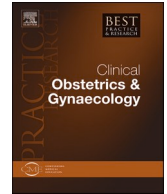


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An overview of diabetes mellitus in pregnant women with obesity

Mohammed Bashir^{a,d,*}, Yassin Fagier^b, Badreldeen Ahmed^{c,e,f}, Justin C Konje^{c,e,g}

^a Qatar Metabolic Institute, Hamad Medical Corporation, Doha, Qatar

^b Women's Clinical Management Group, Sidra Medicine, Doha, Qatar

^c Feto Maternal Centre, Al Markhiya Street, Doha, Qatar

^d Endocrinology, Weill Cornell Medicine, Doha, Qatar

^e Obstetrics and Gynaecology, Weill Cornell Medicine, Doha, Qatar

^f Obstetrics and Gynaecology, Qatar University, Doha, Qatar

^g Obstetrics and Gynaecology, University of Leicester, UK

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ABSTRACT

Rates of obesity are increasing world-wide with an estimated 1 billion people projected to be obese by 2030 if current trends remain unchanged. Obesity currently considered one of the most significant associated factors of non-communicable diseases poses the greatest threat to health. Diabetes mellitus is an important metabolic disorder closely associated with obesity. It is therefore expected that with the increasing rates of obesity, the rates of diabetes in pregnancy will also be rising. This disorder may pre-date pregnancy (diagnosed or undiagnosed and diagnosed for the first time in pregnancy) or may be of onset in pregnancy. Irrespective of the timing of onset, diabetes in pregnancy is associated with both fetal and maternal complications. Outcomes are much better if control is maximised. Early diagnosis, multidisciplinary care and tailored management with optimum glycaemic control is associated with a significant reduction in not only pregnancy complications but long-term consequences on both the mother and offspring. This review brings together the current understanding of the pathogenesis of the endocrine derangements that are associated with diabetes in pregnancy how screening should be offered and management including pre-pregnancy care and the role of newer agents in management.

1. Epidemiology

Obesity is the most common chronic metabolic disorder that affects women of reproductive age. The World Health Organization (WHO) defines obesity as a chronic complex disease with excess adiposity that can impair health [1]. It uses the Body Mass Index (BMI) as a surrogate marker of obesity and defines normal weight as BMI < 25 kg/m², overweight as BMI between 25 and 29.9 kg/m², and obesity as BMI ≥ 30 kg/m². Obesity is recognised as a global pandemic that is projected to affect 1 billion persons by 2030 [1]. An analysis of the Global Burden of Disease Study 2019 (GBD 2019) showed that the prevalence of obesity among women almost tripled (6%–16%) between 1980 and 2020 [2,3]. Besides, among women of childbearing age [20–49], the prevalence of overweight ranged between 29 and 50%, while the prevalence of obesity ranged between 10% and 25% [2,3]. However, there is a vast global variability in the prevalence of obesity among pregnant women. In the United States, 26.7% and 29.5% of women with a live birth in 2020 were overweight and obese, respectively. In Qatar, a study that included 2000 women with a live birth showed that 31.0% were overweight

* Corresponding author. Qatar Metabolic Institute, Hamad Medical Corporation, Doha Qatar.

E-mail address: Mbashir@hamad.qa (M. Bashir).

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and 40.7% were obese at the start of pregnancy [4]. Similarly, data on 14,568 deliveries in Saudi Arabia showed that – 32.9% of the women were overweight while 35.6% were obese [5]. A Study from India showed that – depending on the region-obesity affects 12–71 % of pregnant women [6].

The current WHO-BMI cutoffs underestimate the prevalence of obesity – as a condition of excess adiposity associated with health impairment. Amongst the non-communicable diseases associated with obesity is diabetes mellitus. Observational longitudinal data have shown that Asians with a BMI >25 kg/m² are at a higher risk of developing type 2 diabetes (T2D) [7]. A large prospective study showed that the BMI equivalent for that age and sex-adjusted incidence of T2D was 30.0 kg/m² for Caucasians, 23.0.9 kg/m² for South Asian populations, 28.1 kg/m² for Afro-Caribbeans, 26.9 kg/m² for Chinese populations, and 26.6 kg/m² for Arabs [8]. The prevalence of obesity might, therefore, be higher than reported in the literature.

Gestational diabetes is the most common medical complication of pregnancy. The International Diabetes Federation (IDF) estimates that the global prevalence of GDM is 14.0% [9]. The lowest prevalence of 7.0% was reported in North America, while the highest of 27.6% was in the Middle East and North Africa (MENA). Pre-existing diabetes is estimated to affect 1.0% of all pregnancies worldwide [10]. Similar to GDM, the MENA region had the highest prevalence of pre-existing DM (2.4%), while the lowest prevalence was in Europe (0.5% [10]. More crucially, the IDF reported a twofold increase in the prevalence of pre-existing DM between 1990 and 2000(10).

2. Metabolic complications of obesity

Due to overnutrition, adipose tissue expands to store excess energy in the form of triglycerol [11]. If the amount of stored fat exceeds the storage capacity of the subcutaneous adipose tissue, more fat “spills” into the visceral adipose tissue [11]. Indeed, metabolically healthy obese adults were found to have more subcutaneous fat and less liver and visceral fat compared to a metabolically unhealthy matched group [12]. Stefan et al. showed that metabolically unhealthy lean subjects also have excess visceral and liver fat. Excess visceral and liver fat deposition is associated with increased secretion of inflammatory cytokines, low-grade inflammation, and insulin resistance [13]. Hence, women with pre-pregnancy obesity might have already exceeded their subcutaneous fat storage capacity and have pre-existing elevated liver and visceral fat. Alternatively, excessive gestational weight gain might “tip” some women off their set point and induce excessive liver and visceral fat deposition. Such derangement compounds the effects of diabetes in pregnancy in women with obesity.

3. Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) is a common metabolic disorder affecting about 14% of all pregnancies [9]. It results from increased insulin resistance and reduced insulin secretion [14]. The risk of GDM increases with increased BMI in a dose-dependent pattern. A meta-analysis by CHU et al. showed that the odds ratio of developing GDM were 2.14, 3.56, and 8.56 among overweight, obese, and severely obese women compared with normal-weight pregnant women, respectively [15]. Similarly, Santos et al. showed that, compared to normal weight, the odds ratio of GDM was 2.2, 4.0, 5.8, and 7.6 in women with overweight, obesity class I, II, and III, respectively [16]. As outlined above, fat distribution is central to the metabolic effect of obesity. Indeed, Alwash et al. showed that visceral adiposity carried the highest risk of GDM compared to central and general adiposity [17].

Furthermore, gestational weight gain might tip off the subcutaneous storage capacity of some women, leading to insulin resistance or exacerbation of a pre-existing insulin resistance state and hence increasing the risk of GDM. Santos et al. showed that, within weight classes, the higher the gestational weight gain, the higher the risk of GDM [18]. Compared to women of normal BMI who had a normal weight gain, the odds of GDM were 4.4, 5.1, and 7.8 in obese women with low, adequate, and high gestational weight gain, respectively [16].

As pregnancy progresses, the increase in the secretion of placental hormones such as human placental lactogens (HPL), cortisol and growth hormone induces maternal insulin resistance to ensure adequate flow of glucose to the rapidly growing fetus [19]. However, to avoid excessive nutrient transfer to the fetus, the pancreatic beta-cells expand in number and function to increase insulin secretion to counterbalance the insulin resistance [20]. Longitudinal assessment of insulin sensitivity and secretion before, during, and after pregnancy were central to understanding the pathogenesis of GDM [19,21]. Women with GDM have evidence of reduced insulin sensitivity, which worsens during pregnancy and returns to baseline after delivery. However, there is also evidence of beta-cell dysfunction that persists during and after delivery [19]. Hence, GDM results from the inability of the beta-cells to expand to meet the increase in insulin resistance during pregnancy [20]. As outlined by Taylor’s personal fat threshold hypothesis, due to excess visceral fat deposition, the liver production of very low-density lipoprotein increases (VLDL), leading to an increase in pancreatic lipid deposition and beta-cells failure [22].

Women with GDM are at an increased risk of gestational hypertension, preeclampsia, macrosomia, and delivery by C-section [23]. Furthermore, 50% of the women with GDM progress to type 2 diabetes mellitus (T2D) within five years of the index pregnancy [24]. Offspring of women with GDM are also at higher future risk of childhood obesity and early onset T2D(25). While there is agreement on the existence of GDM as a severe medical complication of obesity, there is a dispute on the definition of GDM. There are currently multiple screening methods and different glucose thresholds for diagnosing GDM(26). We recommend that each centre has a unified method to screen and diagnose GDM(26).

4. Screening for diabetes in obese women

All obese women should be screened for diabetes in pregnancy. The timing and method of screening vary across different guidelines [27]. We recommend screening all women in the first trimester with fasting blood glucose and HbA1c to rule out pre-existing diabetes and if these are normal, a 75 g OGTT at 24–28 weeks.

This screening with an OGTT is not recommended for obese women who have had bariatric surgery. This is more so for those with malabsorptive bariatric surgery. In these women, the dumping syndrome makes the traditional glucose load unreliable as a screening test. For these women, we recommend (in keeping with general recommendations) that in addition to fasting and HbA1c, consideration should be given to serial blood glucose measurements instead of the OGTT.

5. Type 2 diabetes in pregnancy

The prevalence of T2D in pregnancy has doubled over the last 30 years [10]. T2D in pregnancy is associated with severe maternal and fetal complications compared to women with no diabetes [28,29]. Among women with T2D, Murphy et al. reported a congenital malformation rate of 40.5 per 1000 births, almost twice the rate in the general population in England of 21.3 per 1000 births^{28,29}. In a cohort of 383 pregnant women, Bashir et al. compared those with and without T2D for maternal and fetal complications. They showed that complications including gestational hypertension (GH), pre-eclampsia (PET), preterm labour, C-section, large for gestational age (LGA) and NICU admissions were increased by 50–100% [28]. Pregnancy outcomes in women with obesity and diabetes are affected by several factors, which include pre-pregnancy BMI, pre-pregnancy HbA1c, gestational weight gain and third-trimester HbA1c [28]. T2D results from an accelerated loss of beta-cell function. Hence, as pregnancy progresses, the beta-cells cannot expand, and hyperglycemia worsens, requiring augmentation of medical care.

6. Complications of obesity and diabetes in pregnancy

6.1. Hypertensive disorders of pregnancy

Gestational hypertension (GH) and preeclampsia (PET) are associated with an increased risk of maternal and fetal complications, including preterm labour, small for gestational age, and c-section delivery [30]. The risk of GH and PET is increased in women with obesity in a dose-response relationship [16,31]. Indeed, a modelling study from Poland identified Obesity as the leading risk factor for GH and PET [32]. A critical link between obesity and the complications of GH and PET is insulin resistance [30]. Chen et al. performed insulin clamping studies and reported an increase in insulin resistance and a reduction in insulin sensitivity and beta-cell function among women with GH compared to those with normal blood pressure [33]. Jin et al. reported a positive correlation between insulin resistance and GH [34]. Excessive GWG can induce/exacerbate the insulin resistance status in obese women. Among obese women, Santos et al. reported an increased dose-response effect of gestational weight gain on both GH and PET [16]. GDM and T2D are associated with an increased risk of GH and PET, irrespective of obesity [28,35].

While the pathogenesis of PET is not clearly understood, poor placentation seems to play a central role. Poor placentation could result from vasculopathy secondary to Insulin resistance, hyperinsulinemia, elevated triglycerides, and chronic inflammation seen in women with obesity and women with T2D [36]. Placental hypoxia induces an inflammatory process, disrupting the balance of angiogenic factors and inducing platelet aggregation, resulting in endothelial dysfunction [30].

6.1.1. Preeclampsia prevention

As outlined above, there is a dose-response relationship between Obesity and Preeclampsia. Aspirin – started between 12- and 16-weeks gestation, has been shown to reduce the risk of preterm preeclampsia in high-risk patients. Obesity is widely considered one of the risk factors of preeclampsia, and aspirin should be started if there is an additional risk factor such as multiple pregnancy, age > 35 years, Nulliparity, family history of preeclampsia, history of SGA, and IVF(27). The recommended dosage is 100–150 mg/day [37].

6.2. Large for gestational age

A dose-dependent relationship exists between Obesity and the rates of large for gestational age (LGA) [16]. This dose-response relationship is independent of GDM or excessive GWG [36]. Kim et al. reported on 820,000 deliveries in the United States and showed that in women with obesity and no GDM or excessive GWG, there was a dose-dependent increase in the rate of LGA across the three classes of obesity, 8.6%, 11.9%, and 13.9% respectively [38]. Furthermore, among women with no obesity and no excessive GWG, GDM was still associated with an increased risk of LGA [38]. Among obese women, Santos et al. reported a dose-response relationship between GWG and LGA(16). Similarly, the rates of LGA are higher in women with T2D compared to women with no diabetes [28]. In women with T2DM, LGA is linearly associated with pre-pregnancy BMI, GWG, and first and third-trimester HbA1c [28,39].

In the absence of diabetes, LGA is mediated chiefly through maternal hypertriglyceridemia [36]. However, Anam et al. showed that in obese women, hyperinsulinemia increases placental triglycerides (TG) levels and thus contributes to fetal adiposity [40]. Hence, the increase in TG transportation mediated by hyperinsulinemia could be independent of maternal TG levels. In women with GDM and T2D, LGA is secondary to both hyperglycemia and hypertriglyceridemia [36].

6.3. Small for gestational age (SGA)

Poorly controlled T2D can be associated with maternal vasculopathy which can lead to poor placentation resulting in placental insufficiency and fetal growth restriction [41]. GDM is associated with changes in the structure of the placenta; the surface area and volume can be affected, as well as histological changes, including an increased volume of intervillous space and terminal villi, syncytiotrophoblast number, fibrinoid areas, and glycogen deposits. These changes may compromise the placental function, resulting in placental insufficiency leading to intrauterine growth restriction [42]. Moreover, tighter glycaemic control in T2D and GDM has been associated with intrauterine growth restriction [43].

7. Management of obesity and diabetes in pregnancy

7.1. gestational weight gain

For women who start their pregnancy with saturated subcutaneous fat depots, any extra weight gain might induce or exacerbate insulin resistance, chronic inflammation, and hypertriglyceridemia [31]. In obese women, the early management of gestational weight gain is critical. Weight reduction is the most effective method to alleviate the metabolic effects of obesity [22]. However, in pregnancy, there remains concern that weight reduction could induce a catabolic state, resulting in ketosis and adverse pregnancy outcomes. Controversies exist on what is adequate gestational weight gain for obese women. The Institute of Medicine (IOM) recommends 5–9 kg weight gain in Obese women [44]. However, these liberal weight gain recommendations are geared towards reducing fetal growth restriction. Extensive cohort studies have shown that Obese women are more likely to supersede these weight gain recommendations [45]. A recent meta-analysis of over 30 million pregnancies showed no increase in the rates of small for gestational age (SGA) among obese women who gained less than the IOM recommendations [46].

On the contrary, weight gain less than IOM was associated with lower rates of LGA, preeclampsia, and preterm labor [46]. The Lifecycle Project-Maternal Obesity and Childhood Outcomes examined the relationship between gestational weight gain and any adverse pregnancy outcomes (preeclampsia, GH, GDM, caesarean delivery, preterm birth, SGA, and LGA) [47]. The study showed that for obesity class I, a weight gain between 2 and 6 kg is optimum, while for classes II and III, a weight gain between 0 and 6 kg is adequate [47]. Hence, we believe that the IOM weight gain recommendations are very liberal, and the Lifecycle recommendations should be adopted in clinical practice.

In our practice, we recommend no gestational weight gain in the first 20 weeks and aim for a maximum of 8 kg in obese class I and 5 kg in classes II and III. We use low-glycaemic index-based 2000 kcal meal plans, which could be reduced to 1800 and 1600 kcal.

Irrespective of weight loss, exercise in obese women is associated with a myriad of metabolic benefits, such as a reduction in glucose levels, TG, liver fat, hyperinsulinaemia, and increased fatty acid oxidation and insulin sensitivity [48]. A Cochrane review showed that diet, exercise, or both were associated with a lower risk of excessive GWG and potentially lower risk of caesarean delivery, macrosomia, and neonatal respiratory morbidity [49]. A recent meta-analysis of 22 randomised controlled trials (RCT) showed that exercise during pregnancy was associated with lower rates of GWG and risk of GDM, GH, and macrosomia [50]. Current recommendations include a weekly 150 min of aerobic and anaerobic exercise for all pregnant women with obesity [27]. A pragmatic recommendation is to start with 25-min daily walking and then increasing it by 2 min per week to reach a 40-min daily walking average [27].

7.1.1. Metformin

Metformin is an anti-diabetic medication whose mechanism of action is not fully understood. Recent data suggest that Metformin reduces hepatic insulin resistance, reduces post-prandial glucose absorption, and improves peripheral insulin sensitivity [51]. Metformin can also reduce appetite by increasing the production of Glucagon-like Peptide 1 (GLP-1) and growth differentiation factor 15 (GDF15) [51]. Hence, there is a growing interest in Metformin use during pregnancy to reduce excessive GWG, prevent GDM, and improve glycaemic control.

Metformin has been studied in women with obesity during pregnancy in a few RCTs with inconsistent results. The GROW study recruited obese women with a median BMI of 32.3 kg/m² and showed that women randomised to metformin had reduced weekly average GWG but no difference in the rates of macrosomia compared to placebo [52]. The EMPOWAR trial recruited obese women with a median BMI of 37.8 kg/m² and showed no difference in maternal weight gain, neonatal weight, or risk of GDM between metformin compared to placebo [53]. The MOP trial recruited women with a median BMI of 38 kg/m² and showed that, compared to placebo, metformin was associated with lower GWG and reduced risk of PET [54]. The differences between the three trials could be attributed to differences in ethnicities, median BMI, and metformin dosage [55]. A meta-analysis that included data from EMPOWAR and MOP trials showed that Metformin significantly reduced maternal weight gain, risk of PET and NICU admission [56]. Another meta-analysis showed that Metformin reduces gestational weight gain and the risk of GDM, albeit quite modestly [57].

Metformin use is more established in the management of GDM. A meta-analysis of 38 RCTs that included 6086 women showed that, compared to insulin, there was lower maternal gestational weight gain, maternal hypoglycaemia, neonatal hypoglycaemia and LGA [58]. In addition, a meta-analysis of RCTs that included 8038 women reporting on maternal outcomes showed that, compared to other treatments, metformin reduced the risk of PET [59]. Finally, a meta-analysis of the neonatal outcomes of RCTs showed that, compared to insulin, metformin reduced the risk of macrosomia, NICU admissions and neonatal hypoglycaemia [60].

The MITTY trial (Metformin in women with type 2 diabetes in pregnancy) was an RCT in which women with T2D during pregnancy were randomised to metformin or placebo [61]. The primary outcome was a composite of fetal and neonatal outcomes, including one or more of the following: pregnancy loss (miscarriage, termination, stillbirth, or neonatal death up to 28 days), preterm birth (<37

weeks' gestation), birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycaemia, and NICU admission lasting >24 h). The primary outcome was not different between the two groups. However, women who received metformin gained less weight, had lower third trimester HbA1c, were more likely to achieve glycaemic targets, used fewer insulin doses and were less likely to deliver via C-section [61].

7.2. Management of GDM

A multidisciplinary team approach (consisting of an endocrinologist, a dietician, an obstetrician, and a diabetic nurse/educator) is central in managing women with GDM. As outlined above, gestational weight gain is a critical determinant of pregnancy outcomes in women with GDM. Hence, the same principles of lifestyle changes for women with obesity apply to women with GDM. Indeed, lifestyle changes that include dietary intervention and exercise allow 15–20% of women with GDM to achieve glycaemic targets without the need for pharmacotherapy [4,62]. If women do not achieve the glycaemic targets within 1–2 weeks, pharmacotherapy, in the form of Metformin and/or insulin, must be started [63].

As outlined, glycaemic monitoring is central to the management of GDM. Home blood glucose monitoring (BGM) is recommended for all women with GDM. However, there are multiple issues related to the use of home glucometers. The FDA approves glucometers if they demonstrate that 99% of the readings are within 20% of the compared lab glucose readings [64]. This margin of error is quite significant in women with diabetes in pregnancy [64]. Hence, it is our practice to ensure that women with GDM are offered a newly calibrated glucometer. We review the accuracy of the glucometers regularly throughout pregnancy and maintain a margin of error of <10% compared to the hospital point-of-care glucose systems.

The glucose targets are FBG ≤ 5.3 mmol/l, 1 h ≤ 7.8 mmol/l and 2 h ≤ 6.7 mmol/l. We aim to maintain 80% of the CBG readings within these targets. There is no significant difference between targeting 1-h or 2-h post-prandial readings. However, we target the 1 h in women post bariatric surgery and in women who have a normal 2 h post-OGTT glucose but elevated 1-h post-OGTT glucose. Women on Metformin are asked to monitor four times per day (FBG and three post-prandial readings), while those on basal-bolus insulin are asked to monitor 6-to 7 times per day (pre- and post-meals). We offer continuous glucose monitoring (CGM) to all women with GDM treated with insulin. While there are currently no agreed targets for the ambulatory glucose profile indices in women with GDM or T2D in pregnancy, we aim to keep the >80% of the readings within the time in range (3.5–7.8 mmol/l) [65]. Regular monitoring of HbA1c is not recommended in women with GDM.

7.3. Management of T2D in pregnancy

Although a team approach to management is strongly recommended for these women, ideally, their care should be started pre-pregnancy. Such care should also be multidisciplinary, including dietary advice, commencing folic acid (5 mg daily), and ensuring that pregnancy is embarked upon when glycaemic control and general health (including assessment of renal function and the eyes) are optimized. Women aiming for pregnancy should achieve HbA1c <6.5%; however, women with HbA1c $\geq 10\%$ should firmly be advised to delay pregnancy and should be placed on appropriate contraception. For those with co-morbidities like hypertension, reviewing the medication should be undertaken, and teratogenic options like ACE inhibitors should be changed to non-teratogenic options.

During pre-pregnancy, women with T2D aiming to conceive should be treated with Metformin and insulin only. The effect of other anti-diabetic agents on embryogenesis is not apparent. Animal data showed that the treatment with GLP1 receptor agonist was associated with reduced maternal weight and food intake, SGA and delayed ossification [66]. However, there is no evidence of placental transfer of exendin-based GLP1 or GLP1 receptor analogues [66]. Besides, once GLP-1 receptor agonists are stopped, there is a rebound increase in weight gain and in glucose levels⁶⁴. Hence, we advise stopping GLP1 receptor agonist at least 3 months before pregnancy. Animal data showed that exposure to Sodium-glucose transporter-2 inhibitors (SGLT2i) was safe in the first trimester but was associated with widened renal and pelvis tubules after that [66]. Observational data suggested an increased risk of miscarriage with the use of SGLT2i [66].

For pregnant women with T2D, lifestyle changes are pivotal to their care, just as for women with obesity and T2D. We generally treat all women with Metformin and insulin. We do not start metformin on women at high risk of SGA i.e that have more than one of the following risk factors: chronic hypertension, albuminuria, recent history of bariatric surgery and history of SGA [67]. The BGM and CGM targets are similar to those for GDM (see above).

7.4. Fetal anomaly screening

Scanning women with obesity during pregnancy is challenging and indeed reduces the accuracy or detection rates of anomalies [68]. Furthermore, the excess abdominal fat reduces the accuracy of clinical assessment of fetal size, presentation, and even fetal monitoring during labour. Abdominal palpation and symphyseal fundal height measurement may not be sufficient in assessing fetal size, particularly in women with a BMI >35 kg/m²; serial growth scans are therefore recommended to improve assessment of fetal size [69,70].

Fetal structural screening can be challenging in obese patients, increasing the risk of missing some of these congenital malformations [71]. Transvaginal scanning may be required for obese diabetic women, particularly in the first trimester as abdominal scanning may not be accurate in assessment, particularly first trimester anomaly screening and nuchal translucency measurement [72]. Women should be counselled that all forms of structural screening during pregnancy can be affected by obesity. Obesity and diabetes are associated with several congenital malformations. These malformations include neural tube defects [73,74], heart defects

[75] and orofacial clefts [76].

7.5. Fetal monitoring during pregnancy in obese diabetic women

Umbilical artery velocimetry has been used to assess fetal well-being in high-risk non-diabetic pregnancies. It provides an indirect measure of the placental function. Flow velocity profile include Umbilical artery pulsatility index (PI), resistance index (RI), and systolic/diastolic ratio (SD ratio). During pregnancy, the blood flow through the uterine/spiral arteries to the uterus changes from low flow/high resistance status to high flow/low resistance status [77,78]. Diabetes may affect this relationship. Poor oxygen transfer through the placenta leads to fetal hypoxia. Moreover, delayed removal of various metabolites may lead to fetal hypoxia [79]. These changes lead to a reduction in the placental perfusion, which results in a sparing effect and lowering of the resistance and the pulsatility indices in the middle cerebral artery (MCA) and an increase in the resistance and pulsatility indices in the umbilical arteries [80,81]. It is unclear to what extent these changes occur in pregnancies affected by diabetes. In a meta-analysis by Perkovic-Kepeci et al., it was shown that in pregnancies complicated by diabetes, there are haemodynamic changes in the uterine artery (pulsatility index- UtA-PI, UtA S/D ratio) and umbilical artery resistance index (RI) resulting in higher indices compared to pregnancies not affected by diabetes. They found no changes in the middle cerebral artery (MCA) indices. Further studies are required on the effects of pregestational versus gestational diabetes on haemodynamic changes during pregnancy [82].

Sarno et al. showed in their study that obesity has a negative effect on the fetomaternal vessels, demonstrated by higher umbilical artery PI index in obese women compared to non-obese women [83]. A systematic review by Rane et al. showed that an abnormal umbilical artery pulsatility index is more accurate in predicting poor perinatal outcomes than the cerebroplacental ratio and middle cerebral artery pulsatility index in diabetic pregnancies [84].

In diabetic women with vascular disease with reduced retroplacental blood flow, the interpretation of the umbilical artery Doppler indices should be treated with caution [85]. Until recently, umbilical artery velocimetry was considered valuable in monitoring fetal well-being in high-risk pregnancies. This may not be the case for fetuses of diabetic mothers because of the several haemodynamic changes mentioned above. Wong et al. show that umbilical artery Doppler velocimetry is not a good predictor of poor outcomes in diabetic pregnancies. It was shown that only 30% of pregnancies associated with adverse perinatal outcomes had abnormal umbilical arterial Doppler [86]. Another study by the same team found no differences in umbilical artery Doppler indices between the various outcome groups. The use of umbilical artery Doppler in diabetic women has been criticized and considered controversial by some researchers [87,88].

The use of the ductus venosus (DV) peak velocity index for veins (DV PVIV) has been studied as an alternative. Wong and colleagues' showed a positive correlation between increased DV PVIV and poor perinatal outcomes in pregnancies complicated by diabetes, with a sensitivity of 53% and a specificity of 75% [89]. The use of hepatic artery Doppler has been suggested but this is still being investigated. Fetal monitoring during labour can be challenging, and the use of other methods, like invasive testing, may be required [90,91].

7.6. Timing of delivery in diabetic obese women

Unexpected intrauterine fetal death (IUFD) and perinatal mortality are significant concerns of obstetricians caring for obese pregnant women with diabetes. Fetal monitoring modalities like umbilical artery Doppler, electronic fetal monitoring and biophysical profile have not been proven beneficial in preventing perinatal mortality in these patients. It has been suggested that alternative approaches like measurement of erythropoietin in the amniotic fluid and MRI spectroscopy may be practical. More evidence is needed before these tests can be recommended. Obese diabetic women are at an increased risk of stillbirth and increased perinatal mortality and morbidity. Careful planning of the timing of delivery may help to reduce this risk [92].

7.6.1. Gestational diabetes

Various national guidelines address the timing of delivery in pregnancies affected by gestational diabetes. There is no consensus on the optimal delivery time. The National Institute of Health and Care Excellence (NICE) in the UK recommends delivering women with uncomplicated gestational diabetes no later than 40⁺⁶ weeks. Women who had maternal or fetal complications should be delivered before this gestation [93]. The ACOG does not recommend delivery before 39 weeks but waiting until 40⁺⁶ weeks for spontaneous delivery [94]. On the other hand, the Society of Obstetrics and Gynaecology of Canada (SOGC) does not recommend waiting beyond 40 weeks [95]. Induction of labour before 39 weeks has been shown to be associated with an increased risk of neonatal jaundice, admission to neonatal intensive care units and neonatal hypoglycaemia [96]. For diet-controlled gestational diabetes, Yin et al. recommend delivery between 39⁺⁰ and 40⁺⁶ weeks for women with reasonable glycaemic control [97]. The later gestation is recommended for women with an unfavourable Bishop score. Sijak et al. recommend delivery at 40⁺⁰ weeks [98,99]. For gestational diabetes requiring treatment, the National Institute of Child Health and Human Development (NICHD) recommends delivery at 39 weeks of gestation [100] for the same group, and ACOG recommends delivery at 39-39⁺⁶ weeks gestation [101]. For women with poorly controlled gestational diabetes, it recommends delivery before 39 weeks. The exact timing of delivery should be individualized, considering the cervical assessment and fetal lung maturity [97].

7.6.2. Pre-pregnancy type 1 and 2 diabetes mellitus

For women with well controlled type 1 and 2 diabetes mellitus, delivery should be between 37 and 38⁺⁶ weeks gestation. Delivery should be considered before 37 weeks in women with type 1 and 2 diabetes in the presence of metabolic or other fetal or maternal

complications [93]. Brown et al. In a population-based study concluded that, in pregnancies of women with pregestational diabetes (type 1 and 2), induction of labour at 38⁺⁰-38⁺⁶ weeks was not associated with an increased caesarean delivery rate but was associated with an increase in specific perinatal outcomes compared to expectant management. Induction of labour during this time was associated with increased rates of admission to the neonatal intensive care unit, hypoglycaemia and jaundice compared to expectant or induction beyond 39 weeks [102].

7.6.3. Delivery considerations

Pregnant obese women are at an increased risk of preterm birth, whether this is medically indicated or spontaneous [103]. Obesity is associated with an increased likelihood of the need for delivery by caesarean section [104]. If caesarean section is required for obese women, appropriate multidisciplinary planning should be made taking into consideration any other comorbidities and the woman's wishes. Obese pregnant women are at an increased risk of failed intubation and failed epidural and anaesthetic complications; an antenatal referral to the anaesthetist for risk assessment and evaluation should be considered for these women especially in those with a BMI ≥ 40 kg/m² [105].

Obese nulliparous women have been shown to have a twofold increased risk of major postpartum haemorrhage compared to women with normal BMI [106,107]. Active management of the third stage of labour should therefore be instituted for these women.

8. Postnatal care

Care of women with obesity who are diabetic must not only focus on the antepartum and intrapartum period but also on the postnatal period. During these periods, education and support will ensure that weight gain is avoided and indeed weight loss is encouraged. For those with gestational diabetes, it is recommended that they are seen at 6–13 weeks where screening with a fasting blood glucose is performed to ensure that they have not become type 2 and then offered annual HBA1c as screening for type 2 diabetes. This is also an opportunity to educate those whose diabetes was diagnosed for the first time in pregnancy on the value of optimising diabetic control and weight prior to another pregnancy.

9. Practice points

- All obese women should be screened for diabetes in pregnancy in a staged approach - a fasting blood glucose and HBA1c at booking and a 75 g OGTT at 24–28 weeks if these are normal.
- Multidisciplinary care is associated with the best outcome. This must start pre-pregnancy focusing on weight loss. In pregnancy, this should focus on minimising gestational weight gain and ensuring good glycaemic control.
- Fetuses of women with diabetes are at an increased risk of congenital malformations (especially cardiovascular), fetal macrosomia and intrauterine fetal death. Attention must therefore be focused on identifying these malformations and monitoring for fetal growth and wellbeing.
- Timing delivery should be based on a combination of factors including type of diabetes and control, gestational age, comorbidities, and the state of the fetus.
- Postnatal care must include weight management and monitoring (especially those with GDM) for the onset of type 2 diabetes.

10. Research agenda

With increasing obesity rates and concomitant increasing rates of diabetes in pregnancy, a better understanding of this relationship would allow for better approaches to reducing the rates of diabetes in pregnancy especially in obese women. Since gestational weight gain is central not only to diabetic control but pregnancy outcome, a greater understanding of how this affects diabetic control and pregnancy outcome is critical. Furthermore, since an increasing greater number of women are on weight-losing drugs, researching into the safety of these drugs and how they may not only affect the fetus but how they may interfere with diabetic control will allow for a safe expansion of the tools available for weight control in these women.

MCQs

Concerning the epidemiology of diabetes in pregnancy in obese women.

1. The global prevalence of GM is approximately 10% (F)
2. The highest prevalence is reported in North America (F)
3. The reported congenital malformation rate in women with T2 DM is about double compared to that in those without diabetes (T)

Gestational diabetes is the most common medical complication of pregnancy. The International Diabetes Federation (IDF) estimates that the global prevalence of GDM is 14.0%. The lowest prevalence of 7.0% was reported in North America, while the highest of 27.6% was in the Middle East and North Africa (MENA). Among women with T2D, Murphy et al. reported a congenital malformation rate of 40.5 per 1000 births, almost twice the rate in the general population in England of 21.3 per 1000 births.

With regard to gestational weight gain for obese women with diabetes in pregnancy.

4. There is robust evidence to support the benefits of the Institute of Medicine (IOM) recommended weight gain in obese women with regards to reducing the rates of small for gestational age (F)
5. The use of metformin has been shown from meta-analysis to result in lower maternal weight gain compared to placebo (T)

A recent meta-analysis of over 30 million pregnancies showed no increase in the rates of small for gestational age (SGA) among obese women who gained less than the IOM recommendations. A meta-analysis that included data from EMPOWAR and MOP trials showed that Metformin significantly reduced maternal weight gain, risk of PET and NICU admission [56]. Another meta-analysis showed that Metformin reduces gestational weight gain and the risk of GDM, albeit quite modestly.

In the management of gestational diabetes

6. Metformin is the option of choice following the initial diagnosis (F)
7. The use of GLP-1 receptor agonist has been shown to be safe in pregnancy (F)

Following the diagnosis of GDM lifestyle changes that include dietary intervention and exercise are instituted first. This allows 15–20% of women with GDM to achieve glycaemic targets without the need for pharmacotherapy. If women do not achieve the glycaemic targets within 1–2 weeks, pharmacotherapy, in the form of Metformin and/or insulin, must be started. We advise stopping GLP1 RA at least 3 months before pregnancy. Animal data showed that exposure to Sodium-glucose transporter-2 inhibitors (SGLT2i) was safe in the first trimester but was associated with widened renal and pelvis tubules after that.

CRedit authorship contribution statement

Mohammed Bashir: Writing – review & editing, Writing – original draft. **Yassin Fagier:** Writing – review & editing. **Badreldeen Ahmed:** Writing – review & editing. **Justin C Konje:** Writing – review & editing.

Declaration of competing interest

None of the authors have a conflict of interest to declare.

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