Management of pregnancy in women with type 1 diabetes mellitus: Guidelines of the French-Speaking Diabetes Society (Société francophone du diabète [SFD])

E. Bismuth a, C. Bouche b,*, C. Caliman c, J. Lepercq d,e, V. Lubin f,g, D. Rouge h, J. Timsit e,i, A. Vambergue j

a Department of Paediatric endocrinology-diabetology, Robert-Debré Hospital, AP–HP, 48, boulevard Séraurier, 75019 Paris, France
b Department of Endocrinology-Diabetology-Nutrition, Saint-Louis Hospital, AP–HP, 1, avenue Claude-Vellefaux, 75475 Paris cedex 10, France
c Department of Endocrinology, ULB Erasme Hospital, 808, route de Lennik, 1070 Brussels, Belgium
d Department of Obstetrical-Gynaecology, Saint-Vincent-de-Paul Hospital, AP–HP, 74-82, avenue Denfert-Rochereau, 75064 Paris cedex 14, France
e Faculty of Medicine, Paris V, 24, rue du Faubourg-Saint-Jacques, 75014 Paris, France
f 52, Cours Mirabeau, 13100 Aix-en-Provence, France
g Maternité de l’Étoile, RD 14, 13540 Puyricard, France
h Department of Dietary, Paule-de-Viguier Hospital, 330, avenue de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex 9, France
i 52, Cours Mirabeau, 13100 Aix-en-Provence, France
j Department of Immunology and Diabetology, Cochin-Saint-Vincent-de-Paul Hospital, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France

Received 16 February 2012; accepted 17 February 2012

Abstract

Aim. – The clinical guidelines reported by the French-Speaking Diabetes Society (Société francophone du diabète) include updated recommendations for preconceptual planning and care in the management of pregnancy in women with type 1 diabetes mellitus (T1DM).

Methods. – The working group included diabetologists, as well as an obstetrician, a nurse and a dietician. A review of the literature was performed using PubMed and Cochrane databases. Guidelines published by foreign diabetes societies were also consulted.

Results. – In women with T1DM, pregnancy increased the risks of hypoglycaemia, diabetic ketoacidosis, pregnancy-induced hypertension, infections and worsening of diabetic microvascular disease. Moreover, T1DM during pregnancy had an impact on the embryo and the fetus, and may have increased the risk of spontaneous miscarriages, malformations, premature births, and fetal and neonatal complications. However, intensive glycaemic control and preconception care have been shown to decrease the rate of fetal demise and malformations. Also, the use of insulin analogues during pregnancy is now regarded as safe. Tight glucose control and frequent follow-up are recommended throughout pregnancy in women with T1DM. Their obstetric management should take place in a maternity hospital with an appropriate perinatal environment and in close collaboration with diabetologists.

Conclusion. – Pregnancy planning and adequate management during pregnancy are mandatory for improving the outcomes of women with T1DM.

© 2012 Elsevier Masson SAS. All rights reserved.

Keywords: Pregnancy; Type 1 diabetes; Guidelines; Review

Résumé

Prise en charge de la grossesse au cours du diabète de type 1.

But. – Ce référentiel de la Société francophone du diabète a pour objet de préciser les modalités de la prise en charge préconceptionnelle et pendant la grossesse des femmes atteintes de diabète de type 1 (DT1).
Méthodes. — Le groupe de travail a été constitué de diabétologues, d’un obstétricien, d’une infirmière et d’une diététicienne. La revue de la littérature a été faite à partir des banques de données PubMed et Cochrane. Les recommandations émanant de sociétés de diabétologie étrangères ont également été consultées.

Résultats. — Chez les femmes qui ont un DT1, la grossesse comporte des risques pour la mère et l’enfant. Chez la femme, il existe un risque accru d’hypoglycémies, d’acidocétose, d’hypertension artérielle gravidique, d’infections et d’aggravation des complications microvasculaires. Le diabète augmente également les risques de fausse couche spontanée, de malformations, de prématurité et de complications fetales et néonatales. Il est établi qu’une prise en charge préconceptionnelle et un bon contrôle glycémique diminuent les risques de mort fœtale et de malformations. L’utilisation des analogues de l’insuline est désormais considérée comme sûre au cours de la grossesse. L’obtention d’un contrôle glycémique strict et une surveillance rapprochée sont recommandées pendant toute la grossesse. La prise en charge obstétrique doit avoir lieu dans une maternité qui dispose d’un environnement néonatal adapté et travaillant en collaboration avec les diabétologues.

Conclusions. — La programmation et une prise en charge adéquate tout au long de la grossesse sont indispensables pour améliorer le pronostic de la grossesse chez les femmes qui ont un DT1.

© 2012 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Grossesse ; Diabète de type 1 ; Recommandations ; Revue

Abrevations

T1DM Type 1 diabetes mellitus
SFD Société francophone du diabète, French-Speaking Diabetes Society
DKA Diabetic ketoacidosis
PIH Pregnancy-induced hypertension
CM Congenital malformations
ACE Angiotensin-converting enzyme
ARBs Angiotensin-II receptor blockers and inhibitors
CSII Continuous subcutaneous infusion of insulin
FHR Fetal heart rate

Pregnancy in women with type 1 diabetes mellitus (T1DM) is associated with many potential risks for both the mother and child that can, however, be reduced by optimal care implemented before conception and pursued throughout pregnancy. Nevertheless, the goals of the Saint-Vincent declaration [1] — to achieve pregnancy outcomes in women with diabetes that approximate those of non-diabetic women — have yet to be achieved. Thus, the aim of the present report, which was focused on T1DM, was to review the measures currently proposed for reducing these risks.

1. Risks associated with pregnancy in women with type 1 diabetes mellitus

1.1. Influence of the pregnancy on glycemic control

1.1.1. Changes in insulin needs

During the first trimester of pregnancy, insulin needs can decrease by 20% compared with pregestational needs [2], and may be associated by nausea and vomiting. Insulin needs then increase from the second trimester, and often up to weeks 30–34 of gestation, by an average of 50% [3]. A marked increase in the dosage of fast-acting insulin in the morning has often been observed. During the last weeks of gestation, insulin requirements may stabilize or decrease until delivery. All these changes can vary considerably from one woman to another [4].

After delivery, insulin should then return to pregestational levels or even lower in cases of breastfeeding. Women need to be informed of such changes in requirements, and the insulin doses used after delivery should be given to avoid the occurrence of hypoglycaemia. Glycaemic targets also need to be higher postpartum.

1.1.2. Hypoglycaemia

Hypoglycaemic events are commonly seen, particularly during the first trimester of pregnancy. Its occurrence is facilitated by efforts to achieve normoglycaemia, the initial decrease in insulin needs and a history of hypoglycaemia before pregnancy. Recurrent hypoglycaemia induces desensitization and increases the risk of severe hypoglycaemia, which was seen in 40–45% of pregnant women in recent series [5,6]. However, cases of maternal mortality most likely due to severe hypoglycaemia are unusual [7]. Optimal management of diabetes before pregnancy reduces the risk of severe hypoglycaemia (level B) [6]. Although hypoglycaemia is teratogenic in rodents, there are currently no data associating hypoglycaemia, including recurrent and severe cases, with congenital malformations (CM), fetal death or short- and long-term impairment of children’s development. Nevertheless, further studies are necessary to confirm that maternal hypoglycaemia is not harmful to the infant [8,9].

However, the definition of hypoglycaemia during pregnancy remains vague. Fasting blood glucose physiologically decreases during gestation [10]: in non-diabetic pregnant women, the mean capillary blood glucose is 75 ± 5 mg/dL (4.2 ± 0.28 mmol/L) whereas, during the third trimester, fasting blood glucose is approximately 55 mg/dL (3.1 mmol/L) [11]. Thresholds for the secretion of counter regulatory hormones are also lower during pregnancy [12]. It is therefore possible that the capillary blood glucose threshold that defines hypoglycaemia should be set at around 60 mg/dL (3.3 mmol/L) in pregnant women with T1DM.

1.1.3. Diabetic ketoacidosis

The frequency of diabetic ketoacidosis (DKA) during pregnancy is 2–3% [13,14]. Pregnancy increases the risk of DKA through metabolic changes that promote ketogenesis and reduce the buffering power of plasma. This also explains why DKA can be observed even at modest levels of hyperglycaemia such as
less than 300 mg/dL (16.5 mmol/L) [15]. However, the risk of DKA can also be increased by corticosteroids or beta-2 agonists, infections, inappropriate decreases in insulin doses because of nausea or vomiting, poor compliance with treatment, insufficient frequency of blood glucose self-monitoring and treatment with an insulin pump [16]. DKA carries a 10–20% risk of fetal death [15]. For this reason, patients need to be made aware of its warning signs. Measurement of ketonuria or plasma ketone bodies should be carried out in cases of unexplained hyperglycaemia (≥ 200 mg/dL or 11 mmol/L), so that doses of rapid-acting insulin can be increased immediately. In such situations, women should contact their diabetologist immediately. Indeed, any suspicion of DKA should prompt emergency hospitalization and treatment.

1.2. Risks associated with diabetes during pregnancy

1.2.1. Arterial hypertension and preeclampsia

The frequencies of pregnancy-induced hypertension (PIH) and preeclampsia are both increased in women with T1DM. PIH is defined as systolic arterial blood pressure above or equal to 140 mmHg and/or diastolic arterial blood pressure above or equal to 90 mmHg after 20 weeks of gestation on two separate occasions with a minimum interval of 6 h in women who were previously normotensive. Preeclampsia is defined as the combination of PIH and proteinuria above or equal to 300 mg/24 h [17]. Its diagnosis can be difficult in cases of pre-existing nephropathy, and is based on an increase in both blood pressure values (by ≥ 15%) and proteinuria. The overall prevalence of preeclampsia in pregnant T1DM women is 12–20%, five times higher than in the general population [18,19]. The risk is increased by pre-existing retinopathy or nephropathy, and varies according to the stage of renal involvement: 30–40% in women with microalbuminuria; 40–50% in those with proteinuria; and more than 50% in cases of renal failure [20–22]. Intrauterine growth restriction is also more common in these conditions.

1.2.2. Premature births

Premature delivery is more commonly seen in women with T1DM. Mild prematurity, defined as a gestational age between 32 and 37 weeks of gestation, is five to ten times more frequent in women with T1DM than in the general population [21,23]. Spontaneous and induced premature delivery is also both increased. All of the causes have yet to be identified. However, poor glycaemic control is associated with an increased frequency of both types of prematurity, while nulliparity and preeclampsia are associated with an increased risk of induced premature birth [23]. In women with nephropathy, the risk of prematurity, including severe cases (before 32 weeks), is increased, but might be reduced through good blood pressure control [24].

1.2.3. Infections

There is no increased risk of acute pyelonephritis if lower urinary tract infections are screened for and treated during pregnancy. Monthly urine cultures are more sensitive than urine dipstick screening tests [25]. However, an increased frequency of postpartum endometritis has been reported after caesarean section in the absence of prophylactic antibacterial therapy [26].

1.3. Impact of diabetes on embryo and fetus

1.3.1. Spontaneous miscarriages

These occur two times more frequently in women with poor glycaemic control (in around 30% of cases when HbA1c is greater than 8%) [27] and are partly due to CM.

1.3.2. Congenital malformations

The risk of CM is increased primarily because of the teratogenic effects of maternal hyperglycaemia during the first eight weeks of pregnancy. The prevalence of CM ranges from 4% to 15% (versus 2.1% in the general population); it also increases from 2% when HbA1c is 5.5% to 6% when HbA1c is 9% [28]. There is no threshold in the relationship between the risk of CM and maternal HbA1c (Fig. 1). The observed CM, which are not specific to diabetes, mostly involve the cardiovascular system (interventricular communication, coarctation of the aorta), central nervous system (spina bifida, hydrocephaly and anencephaly), skeleton and genitourinary system. They are the main causes of neonatal morbidity and mortality [29].

1.3.3. Neonatal and fetal complications

Macrosomia (fetal or neonatal measurements >90th percentile for gestational age) can be explained by fetal hyperanabolism, which is partially due to fetal hyperinsulinism that, in turn, results in increased adiposity (mainly affecting the face and trunk) and organomegaly, while bone growth remains normal. Cardiac septal hypertrophy arises as part of this organomegaly, but its consequences on fetal prognosis have yet to be determined.

The occurrence of hypoxia has also been reported in macrosomic fetuses, leading to excess production of erythropoietin, which leads to polycythaemia and hyperbilirubinaemia in the
newborn [30]. The synthesis of surfactant is reduced due to fetal hyperinsulinaemia, and may cause delayed lung maturation and neonatal respiratory distress, which is further worsened by preterm birth.

The risk of fetal death is increased during the third trimester and is enhanced by maternal hyperglycaemia. In addition, hypertension or maternal nephropathy can be associated with vascular anomalies of the placenta, causing fetal growth restriction. Because of this, normal fetal biometry should be interpreted with caution. Nevertheless, in general, premature delivery remains the main source of morbidity.

2. Pregnancy planning

An effort to educate women should be made before pregnancy and, in particular, during adolescence in women with early-onset T1DM [31]. Such information should provide reassurances of fertility, the absence of an increased risk of chromosomal anomalies, the possibility of having a normal pregnancy and the risk of having T1DM in their children (which is around 3%). It is also a good time to choose an effective contraceptive method.

The benefits of planning a pregnancy have already been established (level B). Preventing the risk of CM has to be done before week 8 of pregnancy, and requires detailed information on glycaemic goals, the means to achieve it and the risks involved if they are not met. However, it has been shown that complete information is not always delivered by health professionals and/or is not fully understood by women with T1DM [31].

2.1. Contraception in type 1 diabetes mellitus women

Contraception should be systematically addressed during clinical visits in T1DM women of childbearing age. The choices should combine acceptability, efficacy, reliability and the absence of harmful metabolic effects; it may be hormonal (combined contraceptive pill, progestogen-only pill or an implant) or an intrauterine device (level E).

2.2. Optimalization of diabetes treatment and glycaemic goals

See Chapter 3.

2.3. Folic-acid supplementation

Folic acid blocks hyperglycaemia-induced oxidation, and reduces the risk of neurological and cardiac malformations [32–34]. Administration of a daily dose of 400 μg or 5 mg of folic acid should be started as soon as conception has been planned, and continued until week 12 of gestation (level B) [35].

2.4. Other associated treatments

Pregnancy planning is also crucial for adaptation of potentially fetotoxic treatments before conception. The French Reference Centre on Teratogenic Agents provides information and advice to practitioners, and can be contacted via telephone (+33 1 43 41 26 22) or through the Internet [36].

2.4.1. Antihypertensive agents

2.4.1.1. Angiotensin-converting enzyme. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) [37] are teratogenic during the first trimester, although this has recently been disputed [38,39]. Fetal exposure to ACE inhibitors has been associated with increased neonatal morbidity and mortality. Long-term follow-ups of children exposed in utero have shown irreversible renal toxicity (renal failure, arterial hypertension and proteinuria). Thus, ACE inhibitors and ARBs should be discontinued once pregnancy is planned. However, in some patients with advanced nephropathy, the decision may be left to the nephrologist as to whether to discontinue these drugs before conception or to maintain them until pregnancy is confirmed.

2.4.1.2. Diuretics. The hypovolaemic effects of these drugs can result in decreased placental blood flow and ischaemia of the fetal–placental unit. However, there is a large amount of reassuring data on women exposed to furosemide at various stages of pregnancy to allow its use in pregnancy. Furosemide does, however, cross the placental barrier, and extremely rare electrolyte disorders with no clinical consequences (hypokalaemia, hypocalcaemia, hyponatraemia), as well as increased diuresis, have been reported in newborns whose mothers were treated with furosemide near the end of pregnancy.

There are few published data on women exposed to amiloride during pregnancy, but no worrying events have so far been demonstrated. Also, there are no published data on women exposed to indapamide, and little published data on women exposed to spironolactone during pregnancy. In animals, spironolactone at high doses during the second half of gestation caused feminization in male fetuses.

2.4.1.3. Calcium inhibitors. Published data on pregnant women treated with nifedipine during the second and/or third trimesters have not demonstrated fetotoxic effects, and these findings were supported by animal studies. It is therefore preferable to use nifedipine as the first-line therapy, with nicardipine or verapamil as second-line therapies during pregnancy.

2.4.1.4. Beta-blockers. There are few published data on women exposed to beta-blockers in the first trimester, but no malformative effects have been shown to date. In the second and/or third trimesters, the published data — which is mostly on labetalol — are reassuring. Other beta-blockers have been less studied, and placental hypoperfusion associated with intrauterine growth restriction has been reported [40]. This suggests that the use of labetalol during pregnancy should be favoured.

2.4.2. Lipid-lowering agents

The National Registry in the United States has suggested an increased risk of cardiopulmonary and neurological malformations with statin drugs [41]. The controversy continues due to the low frequency of these malformations [42]. Nevertheless,
given the current state of knowledge, the use of statins during pregnancy should remain contraindicated [43]. Fibrate’s studies on teratogenicity in animals have found a reduction in adiposity, but not in fetoplacental growth [44]. Given its sparse data in the literature, the use of fibrates during pregnancy is not advised.

2.4.3. Aspirin

Low-dose aspirin is not contraindicated during pregnancy. However, to limit the per- and post-partum risk of haemorrhage, the drug should be stopped at 37 weeks of gestation at the latest. In women with T1DM, recommendations for the use of aspirin are mostly related to the prevention of pre-eclampsia, with initiation of the treatment before week 20 of gestation [45,46].

2.5. Assessment of diabetes complications

Such an assessment should be done before conception to allow for early management of complications, which can worsen during pregnancy. The standard assessment includes screening for retinopathy, nephropathy and coronary heart disease. Screening for Hashimoto’s thyroiditis (thyroid-stimulating hormones, anti-thyroperoxidase antibodies) is also worthwhile.

2.6. Gynaecological assessment

A gynaecological workup, including at least a physical assessment with a recent Pap smear, is essential, and management of subfertility is sometimes required [47]. Several tests should also be done before pregnancy, including blood group, Rhesus factor, and serology testing for syphilis, rubella, toxoplasmosis, hepatitis B virus (HBV) and human immunodeficiency virus (HIV). The serology tests to be performed during the first trimester are the same as those for all pregnant women.

3. Modalities of diabetes management

3.1. Dietary management

Dietary guidelines for women with T1DM during pregnancy have been modified over the past few decades to match more closely those recommended in non-diabetic pregnancy [48]. However, specific issues include the risk of hypoglycaemia, DKA and hyperglycaemia (see above). The proposed diet should meet the needs of both the mother and fetus, allowing adequate weight gain while maintaining good blood glucose levels. The dietary guidelines should also take into account the particular preferences, culture, religion and economic means of the woman.

3.1.1. General principles

The dietitian consultation should preferably be delivered by a dietitian who specializes in diabetes care. The diet should be divided into three meals a day, with the addition of snacks if necessary. Dietary management is made easier when the woman brings along a food log, a record of all her consumed food and beverages, to each appointment. The woman’s weight should be recorded at each visit to allow adjustment of dietary intakes and physical activity. Excess weight increases the risks of macrosomia, caesarean section and maternal overweight after delivery [49]. Recommendations for weight gain during pregnancy in diabetic women are similar to those of non-diabetic women, and take into account the body mass index (BMI) before conception (level C) [49–52] (Table 1).

3.1.2. Different needs

The theoretical recommendations for pregnant women include increasing food intakes by 150 kcal/day during the first trimester, and by 250 kcal/day during the second and third trimesters [53]. The energy requirements of pregnant women are, on average, more than 2000 kcal/day [54]. Obese or overweight pregnant women can restrict their intakes [55], but never to less than 1600 kcal/day [54]. Protein requirements of pregnant women with T1DM are similar to those of non-diabetic women [56], and should generally account for 15–20% of the total daily energy intake [55]. The protein intake in diabetic patients is 0.8–1 g/kg body weight/day [57]; in pregnant women, it should not be less than 1.1 g/kg body weight/day [49] or should be, at minimum, 60 g/day [53].

Lipid requirements during pregnancy are around 35–40% of the total daily energy intake [58]. It is recommended to promote the consumption of polyunsaturated fatty acids or omega-6 and omega-3 essential fatty acids to limit intakes of saturated fatty acids, and to reduce intakes of trans fats to the lowest amounts possible [49]. Lipid sources should also be varied, with fish consumed at least twice a week [55]. The consumption of products enriched with phytosterols (such as margarine and yogurt) is not recommended during pregnancy due to the lack of specific studies [50].

Carbohydrate requirements should be a minimum of 50% of the total daily energy intake [54], while high glycaemic-index foods can also contribute to postprandial glucose increases [48]. The consumption of sucrose in a diabetic diet remains controversial, although it can be consumed occasionally in small quantities during a meal, preferably one rich in fibre (level E) [48,54]. Artificial sweeteners approved by the European Union are listed in the Official Journal [Directive 94/35/EC]. There has been no demonstrated risk related to the consumption of aspartame during pregnancy [50].
The benefits of splitting meals are still under debate [56]. Three carbohydrate meals per day are essential for avoiding the risk of ketosis, and snacks may be considered on a case-by-case basis. Splitting meals also helps to avoid hunger pangs and to reduce nausea [50].

However, regarding other ‘nutrients’, fibre reduces the postprandial glycaemic response and its recommended consumption is at least 28 g/day [49]. The requirements for vitamins, minerals, iodine and calcium are similar to those of non-diabetic pregnant women. Hydration should include a total of 2.5 L/day of water, with 1 L provided by food and 1.5 L by beverages. The consumption of alcohol is contraindicated during pregnancy.

3.2 Insulin therapy

3.2.1 Glycemic goals

Levels of HbA1c should be as close to normal as possible before pregnancy, determined on a case-by-case basis according to the clinical, social and psychological situation (level E). In non-diabetic women, HbA1c levels are 5.5 ± 0.4% in the non-pregnant state, 5.1 ± 0.3% at the beginning of pregnancy and 5.0 ± 0.3% at the end of pregnancy [59]. In the absence of standardization of the measurement technique, fructosamine is of little benefit.

Recommended capillary blood glucose targets are 60–90 mg/dL (3.3–5.0 mmol/L) before meals, less than 140 mg/dL (7.8 mmol/L) at 1 h after meals and less than 120 mg/dL (6.7 mmol/L) at 2 h after meals [49], although it has recently been suggested that lower postprandial targets should be achieved to reduce the risk of macrosomia [60]. Blood or urine ketone levels should also be measured in cases where capillary blood glucose is more or equal to 200 mg/dL (11 mmol/L; level B).

3.2.2 Insulin regimens

Insulin analogues are often used in T1DM patients. Rapid-acting insulin analogues improve HbA1c with less hypoglycaemia and provide better quality of life [61]. The use of long-acting analogues is associated with a decreased risk of hypoglycaemia, especially nocturnal, compared with neutral protamine Hagedorn (NPH) insulin [62]. Although some concerns have been raised regarding the safety of insulin analogues during pregnancy, recent data favour their use (level C).

Insulin lispro (Eli Lilly, Indianapolis, IN, USA) has shown no teratogenicity or toxicity in animal studies, and was not detected in the cord blood of women treated during labour [63,64]. In a retrospective study of 496 women with T1DM treated with lispro during pregnancy, there was no increase in the rate of CM compared with patients treated with regular insulin [65,66].

Insulin aspart (Novo Nordisk, Bagsvaerd, Denmark) has been compared with human insulin in prospective studies, which showed that the use of aspart was associated with fewer miscarriages, fewer preterm births and better glycaemic control [67,68]. A randomized prospective study of 322 pregnant women with T1DM compared the safety and efficacy of insulin aspart with human insulin, and led to the removal of the precautions for use in its legal notice [56]. Also, there was no demonstration of insulin aspart crossing the placenta, therefore suggesting that it can be used in pregnant women (level A).

Insulin glulisine (Sanofi-Aventis, Paris, France) has not been studied in pregnant women and therefore should not be used.

Insulin glargine (Sanofi-Aventis) has an increased affinity for the insulin-like growth factor (IGF)-1 receptor compared with regular insulin [69]. Animal studies in vivo using high doses of glargine showed increased rates of abortions and intrauterine deaths, but no direct or indirect deleterious effects on gestation, fetal development, delivery or postnatal development when physiological doses were used [70]. In humans, retrospective data available from 437 pregnancies in women with T1DM showed no increase in CM or fetal deaths [67,71,72]. Moreover, glargine does not cross the placenta [69]. Recently, the precautions for use during pregnancy were removed from its legal notice.

Insulin detemir (Novo Nordisk) was compared for safety and efficacy against NPH insulin in a randomized prospective study of 310 pregnant women with T1DM. The results led to the removal of the precautions for use from its legal notice [73].

3.2.3 Use of subcutaneous insulin pumps

The need for strict metabolic control may require treatment with continuous subcutaneous infusion of insulin (CSII), using an external pump, starting from before conception or during pregnancy. Compared with multiple daily insulin injections (MDI), CSII, in addition to resulting in better quality of life, reduces blood glucose excursions, particularly nocturnal hypoglycaemia and early-morning hyperglycaemia [70]. Some authors consider pregnancy a favourable situation for treatment with CSII [71]; however, its use should be reviewed on a case-by-case basis and justifies care at a reference centre (level E).

CSII treatment can achieve rapid and consistent improvement of blood glucose levels when diabetes is poorly controlled by MDI in early pregnancy [71]. Nevertheless, there is a risk of ketoacidosis with CSII, particularly during the third trimester [71]. Furthermore, there has been no clear demonstration that fetal prognosis is improved by treatment with CSII [72]. However, one meta-analysis showed an additional 0.5% reduction of HbA1c in pregnant women treated with CSII, which may be relevant for the prevention of CM and fetal complications [74].

3.3 Diabetes medical management

Diabetes monitoring should be frequent, with a medical visit every two weeks, or once a month if telephone contacts and a system of transmitting data from self-monitoring can be set up. Metabolic monitoring is based on capillary blood glucose measurements, which need to be performed before meals, 1–2 h after meals and at bedtime (level E). However, whether continuous glucose monitoring is of any additional help for controlling diabetes during pregnancy has not yet been extensively studied [75].

Nevertheless, multidisciplinary monitoring and coordination of care are crucial. This can be organized in a day-care clinic if available. Hospitalization in a diabetes or obstetrics
department, depending on the gestational age, is necessary in cases of uncontrolled glycaemia (level E).

4. Effects of pregnancy on chronic complications of diabetes

Although complications of macrovascular disease are rare in women of childbearing age, non-revascularized coronary disease is a contraindication to pregnancy. Indeed, pregnancy places the woman with T1DM at particular risk of worsening of diabetic microvascular disease.

4.1. Diabetic retinopathy

Diabetic retinopathy is a common complication of T1DM, with 60% of patients having some degree of retinopathy 5–15 years after the diagnosis of diabetes. The frequency of retinopathy during pregnancy in a woman whose previous ophthalmological examination was normal is around 10–20%, and usually in a mild or moderate form.

However, worsening of pre-existing retinopathy during pregnancy is common, affecting 25–80% of cases according to the stage of retinopathy before pregnancy: 60% of initially non-proliferative retinopathies worsen to become proliferative in some cases, thus requiring urgent treatment with laser photocoagulation. Proliferative retinopathy also systematically worsens, with a risk of severe complications (intravitreal haemorrhage) and sequelae [76,77].

Several factors are involved in the occurrence or worsening of retinopathy: the pregnancy itself; duration of diabetes; presence of arterial hypertension; severity of the pre-existing retinopathy; and rapid correction of hyperglycaemia in cases of uncontrolled diabetes at the beginning of pregnancy. The risk of worsening is at maximum during the second trimester, and persists for a year after delivery. However, the phenomenon is usually transient, and the long-term retinal prognosis is the same for women with T1DM whether they have been pregnant or not [8,78]. An examination should therefore be done before pregnancy by an experienced ophthalmologist. The presence of retinopathy is not a contraindication to pregnancy, but at-risk lesions should be treated before conception. Ophthalmological examinations should be repeated at the beginning of pregnancy, then every 3 months in the absence of retinopathy, and every month or more frequently if retinopathy is present (regardless of stage) and during the postpartum period.

4.2. Diabetic nephropathy

Fifteen years after the diagnosis of T1DM, a maximum of 20–30% of patients have early-stage nephropathy. During pregnancy, a physiological increase in glomerular filtration occurs. Thus, urinary albumin excretion can increase to the microalbuminuria range (30–300 mg/24 h) in women in whom it was previously normal, and incipient nephropathy (microalbuminuria) can progress to overt nephropathy (proteinuria > 300 mg/24 h) or even to nephrosis (> 3 g/24 h). In women with early-stage nephropathy, and even more so in those with overt nephropathy, the risks of pregnancy-induced hypertension (60% at the end of pregnancy), preeclampsia (40%) preterm delivery, fetal growth restriction and caesarean delivery are all increased. All these risks are further increased in women with renal failure before pregnancy. Women with proteinuria above 3 g/L and/or serum creatinine above 130 µmol/L constitute a group at high risk of maternal and fetal morbidity [20].

In women with nephropathy, but no kidney failure, the renal prognosis remains good. The increase in proteinuria is transient, with no long-term effects on renal function or patient survival [8,78,79]. In women with moderate renal failure prior to pregnancy, some studies have concluded deterioration of renal function [80], while others did not [81]. However, the sample sizes of these studies were small.

In any case, the risks associated with the presence of nephropathy underscore the importance of management before conception, and of multidisciplinary monitoring during the pregnancy involving diabetologists, nephrologists and obstetricians. The treatment of arterial hypertension is particularly important [82].

4.3. Gastroparesis and hyperemesis gravidarum

In women with vomiting or in cases of diabetic gastroparesis, standard antiemetics can be used, and injections of rapid-acting insulin analogues given after meals, with no significant deterioration of glycaemic control [83]. In cases of severe or persistent disorders, however, the consequences should be evaluated (blood electrolytes), a cause should be sought (particularly hyperthyroidism) and upper gastrointestinal endoscopy should be performed.

Severe vomiting in pregnancy (hyperemesis gravidarum) is rare, but justifies hospitalization because of the risks of severely uncontrolled diabetes, dehydration and vitamin B1 deficiency.

5. Modalities of obstetric management

5.1. Choice of delivery site

Obstetric management is likely to take place in a maternity hospital with an appropriate perinatal environment. Proximity is an important factor, as is consideration of the regional distribution of healthcare facilities. It is necessary that diabetologists establish close relationships with nearby maternity hospitals for their T1DM patients (level E). Specific procedures for the management of women with T1DM before, during and after delivery are highly desirable (level E), as is the prevention of neonatal hypoglycaemia, while simultaneously encouraging continuity of the mother–child relationship.

Although there is an increased risk of premature birth, the risk of severe prematurity (< 32 weeks of gestation) only applies to patients with nephropathy.

As the perinatal environment depends on the level of paediatric care, a level I perinatal centre is unlikely to be appropriate unless there is an on-site paediatrician; a level II perinatal centre
is generally sufficient except perhaps in cases of pre-existing nephropathy (level E).

5.2. Obstetric monitoring

In the absence of complications and where glycaemic goals have been met, obstetric monitoring can be based on monthly prenatal medical visits, including screening for urinary infections. Except in particular circumstances, obstetric monitoring can usually be performed by a physician with the cooperation of midwives for certain monitoring procedures (level E).

5.3. Ultrasound monitoring per trimester (as recommended in France)

The first ultrasound, performed at 12–14 weeks of gestation, pinpoints the start date and development of the pregnancy, and the number of embryos. It also allows early morphological study and measurement of the thickness of the nuchal translucency (a warning sign for Down syndrome), which is not influenced by glycaemic control [84].

The second ultrasound, at 22–24 weeks of gestation, aims to detect fetal malformations. This has an overall sensitivity of 70%, but is only 30% in cases of obesity [85]. The sensitivity of ultrasound is 40% for malformations of the heart and large vessels [86]. If there is doubt, however, it can be supplemented by fetal echocardiography, which can boost sensitivity up to 75% [87]. In cases of pre-existing nephropathy, a uterine Doppler study can help to identify any increased risk of preeclampsia and fetal growth restriction (level B).

The third ultrasound, performed at 32–34 weeks of gestation, allows calculation of fetal biometric measurements, assessment of the quantity of amniotic fluid, and determination of fetal presentation and location of the placenta.

A final ultrasound is generally performed at around 37 weeks of gestation for fetal biometric measurements and to help in choosing the delivery route (level E).

5.4. Management of threat of premature delivery

Beta-agonists are contraindicated due to the risk of DKA. If tocolysis is necessary, calcium inhibitors or atosiban should be used in the absence of any contraindications (level B). The neonatal benefits of using glucocorticoids to accelerate fetal lung maturation (betamethasone 12 mg/day for two days) have not been demonstrated in the context of diabetes [88]. However, their use is justified in cases of severe prematurity risk, provided that careful diabetes monitoring is in place and that insulin doses are increased for several days (by 25–50% for three to five days) [89]. Treatment with steroids is not indicated after 34 weeks of gestation (level A).

5.5. Monitoring at end of pregnancy

After 32 weeks of gestation, monitoring fetal vitality is based on repeated recordings of fetal heart rate (FHR; Level E). There is no consensus as to the frequency of recordings. The risk of fetal death in utero within the week following a normal FHR has been calculated to be 1.4% [90]. Taking into account the limitations of the FHR recording for predicting fetal acidosis [30], the occurrence of an unresponsive FHR requires emergency hospitalization. In the absence of complications (nephropathy, preeclampsia, fetal growth restriction) and if glycaemic objectives have been met, two to three FHR recordings per week until delivery can reduce the risk of fetal death in utero compared with the general population [91]. These can be done as an outpatient or through telemonitoring (level C). The benefit of systematic umbilical Doppler has not been demonstrated.

However, if glycaemic goals have not been met, then hospitalization is required to improve blood glucose control, intensify monitoring and allow a decision to be made concerning possible extraction before term if FHR anomalies arise. Although there is no glycaemic threshold that justifies hospitalization, the risk of fetal death increases if mean glycaemic levels exceed 150 mg/dL (8.3 mmol/L) [92]. The choice of hospitalization site, whether in a diabetology or obstetric unit, depends on the term of pregnancy and fetal risk. If there is fetal risk at a viable term, then hospitalization in an appropriate perinatal centre is preferable.

5.6. Delivery

Delivery should take place in an appropriate paediatric environment, and be managed by pre-established protocols for the management of diabetes and anaesthesia. Glucose infusion and intravenous insulin therapy using an electric syringe pump should be delivered, with a flow rate adjusted according to hourly capillary blood glucose monitoring [93]. The goal is to maintain blood glucose close to normal, as the risk of neonatal hypoglycaemia is increased with maternal hyperglycaemia during labour [94].

The delivery is schedule around 38–39 weeks of gestation. In the event of complications (threat of premature birth, premature rupture of membranes, preeclampsia, fetal growth restriction), premature extraction, adapted to the term of the pregnancy, may be necessary in a perinatal centre (level B). If diabetes is unstable despite hospitalization and intensification of insulin therapy, then a decision should be made on a case-by-case basis according to the term and risk of fetal death. Repeated daily monitoring of the FHR or even an oxytocin challenge test and assessment of fetal lung maturity can help in making the decision.

In the absence of complications and if glycaemic objectives have been met, the pregnancy should be allowed to go to term — in other words, to 38–39 weeks of gestation. Waiting beyond this term increases the rate of shoulder dystocia and the risk of fetal death (level E).

The delivery route depends on the obstetric history (uterine scar), suspicion of macrosomia, adequacy of the pelvis (radiopelvimetry), fetal presentation and local conditions. The caesarean rate in T1DM women is 60% overall, compared with 17% in the non-diabetic population, and is related to the increased risk of shoulder dystocia in macrosomic fetuses [95]. There is also an increased risk of genital lesions and haemorrhage during delivery.
Shoulder dystocia is a worrying complication for obstetricians. Its frequency is 1.4% of births in the general population. When birth weight exceeds 4500 g, the rate is 9.2–24% in the absence of diabetes and 20–50% in the presence of maternal diabetes [96]. The risk of fetal death related to shoulder dystocia is around 2–4 per 100,000 births [97]. The risk of brachial-plexus injury increases with each extraction manoeuvre necessary in cases of dystocia. Its frequency is 0.5–3 per 1000 births in industrialized countries [98], and 4–40% in cases of shoulder dystocia [96]. The vast majority of brachial-plexus injuries are transient, however, with a frequency of serious sequelae of 1.5%. It has been reported that brachial-plexus injury resolves spontaneously in the first year in 92% of cases [99]. However, a study of 186 children with such injury showed complete regression in only 22% of cases, and mild or moderate permanent injury in 78% of cases [100].

The risk of shoulder dystocia underlines the importance of a prenatal diagnosis of macrosomia in choosing the delivery route. Such a diagnosis remains difficult, however [101]. Although direct measurement of the biacromial diameter using computed tomography [102] or magnetic resonance imaging may be helpful [103], the positive predictive value of physical examination and ultrasound are poor. In addition, the specificity and negative predictive value should also be taken into consideration to avoid a misdiagnosis of macrosomia, which could increase the caesarean rate. At full term, the mean error for estimations of fetal weight by ultrasound is around 15% [104]. Measurement of the abdominal circumference is a useful criterion in cases of diabetes for predicting birth weights above 4500 g. Also, an abdominal circumference above 36 cm has a positive predictive value of 80% and a negative predictive value of 91% [105]. However, these findings, from a small series, have not been replicated.

Thus, in the absence of consensus, the following management protocol can be proposed: if the fetal weight estimated is above 4000 g or the abdominal circumference is above 36 cm, then caesarean delivery should be planned. Otherwise, the vaginal route is acceptable, provided that the other obstetric parameters allow it (level E).

5.7. Postpartum

After delivery, insulin doses should be reduced to prepregnancy levels. Capillary blood glucose monitoring should be continued until the return to a normal diet and stable insulin doses. Glycaemic targets should also be less strict, particularly as the risk of hypoglycaemia is high and especially if the woman is breastfeeding (level E). Breastfeeding can be done without restrictions and should even be encouraged, considering the epidemiological data suggesting an increased risk of T1DM in the child when artificial feeding is introduced early on (level C).

Contraception before return of the menses can be local or oral with progesterone mini-pills; appropriate contraception must be planned for after the menses return or two months after delivery.

6. Management during delivery

6.1. Diabetes management during delivery

Maternal hyperglycaemia induces fetal hyperinsulinism, which causes hypoglycaemia in the newborn. It is therefore advisable to avoid hypoglycaemia during labour. Delivery is a physical effort that requires glucose delivery to the tissues, thereby justifying intravenous glucose infusions of 150–200 g of glucose per 24 h to cover its needs.

The modalities of insulin administration should be adapted to the knowledge level of the staff. The attending diabetologist should prescribe the insulin regimen. Administration of regular insulin through a continuous intravenous route using an electric syringe pump is the optimal choice. Capillary blood glucose needs to be checked hourly and the insulin infusion rate modified according to protocol [89,93]. In women treated with CSII, the insulin pump can be continued only if the staff has been appropriately trained (level E).

Given the rapid fall in insulin needs immediately after delivery, capillary blood glucose monitoring and insulin dose adjustments also should be continued.

6.2. Management of the newborn

The newborn of the diabetic mother remains fragile and requires the presence of a specifically trained team. It is essential that a paediatrician be present at birth (level E). In the absence of immediate complications, the newborn can remain with the mother, provided that close monitoring is instituted. It is essential to have a neonatology unit within close proximity in case specific care is needed (such as oxygen therapy, continuous enteral nutrition or intravenous fluids).

At the time of delivery, macrosomia can cause bone fractures (humerus or clavicle) or neurological lesions (brachial-plexus palsy) as well as hypoxic–ischaemic encephalopathy in cases of fetal asphyxia. Cardiac septal hypertrophy can result in neonatal cardiac insufficiency and may, on rare occasions, require beta-blocker treatment. It usually resolves within ten to 15 days.

Neonatal respiratory distress syndrome is more frequent in the newborns of diabetic mothers. Several factors can increase the risk, including delay in surfactant maturation, premature birth, caesarean delivery before labour, fetal asphyxia and inhalation.

Of the metabolic disorders, the main risk is hypoglycaemia [blood glucose below 40 mg/dL (2.2 mmol/L) in the full-term newborn, and below 35 mg/dL (1.9 mmol/L) in small-for-gestational-age or premature infants]. Its prevention requires repeated carbohydrate administration (split-feeding) after birth, best done through immediate breastfeeding, or using a bottle or enteral nutrition through tube-feeding if necessary. Blood glucose levels need to be checked within an hour of birth, then every 3 h for at least 48 h. If hypoglycaemia occurs despite enteral intakes (enriched if necessary), a continuous intravenous infusion of 10% glucose solution should be started at a minimum rate of 0.5 g/kg/h, according to blood glucose levels (level E). Glucagon is not used systematically, but according to the teams’
habits in the birthing room, or as an emergency in cases of hypoglycaemia despite administration of glucose at 13 g/kg/day. It can be given intravenously or via intramuscular injection (0.3 mg/kg); some teams use a continuous intravenous route at 1 mg/day (level E).

Hypocalcaemia and hypomagnesaemia are usually asymptomatic; intravenous calcium should be given if serum calcium is less than 1.8 mmol/L. Hyperbilirubinaemia is treated with phototherapy, and polycythaemia by bleeding if necessary to reduce the haematocrit to less than 60%.

7. Conclusion

The management of pregnant women with T1DM needs to begin before the pregnancy begins. Educational efforts must be made in this regard, as the rate of pregnancy planning remains insufficient and the frequency of congenital malformations remains high. Optimal treatment aiming to lower blood glucose levels to as near normal as possible reduces most of the risks associated with diabetes. The rates of macrosomia and caesarean delivery are, nevertheless, still high. A near-normal pregnancy can be achieved in the majority of cases, albeit requiring intensive medical procedures, and such management requires multidisciplinary collaboration.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


