safety profile acceptable for use in pregnancy [75]. The aim is to facilitate near physiological glycemic control. It is particularly applicable to T1D pregnancy as in this setting it is crucial that hyperglycemic excursions are controlled without increasing hypoglycemia. The authors' group has demonstrated reduced hypoglycemia and noninferior glycemic control using 24-h closed-loop in a clinical research facility setting [76], and will soon begin a Phase II clinical trial of closed-loop at home in pregnancy. Other areas where research may yield clinically important results are the analysis of variability in outcomes for different populations. This would point to the most appropriate interventions to best reduce adverse outcomes. An example, is a closer examination of optimal treatment of microalbuminuria with a view to further reducing pre-eclampsia and preterm labor. The effect of lifestyle changes should be more carefully researched toward optimizing targets for diet, exercise and weight gain, and understanding how best these targets can be achieved by a greater number of individuals. In terms of fetal outcomes, recent work has led to the development of a clinically useful tool to assess fetal hypoxia in the latter stages of pregnancy [58], and the authors' group is soon to evaluate fetal glycemic profiles using CGM to determine how they relate to the mothers glycemic control in the peripartum. Other areas that warrant further research are defining what constitutes neonatal hypoglycemia and what is the appropriate timing of steroids necessary to induce fetal lung maturation. Ongoing research will ensure maternal and fetal risks are minimized and pregnancy outcomes improved for all women with T1D.

Disclaimer

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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