Trends in Anaesthesia and Critical Care 24 (2019) 26–31

Contents lists available at ScienceDirect

Trends in Anaesthesia and Critical Care

journal homepage: www.elsevier.com/locate/tacc

Review

Implications of diabetes in obstetric anaesthesia

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ARTICLE INFO

Article history:
Received 29 April 2018
Received in revised form
11 July 2018
Accepted 12 July 2018

Keywords:
Obstetric anaesthesia
Diabetes
Labour pain
Caesarean section
Gestational diabetes

ABSTRACT

Diabetes during pregnancy can be classified as gestational diabetes mellitus (GDM) or pre-existing diabetes. Many women identified as having diabetes mellitus for the first time in pregnancy are classified as having GDM, although they may actually have pre-existing diabetes. This diagnosis has significant implications for obstetric anaesthesia with regards to maternal and fetal outcomes.

Parturients with diabetes, especially pre-existing diabetes are at increased risk of fetal anomalies, macrosomia, poorly controlled diabetes during pregnancy, and neonatal complications, especially shoulder dystocia. Furthermore, a long duration of pre-existing diabetes could put parturients at risk of other concurrent comorbidities associated with diabetes. These patients should be screened antenatally for associated comorbidities and be managed in a multi-disciplinary approach. The anaesthetist should be involved in the third trimester to screen and counsel the patient on suitable analgesia and anaesthetic options.

The aim of this review is to discuss the anaesthetic considerations of parturients with diabetes, focusing especially on the principles of prepartum assessment, perioperative management of glycemic control according to the latest guideline recommendations, and anaesthetic considerations during caesarean section, taking into account of the patient's comorbidities.

Contents

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https://doi.org/10.1016/j.tacc.2018.07.008
2210-8440/

Abbreviations

BMI	body mass index
GDM	gestational diabetes mellitus
HbA1C	glycated hemoglobin
IV	intravenous
SC	subcutaneous

1. Introduction

Diabetes during pregnancy has been increasing in recent years and can be commonly classified as gestational diabetes mellitus (GDM) or pre-existing diabetes. Many women who are identified as having diabetes mellitus for the first time in pregnancy are classified as having GDM, although they may actually have pre-existing diabetes. The implications for obstetric anaesthesia could be significant in affecting maternal and fetal outcomes [1–5].

Risk factors for diabetes during pregnancy include previous history of GDM, previous large-for-gestational age infant, higher parity, advanced maternal age, family history of diabetes mellitus, non-white race, and obesity [2]. Parturients with diabetes, especially pre-existing diabetes are at increased risk of fetal anomalies, poorly controlled diabetes during pregnancy, and neonatal complications [6]. Furthermore, patients with a long duration of pre-existing diabetes could be at risk of other concurrent comorbidities associated with diabetes [7]. These are important considerations for the anaesthetist in the prepartum evaluation, provision of labour analgesia and perioperative management of Caesarean section. Guidelines for the screening, intrapartum and intra-operative management of these parturients are constantly evolving, but all emphasize on the need for good glycemic control during pregnancy and close glycemic monitoring during labour and operative delivery [3–5].

The aim of this review is to discuss the anaesthetic considerations of parturients with diabetes, focusing especially on the principles of prepartum assessment, perioperative management of glycemic control taking into account the latest guideline recommendations, and main anaesthetic considerations during caesarean section.

2. Epidemiology

The rate of hospital delivery with diabetes is estimated to be 4.3%–6.5% in the United States between 1994 and 2004, and appears to be increasing [8,9] with the rise of obesity and type 2 diabetes in the underlying population [10,11]. The majority of these women identified as having diabetes mellitus for the first time in pregnancy are classified as having GDM, although they may actually have pre-existing diabetes [2]. Indeed, of over 1 million hospital delivery discharges in the United States over an 11-year period, GDM was the most common (84.7%), followed by type 1 (7%), type 2 (4.7%), and unspecified diabetes (3.6%) [8]. Thus, a postpartum oral glucose tolerance test is required to distinguish between GDM and pre-existing diabetes. This distinction is important because pre-existing diabetes is associated with an increased risk of fetal birth defects, and women with pre-existing diabetes in pregnancy may have higher antenatal glycated hemoglobin (HbA1C), poorer glycemic control, greater insulin requirements and higher pre-pregnancy body mass index (BMI) compared to those with GDM [6].

GDM is defined as impaired glucose tolerance with onset during pregnancy and that usually disappears shortly after a woman gives birth [4]. Changes in metabolism during pregnancy is associated with fasting hypoglycemia, due to insulin-independent glucose uptake by the placenta, together with increased circulating diabetogenic placental hormones, resulting in postprandial hyperglycemia and carbohydrate intolerance. Insulin resistance increases exponentially during the second trimester and levels off toward the end of the third trimester [5].

Risk factors for GDM include previous history of GDM, previous large-for-gestational age infant, higher parity, advanced maternal age, family history of diabetes mellitus, non-white race, and obesity [10–12]. The odds of developing GDM increase from 2.14 (95% CI 1.82–2.53), 3.56 (3.05–4.21), to 8.56 (5.07–16.04) among overweight, obese, and severely obese respectively, compared with normal-weight pregnant women [13]. GDM is also associated with a higher risk of developing type 2 diabetes later in life in both the mother and child [14].

3. Fetal morbidity and mortality associated with diabetes in pregnancy

The incidence of fetal structural defects associated with maternal pre-existing diabetes is three-to fourfold higher than that caused by non-diabetic pregnancy and is also higher in mothers with type-2 diabetes compared to type-1 diabetes [1,15,16]. Diabetes affects embryogenesis. The anomalies and organs involved include: central nervous system (anencephaly, spina bifida), skeletal system (limb defects), renal system (renal agenesis), cardiovascular system (transposition of the great vessels, ventricular septal defects, atrial septal defects, coarctation of the aorta), and gastrointestinal system (duodenal atresia, anorectal atresia) [17]. There is also an increased risk of neonatal hypoglycaemia, hyperbilirubinemia, fetal respiratory distress syndrome as hyperglycemia delays fetal lung maturity, and intrauterine death [7].

Diabetes in pregnancy is associated with an increased rate of large-for-gestational-age infant and shoulder dystocia. Verily, diabetes is independently associated with higher odds of shoulder dystocia of 1.7 [18]. While the incidence of shoulder dystocia increases with fetal weight, occurring in 0.6–1.4 percent of infants with a birth weight of 2500 g–4000 g, and increasing to a rate of 5–9 percent among the fetuses weighing 4000–4500 g born in mothers without diabetes [18–20], when maternal diabetes is present, the incidence of shoulder dystocia is even higher for infants of the same birth weight, compared to those born to non-diabetic mothers [18]. Fetal and maternal morbidity increases with the number of manoeuvres employed to resolve shoulder dystocia [21].

In order to reduce the incidence of fetal malformation and structural anomalies, fetal macrosomia, intrauterine death and neonatal morbidity, diabetic parturients should strive to maintain maternal glucose control near physiologic level before conception and throughout pregnancy [22]. It is also recommended that

patients with well-controlled diabetes be allowed to progress to their expected date to delivery as long as antenatal testing remains reassuring [22]. However early delivery may be indicated in some patients with vasculopathy, nephropathy, poor glucose control or a prior stillbirth, and "expectant management beyond the estimated due date is generally not recommended". Caesarean delivery may also be considered if the estimated fetal weight is greater than 4.500 g in women with diabetes [22,23].

4. Maternal medical conditions associated with pre-existing diabetes

Diabetes is associated with higher risk pregnancy and delivery complications, resulting in higher maternal perinatal morbidity and mortality. This is especially in women with pre-existing diabetes, with maternal perinatal morbidity and mortality are higher in type 2 diabetes compared with type 1 diabetes in pregnancy [24].

Increased morbidity is attributed to the associated comorbidities and more difficult deliveries. Diabetic mothers have a higher incidence of large-for-gestational age infants [6] and associated pre-pregnancy obesity and advanced maternal age [1]. There is a higher rate of instrumentally assisted delivery, episiotomy and conversion to urgent caesarean section.

Long-standing pre-existing diabetes is associated with a higher risk of hypertension, pre-eclampsia with possible end-organ involvement. Pre-eclampsia presenting as new onset hypertension associated with proteinuria or organ dysfunction in the second half of pregnancy [25] is increased two to four-fold among women with type 1 or type 2 diabetes. These women may be prescribed low-dose aspirin after 12 weeks gestation to reduce the occurrence of pre-eclampsia and preterm birth and administration of these could have implications to regional anaesthesia [26,27] End-organ involvement consequent to prolonged diabetes include retinopathy, nephropathy, cardiac autonomic neuropathy and ischemic heart disease. Worsening proteinuria during pregnancy is common in women with diabetic nephropathy due to increased glomerular filtration rate [26]. Parturients with diabetic nephropathy tend to have concomitant chronic hypertension (42%) with 60% of women manifesting hypertension by the third trimester; 41% developed pre-eclampsia; 63% had proliferative retinopathy prior to pregnancy, and 75% underwent caesarean section delivery [28]. Active or previously treated ischemic heart disease is reported to occur in 1 of 350 diabetic pregnant women [29]. Cardiac autonomic neuropathy occurs in 11–33% amongst young adults with diabetes [30]. Autonomic neuropathy in diabetic parturients can lead to orthostatic hypotension, cardiac arrhythmias, silent myocardial ischemia and painless infarction [31]. The risk of ischemic stroke is increased four-to eight-fold in relatively young adult women with type 1 or type 2 diabetes compared with nondiabetic women of similar age, although the absolute risk is still low (4% over 20 years of follow-up of women with type 1 diabetes) [7].

Mothers with type 1 diabetes could also have other associated autoimmune conditions, most importantly autoimmune thyroid disease. Autoimmune thyroid disease is common (35–40%) in women with type 1 diabetes, and previously undiagnosed patients should be screened for thyroid dysfunction before pregnancy. The prevalence of hypothyroidism is increased in women with type 2 diabetes compared to reference populations [7,32].

5. Diagnosis and management of diabetes in pregnancy

International guidelines are designed to allow early detection and tight control of diabetes. Women with gestational diabetes in a previous pregnancy should be offered either early self-monitoring of blood glucose or a 75 g 2-h OGTT (oral glucose tolerance test) as soon as possible after booking (first or second trimester), and a further 75 g 2-h OGTT at 24–28 weeks if the results of the first OGTT are normal. Women with otherwise normal pregnancies should have an OGTT at 24–28 weeks [3].

The developing fetus and increase circulating placental hormones cause insulin requirements to fluctuate during pregnancy and thus frequent titration is needed for mothers who are on insulin for glycaemic control. Targets for pregnant mothers with pre-existing diabetes and gestational diabetes are fasting serum glucose $\leq$5.0 mmoL/L and $\leq$5.3 mmoL/L respectively. For mothers with pre-existing diabetes, insulin is the preferred medication for type 1 and type 2 diabetes not adequately controlled with diet, exercise, and metformin. For mothers with gestational diabetes, a trial of diet, physical activity, and lifestyle counselling is usually attempted before proceeding to metformin and insulin for optimal sugar control [33]. Women with type 1 diabetes are at high risk for hypoglycemia, thus hypoglycemia education is important. Mothers with autonomic neuropathy may have reduced symptomatic awareness of hypoglycaemia and inadequate counter regulatory responses [34]. Women with type 2 diabetes are at risk for obesity, hence they are recommended to avoid excessive weight gain during pregnancy. Capillary ketone testing is advocated for women with type 1 diabetes when hyperglycaemic and for all women with diabetes including, GDM when acutely unwell [3].

6. Role of the anaesthetist

The anaesthetist is involved in peripartum care through the administration of labour epidural analgesia or anaesthesia for caesarean section (see Table 1). Proper prepartum assessment should be conducted to screen for associated comorbidities especially in parturients with pre-existing diabetes. Patients with multiple end-organ involvement should be managed in a tertiary maternity care center with a multi-disciplinary high-risk maternal-fetal obstetrics unit [35].

7. Prepartum assessment

Women with pre-existing diabetes should ideally have been screened for concomitant comorbidities at the booking of pregnancy, and receive multi-disciplinary antenatal care that is coordinated by the obstetrician [35]. The patient should also have an early assessment by an anaesthetist in the third trimester to identify any potential problems that may develop during labour or caesarean section [3]. This includes reviewing history of prior pregnancies and comorbidities such as hyperlipidemia and other cardiac risk factors, hypertension, albuminuria, ischemic heart disease, peripheral vascular disease, peripheral and autonomic neuropathies, thyroid disease and obesity [7]. Some women with pre-existing diabetes and other risk factors for developing pre-eclampsia may be prescribed prophylactic aspirin after 12 weeks gestation. This will usually be discontinued a week prior to elective caesarean section or induced delivery, according to the discretion of the obstetrician [36,37]. This may be of relevance to the anaesthetist when performing central neuraxial anaesthesia. The pre-operative assessment setting is also opportune to counsel the patient about neuraxial analgesia and anaesthesia options during labour and operative delivery, so that these can be incorporated into the patient's birth plans in advance [38].

8. Prepartum investigations

The anaesthetist may like to review the patient's full blood count, HbA1C, renal panel, thyroid status, albuminuria, blood pressure trend, oral hypoglycemic agents, insulin regimen and

Table 1
Broad management goals across perioperative timeline. The overall goals of management are: (i) to avoid clinically significant hyper- or hypoglycemia (ii) to conduct a balanced anaesthesia that takes into consideration the patient's comorbidities associated with pre-existing diabetes (see Table 1).

Prepartum assessment	Intrapartum management	Postpartum management
(i) Screen for end-organ involvement in patients with pre-existing diabetes in the third trimester, order and review relevant preoperative investigations*	Diabetic parturients may receive labour epidural analgesia if they request for it, as long as there are no contraindications. For caesarean section, the choice between general anaesthesia and regional anaesthesia should be individualized according to the patient and her comorbidities and urgency of surgery.	Reduce insulin dose of women with insulin-treated pre-existing diabetes immediately after birth and monitor their blood glucose levels carefully to establish the appropriate dose.*
(ii) Verify control of blood sugar	Ensure adequate fasting, gastric chemoprophylaxis, difficult airway equipment at hand prior to induction of general anaesthesia.	Discontinue insulin and oral hypoglycemic agents for women with gestational diabetes after birth.*
(iii) Anaesthesia counselling for risks associated with labour epidural analgesia and anaesthesia for caesarean section. Screen for potential difficult airway	Choice of mode of regional anaesthesia - spinal, epidural or combined spinal-epidural, depends on complexity of surgery, potential for obstetric complications, as well as any significant autonomic neuropathy or cardiac disease.	Women with insulin-treated pre-existing diabetes are at increased risk of hypoglycaemia in the postnatal period, especially when breastfeeding, and should be advised to have a meal or snack available before or during feeds.*
(iv) To give instructions for management of insulin during fasting for elective surgery	Avoid profound intraoperative hypotension, especially in mothers with co-existing coronary artery, cerebrovascular or renovascular disease. This can be achieved through careful choice of anaesthetic technique, volume expansion, close monitoring and use of vasopressors where indicated.	
	For patients under regional anaesthesia, monitor capillary plasma glucose every hour and titrate SC/IV insulin and IV dextrose as required to maintain it between 4 and 7 mmol/L*	
	For patients under general anaesthesia, monitor blood glucose every 30 min from induction of general anaesthesia until after the baby is born and the woman is fully conscious.*	

Legend: IV = intravenous; SC = subcutaneous.

other medications. A targeted history and physical examination looking out for symptoms of coronary heart disease should be elicited especially in patients with long standing type 1 or type 2 pre-existing diabetes. Selected patients may need electrocardiogram or echocardiography, especially in advanced maternal age ≥35 years old and duration of type 1 diabetes ≥15 years or duration of type 2 diabetes ≥10 years, to screen for the presence of ischemic heart disease or cardiac autonomic neuropathy [7]. A reduction in variability of heart rate (measured by the R-R interval) could be an early indicator of cardiac autonomic neuropathy [31].

9. Anaesthetic management of labour and delivery

Regular blood glucose monitoring and ensuring that the blood glucose is within normal range reduces the risk of neonatal hypoglycaemia. Capillary plasma glucose should be monitored regularly (up to every hour) during labour and birth in diabetic parturients to ensure that it is maintained between 4 and 7 mmoL/L [3]. Oral hypoglycemic agents should be discontinued upon the onset of labour, and capillary plasma glucose managed with subcutaneous insulin sliding scale. Intravenous dextrose and insulin infusion should be considered for women with type 1 diabetes, as well as women with poorly controlled gestational diabetes or type 2 diabetes whose whose capillary plasma glucose is not maintained between 4 and 7 mmoL/L, as an infusion allows more rapid titration of insulin levels [3]. While in labour, intravenous glucose should be provided to prevent catabolism, starvation ketosis, and insulin-induced hypoglycemia. The physiological amount of glucose required to prevent catabolism in an average non-diabetic adult is about 120 g/day or 5 g/h [39].

Diabetic parturients may receive labour epidural analgesia if they request for it, as long as the anaesthetist has screened the patient's latest laboratory values and vital signs and ruled out any contraindications such as severe pre-eclampsia with its associated coagulopathy, and the patient is not on any anti-coagulation. Aspirin alone is not a contraindication to central neuraxial blocks [40]. Effective epidural analgesia can abolish the sympathetic stress response to labour, decrease circulating adrenaline, glucose, and other stress hormones [41].

The anaesthetist should also briefly review the last ultrasound estimate of the fetal weight to estimate the risk of shoulder dystocia, as macrosomia happens more frequently in diabetic parturients. Despite the inaccuracy of ultrasound in estimating fetal birth weights, it remains the most reliable predictor of shoulder dystocia [42]. Current guidelines suggest caesarean delivery if the estimated fetal weight is greater than 4.500 g in women with diabetes [22]. Nevertheless, if the parturient is allowed to go into labour, the anaesthetist may be involved in offering labour analgesia. Epidural anaesthesia may be associated with an increased risk of shoulder dystocia [43] because patients often are not allowed to change into alternate positions of delivery such as lateral, squatting or even kneeling on hands and knees after the epidural catheter is inserted [44]. Thus, when requested, using a minimum effective solution to prevent motor blockade while achieving adequate analgesia is desirable. There are mnemonics available to list a sequence of first-line manoeuvres including episiotomy such as 'HELPERRR' [45,46]. When first line and second line manoeuvres fail, symphysiotomy and hysterotomy have been suggested as last resort. The presence of a working epidural catheter for labour analgesia can allow for the performance of episiotomy and symphysiotomy with greater maternal comfort. It also allows for rapid top-up of the epidural when the decision to perform a hysterotomy is made. The disadvantage is that the mother may require more assistance to get into the 'all-fours' position that is required to dislodge the shoulder [45].

10. Anaesthetic management for caesarean section

10.1. Preoperative instructions

The anaesthetist may be required to give preoperative instructions for fasting and medications for a paturient scheduled for elective caesarean section. In general, all short acting oral hypoglycemic agents such as metformin should be discontinued on the morning of surgery. If the patient is on intermediate acting insulin, she can administer one third of her usual morning dose but no regular insulin. It is recommended to check capillary plasma glucose levels hourly while the patient is waiting for surgery to ensure that it is within desired range [3]. No guidelines exist for preoperative parturients, but generally glucose control should be maintained within the same range as labouring parturients of between 4 and 7 mmoL/L.

10.2. General anaesthesia versus regional anaesthesia

The choice of general anaesthesia versus regional anaesthesia is predicated upon the risks and benefits of each technique individualized to the patient.

The incidence of difficult obstetric intubation is higher in parturients due to the physiological changes and weight gain in pregnancy, and has been quoted to be 1:30 [47]. Parturients with long-standing pre-existing diabetes may have a more challenging airway if they develop the diabetic stiff-joint syndrome, in which tissue glycosylation of collagen happens due to chronic hyperglycema, resulting in limited atlanto-occipital movement during head tilt [48]. Furthermore, GDM and pre-existing type 2 diabetes in the parturient is associated with obesity too, which increases the likelihood of difficult airway [49]. Thus, for all parturients undergoing general anaesthesia, equipment for routine and emergency airway management should be available prior to the induction of anaesthesia. If tracheal intubation is unsuccessful in the first attempt, the difficult airway algorithm should be initiated [50].

Most international guidelines recommend neuraxial techniques over general anaesthesia due to concerns over the risks of aspiration of gastric content and failed endotracheal intubation in general anaesthesia as described above [51,52]. Regional anaesthesia for elective caesarean section is becoming more popular, and its incidence has risen from 69.4% in 1992 to 94.9% in 2002 in the United Kingdom [53,54]. In healthy diabetic parturients with no discernible organ-involvement, the choice of spinal, epidural or combined spinal-epidural anaesthesia may yield similar outcomes in terms of failure rate, need for additional intraoperative analgesia, maternal satisfaction and neonatal outcomes. Spinal anaesthesia is associated with reduced time from start of the anaesthetic to start of the operation and may be more appropriate in urgent caesarean sections when there is fetal compromise. However, it is also associated with an increased incidence of hypotension requiring treatment, via volume expansion with a non-dextrose containing balanced salt solution and short-acting vasopressors such as ephedrine or phenylephrine [55,56]. Nevertheless, in severe diabetics with cardiac autonomic neuropathy, epidural anaesthesia or combined low dose spinal-epidural (CSE) may be the preferred technique over spinal anaesthesia due to the slower onset of sympathetic blockade [57]. Low-dose CSE combines the reliability of intrathecal blockade with the flexibility of an epidural catheter, and allows gradual titration of the block, and prolongation of the block as required while maintaining hemodynamic stability. Compared to epidural analgesia, low-dose CSE technique produces better analgesia and muscle relaxation, and less hypotension when compared to epidural anaesthesia for caesarean section [58–60]. Epidural volume expansion (EVE) has also been used in CSE to extend the level of the block after administration of a low intrathecal dose [61,62]. Low dose CSE has been demonstrated to be produce hemodynamic stability in parturients with severe cardiac disease undergoing caesarean section [58,63].

If a diabetic parturient undergoes general anaesthesia for caesarean section, it is recommended that capillary plasma glucose should be monitored regularly (up to every 30 min) from induction of general anaesthesia until after the baby is born and the woman is fully conscious [3]. Regardless of anaesthesia technique, profound intraoperative hypotension should be avoided, especially in mothers with co-existing coronary artery, cerebrovascular or renovascular disease.

11. Postpartum care

Women with insulin-treated pre-existing diabetes should have their insulin dosage reduced immediately after birth, and close monitoring of their blood glucose levels performed to establish the appropriate dose [3]. Women with GDM should discontinue blood glucose-lowering therapy immediately after birth [3]. Postnatal testing of fasting glucose should be carried out at 6–13 weeks postpartum, or with serum HbA1c beyond 13 weeks postpartum to confirm the diagnosis of GDM.

12. Conclusion

Pre-existing and gestational diabetes is increasingly prevalent in pregnancy. Pre-existing diabetes in particular, is associated with other serious comorbidities that affect maternal and fetal perinatal morbidity and mortality. These patients should be screened antenatally for associated comorbidities, and be managed in a multidisciplinary approach, with the involvement of the anaesthetist in the third trimester to screen and counsel the patient regarding analgesia and anaesthetic options. During labour and caesarean delivery, close blood glucose monitoring is emphasized to reduce neonatal and maternal hypoglycemia.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflict of interest for this article.

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