Diabetes in Pregnancy

17

Agustin Busta, Alberto Franco-Akel, Yuriy Gurevich, Adina Schneider, and Elliot Rayfield

Abstract

Maternal diabetes is a significant cause of short-term and long-term morbidity for the infant and the mother. Infants born from mothers with gestational diabetes have a high prevalence of overweight, obesity, and risk to develop type 2 diabetes later in life. Gestational diabetes affects 18% of pregnancies. Its increasing incidence and prevalence worldwide are mostly attributed to the progressively increasing rates of obesity and a changing lifestyle in the general population. Gestational diabetes is an independent risk factor for the future development of overt postpartum diabetes.

Maternal and fetal complications are more frequent in patients with pre-existing diabetes than those with gestational diabetes. Nondiabetic women should receive universal screening for gestational diabetes, and women at risk for diabetes should be screened on the first prenatal visit. At present, there is general agreement on the strategy for diagnosis as well as the management of labor and delivery and postpartum follow-up in women withpre-existing diabetes and gestational diabetes.

The first-line treatment for gestational diabetes consists of dietary modification and increased physical activity. Subsequent pharmacologic therapy is warranted if this strategy fails. Early diagnosis of pre-existing diabetes, as well as proper diagnosis of gestational diabetes, warrants early treatment and a strict clinical follow-up since early intervention has been shown to improve fetal and maternal outcomes in randomized controlled trials.

Keywords

Gestational diabetes mellitus • Perinatal • Insulin resistance • Macrosomic • Large-for-gestational-age infants • Preeclampsia • Target glucose levels • Maternal ketonemia • Low-glycemic-index diet • Diabetic retinopathy • Teratogenic effects • Pre-existing diabetes • Pre-gestational

A. Busta (✉)
Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: abusta@chpnet.org; MJeffers@chpnet.org

A. Franco-Akel
Division of Endocrinology, Diabetes and Bone Disease, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: albertoafrancoa@gmail.com

Y. Gurevich
Division of Endocrinology and Metabolism, Beth Israel Medical Center, Albert Einstein College of Medicine, New York, NY, USA

A. Schneider • E. Rayfield
Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

L. Poretsky (ed.), *Principles of Diabetes Mellitus*,
DOI 10.1007/978-3-319-18741-9_15

Contents

Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance that first occurs, or is first identified during pregnancy [1]. GDM affects up to 18% of pregnancies [2]. The prevalence of GDM in the USA has more than doubled from 1.5% in 1989–1990 to 4.2% in 2001–2004 [3]. Based on the 2013 birth data in the USA [4, 5], maternal diabetes affects more than 235,000 of the almost four million pregnancies that result in birth and is a significant cause of maternal and fetal morbidity [6]. The majority of these cases are attributed to GDM. Both pre-gestational T1DM and T2DM confer significantly greater risk for complications than GDM [7].

In North America, the prevalence of GDM is higher in Asians, African-Americans, Native-Americans from Canada, and Hispanics, than in non-Hispanic whites [8]. A subset of women with GDM have circulating islet cell antibodies. These patients might have a latent form of T1DM [9].

The majority of complications arise in patients with gestational and undiagnosed T2DM. Patients with GDM usually develop hyperglycemia during the second half of pregnancy. Hyperglycemia at this stage of gestation clearly causes fetal macrosomia and neonatal hypoglycemia. Patients with pre-gestational diabetes are at risk for hyperglycemia early in pregnancy; this hyperglycemia is associated with significantly increased rates of fetal loss and fetal malformations.

Based on information reported from a 12-year outcome database [10], women with T2DM have a less satisfactory pregnancy outcome compared to the general population, with infants having a twofold higher risk of stillbirth, a 2.5-fold higher risk of a perinatal mortality, a 3.5-fold higher risk of death within the first month, and a sixfold higher risk of death up to 1 year, along with an 11 times higher risk of a congenital malformation. Nevertheless, randomized controlled trials (RCT) have demonstrated the benefit of treating maternal hyperglycemia in GDM based on the fact that the achievement of euglycemia decreased the risk of adverse perinatal outcomes [11, 12].

The association between maternal diabetes and birth defects and perinatal mortality has been recognized since the late nineteenth century [13, 14]. About 6–10% of newborns from mothers with T1DM and T2DM have major congenital defects [15]. Developmental malformations in the infants of diabetic mothers exhibit great diversity of these malformations, ranging from congenital structural defects, functional defects, and low birthweight to macrosomia [16, 17]. In the pre-insulin era, maternal diabetes-associated perinatal mortality reached 70%, and maternal mortality was as high as 30–40% [18, 19]. After the introduction of insulin, maternal mortality decreased dramatically, while perinatal mortality was reduced down to the current rates of 4–13% [20, 21].

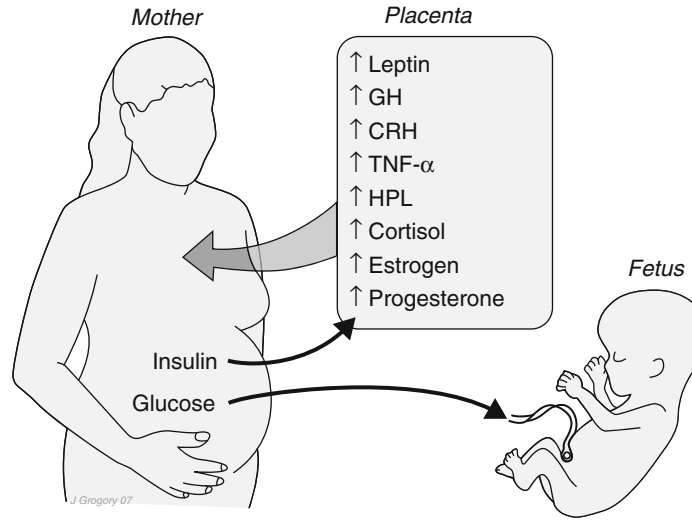

Fig. 1 Movement of hormones and glucose across the placental barrier

Pathophysiology of Glucose Intolerance in Pregnancy

Fasting glycemia is 10–20% lower in pregnant women as compared to nonpregnant women. This physiological adaptation process has been attributed to several mechanisms such as increased storage of glycogen in tissues, increased utilization of peripheral glucose, diminished hepatic glucose production, and fetal utilization of glucose, which occurs predominantly through a glucose transporter (GLUT)-1 isoform on the trophoblast [22].

Development of insulin resistance in late gestation is a process common to all human pregnancies. The underlying pathophysiology of GDM is a function of decreased maternal insulin sensitivity or increased insulin resistance, which is defined as the inability of a defined concentration of insulin to effect a predictable biological response of nutrient metabolism at the level of the target tissue [23]. (see Fig. 1)

Maternal insulin resistance is a normal physiologic response that begins in the second trimester and peaks in the third trimester. This occurs as a result of increased placental secretion of diabetogenic hormones such as growth hormone (GH), corticotropin-releasing hormone (CRH), chorionic somatomammotropin (hCS), also called human placental lactogen (hPL), and progesterone. HPL plays a major role in maternal insulin resistance [24]. In addition, the placenta produces somatostatin, which has the ability to inhibit hPL. Thus, reduction in the secretion of somatostatin in the later part of pregnancy may contribute to insulin resistance [25].

Several other changes that occur in GDM might further impact insulin resistance. Elevated leptin concentrations have been observed in GDM [26]. It has been shown that levels of tumor necrosis factor-alpha (TNF-α) increase from early to late pregnancy [27]. Some investigators suggest that TNF-α is the most important contributor to insulin resistance in pregnancy [28]. In late gestation, hepatic glucose production was reported to increase in women with GDM in comparison with a control group [29].

Secretion of pituitary GH is diminished by 20 weeks and supplanted by placental GH. Human placental growth hormone has been shown to cause insulin resistance in transgenic animals [17]. ACTH levels increase during pregnancy, probably secondary to placental CRH, leading to an increase in plasma cortisol levels.

According to the data presented at the Fifth International Workshop-Conference on GDM, post-receptor mechanism of insulin resistance in

GDM involves β-subunit of insulin receptor as well as IRS-1 in the skeletal muscle [30].

Gestational Diabetes

GDM is defined as carbohydrate intolerance resulting in hyperglycemia with onset or first recognition during pregnancy [1, 2]. The prevalence of GDM is increasing, which has health implications for the mother and the fetus, during pregnancy and later in life [31, 32].

Women with GDM are more likely to give birth to macrosomic or large-for-gestational-age infants. GDM may result in obstructed labor, the death of the mother and the baby, and birth injury for the infants. GDM also has long-term health impact, with more than 50% of women with GDM going on to develop T2DM within 5–10 years of delivery. Moreover, infants of women with GDM have a higher prevalence of overweight and obesity and higher risk of developing T2DM later in life [32].

Screening and Diagnosis of Gestational Diabetes

For women at risk of pre-existing diabetes, early screening is warranted. They should be tested for undiagnosed diabetes at the first prenatal visit using the American Diabetes Association diagnostic criteria for nonpregnant adults [33, 34].

For women without pre-existing diabetes, a universal screening test is recommended at 24–28 weeks of pregnancy [35]. Universal screening is preferred rather than selective screening based on practicality, since only 10% of the general obstetric population in the USA has been found to meet all the low-risk criteria for developing GDM [36], whereas 90% of pregnant women have at least one risk factor for glucose impairment during pregnancy. Furthermore, it has been observed that 2.7–20% of women who are diagnosed with GDM had no risk factors [37, 38].

Diagnosis of GDM can be accomplished with either of two strategies in all pregnant women. The "one-step" approach with a 75-g OGTT or, the "Two-step" approach with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive [39].

One-Step Strategy

In 2011, the ADA recommended for the first time that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [2]. In 2015, the AACE/ACE recommend screening for GDM in all pregnant women using the criteria described in this one-step strategy [40]. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to ~15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis.

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other fields, to consider diagnostic criteria [41], and recommended the two-step approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive. This is a strategy commonly used in the USA.

The lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM (e.g., medicalization of pregnancy with increased interventions and costs) were important determinant factors in the NIH panel's decision-making process.

The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach [42].

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings [43]. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria [44].

Nevertheless, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. In addition, treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births, and shoulder dystocia, without increasing small-for-gestational-age births [45].

The conflicting recommendations from expert groups underscore the fact that there is data to support each strategy. The decision regarding which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

There remains a strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

To deal with disparity in diagnostic testing used throughout the world and its impact on estimation of prevalence of GDM and pregnancy outcomes, a Hyperglycemia and Adverse Pregnancy Outcome (HAPO) prospective observational study was undertaken [46]. Investigators analyzed several pregnancy outcomes in over 23,000 women with impaired glycemic control as determined by 75-g oral glucose tolerance test (OGTT) at 24–32 weeks gestation. Average fasting and 1- and 2-h plasma glucose levels were 80.9 mg/dL, 134.1 mg/dL, and 111.0 mg/dL, respectively. The study demonstrated that primary outcomes (neonatal insulinemia, measured by means of umbilical cord-blood C-peptide level, birthweight, neonatal hypoglycemia, and rate of cesarean delivery) were directly related to the levels of fasting, plasma glucose, and 1- and 2-h post-challenge glucose.

Despite the aforementioned criteria for diagnosis of GDM, there is evidence to suggest that one abnormal glucose tolerance test value is associated with increased risk of macrosomia, preeclampsia, and eclampsia [47]. It has also been demonstrated that treatment of women with one abnormal OGTT value results in reduction of such complications [48].

Morbidity, Long-Term Consequences, and Benefits of Treatment

GDM is characterized by the increased risk for adverse perinatal outcomes. These risks have a greater prevalence among GDM women compared to those who are normoglycemic. GDM has been associated with maternal risks such as hypertension, cesarean delivery, and preterm birth [49].

Fetal and neonatal adverse outcomes result from excessive maternal glucose crossing the placenta, which can lead to fetal hyperinsulinemia and subsequently fetal overgrowth, fat deposition, and demand for oxygen [50].

Other clinically important adverse perinatal outcomes associated with GDM are hyperbilirubinemia, respiratory distress, and prematurity [49].

A multicenter-randomized trial aimed to determine whether pregnancy outcomes were modified by treatment in women with mild GDM. Results of this trial showed that the frequency of stillbirth, perinatal mortality, and complications from maternal hyperglycemia (e.g., hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma) were not significantly reduced. However, this study did show a lower risk of fetal overgrowth, shoulder dystocia, cesarean delivery, and preeclampsia if treatment was provided [51] (see Table 1).

The Australian Carbohydrate Intolerance Study (ACHOIS) in patients with GDM reported a significant lower rate of serious adverse perinatal outcomes, defined as infant death, shoulder dystocia, bone fracture, and/or nerve palsy, in women who received intervention (e.g., dietary advice, blood glucose monitoring, and insulin therapy) than those who received routine care [52]. GDM entails an increased risk for maternal diabetes after pregnancy [53]. A systematic review of the incidence and the factors associated with this conversion to overt diabetes showed a widely variable cumulative incidence of T2DM among studies. These differences could be

Table 1 Morbidity of gestational diabetes

Maternal	Fetal and newborn
Preeclampsia	Neonatal hypoglycemia
C-section	Macrosomia
Polyhydramnios	Shoulder dystocia
	Polycythemia
	Hypocalcemia
	Hyperbilirubinemia
	Future diabetes mellitus, obesity

explained by the length of follow-up, retention of cohort studies, and selection of initial population with GDM. Women from mixed cohorts or non-white cohorts seemed to have a similar rate of progression to T2DM. The rate of progression to T2DM had a steep increase within the first 5 years upon delivery and showed a plateau afterward [54]. Moreover, women who had a diagnosis of GDM have a risk greater than 50% of developing subsequent GDM and later T2DM [55].

Emerging evidence suggests that in utero programming related to the degree of glycemic control in pregnancy may prompt an increased risk of metabolic syndrome, obesity, and diabetes among children of GDM mothers [56].

A systematic review and meta-analysis done in 2013, which included randomized controlled trials and cohort studies, revealed that treating GDM resulted in decreased rates of preeclampsia, shoulder dystocia, and macrosomia [57].

The children of women who have had GDM have an increased risk of developing obesity and abnormal glucose tolerance by the time of puberty. The health-care providers of these children should be aware of this risk so that they can encourage their patients to make appropriate lifestyle changes [58].

Target Glucose Levels

The primary goal of treating GDM is to decrease the risk of adverse perinatal outcomes. The goals for glycemic control in GDM are derived from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [30]. Once the diagnosis of GDM is established, patients should start monitoring their blood glucose levels, ideally fasting levels and 1 or 2 h after meals. Fasting glucose target level should be $\leq$95 mg/dL, 1-h postprandial should be $\leq$140 mg/dL, and 2-h postprandial should be $\leq$120 mg/dL [30, 42]. If glucose targets are achieved by means of diet and exercise, less intensive glucose monitoring is acceptable [34, 42].

Lifestyle Modification

The first-line treatment for GDM consists of diet and physical activity. GDM women should receive individualized nutrition counseling from a dietitian. It is generally recommended to limit carbohydrate intake to 33–40% of calories [30].

Aerobic exercise and resistance training have been shown to improve glycemic control in patients with diabetes; nevertheless, these effects have been inconsistent in clinical trials of women with GDM [59, 60].

Maternal obesity, excessive gestational weight gain, and GDM are well-established independent and additive risk factors for fetal macrosomia. Hence, it makes sense that all possible efforts are made to minimize maternal weight gain [61].

Diet Therapy

A nutritionist or other professional should provide dietary advice to women with gestational diabetes. Fifth International Workshop-Conference recommends 30 min of physical activity a day if possible, consisting of brisk walking or seated arm exercises for 10 min after each meal [30].

There are several strategies to nutritional therapy for patients with GDM. The American Diabetes Association recommends an average of 30 kcal/kg/day based on prepregnant body weight. The ACOG recommends a maximal caloric restriction of 33% and focuses on the avoidance of ketonemia, because of old data that suggests an inverse association between maternal ketonemia and intelligence quotient of the offspring [62]. A low-glycemic-index

diet is considered essential in the nutritional management of patients with non-gestational diabetes, although its effectiveness has not been well explored in patients with GDM. Based on results of small pilot open-label studies, it has been suggested that a low-glycemic diet improved postprandial glucose compared with controls [63]. Although it is reasonable to assume that a low-glycemic diet should be established in the treatment of GDM, data supporting this strategy is not strong. We can conclude that a well-balanced diet that restricts concentrated sweets and simple carbohydrates is culturally sensitive and as much as possible is adapted to the patient's preferences should be implemented.

Exercise

The benefit of physical exercise in the treatment of T2DM is well established. Aerobic exercise rapidly improves glycemia, whereas sustained exercise has been shown to improve insulin sensitivity. As insulin resistance is the basic underlying process in GDM, it is likely that exercise confers short- and long-term benefits. In addition, low-impact activity such as walking, swimming, and resistance training may have great potential benefits with very small risks.

A prospective randomized controlled study of obese pregnant women (BMI $\geq$ 30) in the first trimester, looked into the effects of lifestyle modification, including an exercise component, compared to a control group which received routine prenatal care. The intervention group subjects gained less weight in pregnancy and did not have any increased risk of preeclampsia, cesarean delivery, or low birthweight [64].

A randomized trial of 64 women with diet-controlled GDM looked into the impact of resistance band exercise versus routine management on insulin sensitivity. Results of this study showed that women in the exercise group compared to the control group had >50% reduction of required insulin (56.3% vs. 21.9%) and a higher percentage of time with glycemia in the target range, with no increased rates of hypoglycemia [65].

Pharmacologic Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacological therapy. Nevertheless, in cases of mild to moderate hyperglycemia, if a trial of lifestyle modification does not result in satisfactory glucose control, pharmacologic therapy can be initiated.

Insulin is the first-line agent recommended for treatment of GDM in the USA. Glyburide is a suitable alternative to insulin therapy, except for those women with diagnosis of GDM before 25 weeks gestation [66] and for those women with fasting plasma glucose levels above 110 mg/dL, [67] in which case insulin therapy is preferred. Nevertheless, recent meta-analyses and large observational studies examining maternal and fetal outcomes suggested that glyburide may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia [53].

Metformin is a suitable alternative when patients are not good candidates for glyburide [68].

Neither glyburide nor metformin have been approved by the US FDA for the treatment of GDM. Both of these medications cross the placenta but have not been associated with birth defects or short-term adverse neonatal outcomes [42, 69]. Clinicians may consider counseling patients on the lack of long-term safety data for these medications.

Insulin

Historically, insulin has been the recommended treatment for GDM in the USA. Insulin is required in women who have uncontrolled blood glucose levels despite lifestyle modification, especially if oral medications have failed to achieve target pre- and postprandial plasma glucose values.

Insulin does not cross the placenta, and most insulin types are considered safe for use in pregnancy [70, 71]. Women who require basal insulin should be started on the insulin analog detemir (pregnancy category B). Neutral Protamine Hagedorn (NPH) insulin is also an option,

although it has been associated with problematic hypoglycemia, even if given at appropriate doses [72]. Insulin detemir may also be continued in those women with pre-gestational diabetes who have already successfully taken it before pregnancy.

Whereas insulin detemir is approved by the FDA for use during pregnancy, insulin glargine does not have such approval. It has been suggested that insulin glargine could be continued during pregnancy in women who were already on it and had satisfactory glucose control before getting pregnant [68]. Women treated with insulin glargine during the first trimester have a similar rate of congenital malformations as those treated with NPH insulin [73, 74].

Rapid-acting insulin analogues lispro and aspart are preferred over regular soluble insulin and pregnant women with diabetes. These two analogues allow greater lifestyle flexibility, greater patient satisfaction, and improved quality of life [75]. These also provide better postprandial glucose control [76] and hemoglobin A1C reduction [77]. Insulin glulisine (pregnancy category C) does not have FDA approval for use in pregnancy.

Women who were on subcutaneous insulin infusion before pregnancy should continue it once they get pregnant [68].

Insulin therapy can be started by calculating a total daily dosage of 0.7–1.0 units/Kg. Half of this total daily requirements is to be given as long-acting insulin, and the other half is administered as rapid-acting insulin in three divided doses before meals. The dose should be individualized and tailored as needed [78].

Oral Hypoglycemic Medications

When lifestyle modification does not result in satisfactory glucose control, generally after a trial of one week, pharmacologic therapy is indicated. Randomized controlled trials support the efficacy and short-term safety of glyburide (pregnancy category B) [79].

Metformin therapy can also be used for glucose control in women with GDM who do not have satisfactory glycemic control despite medical nutrition therapy and who are not good candidates, or cannot use insulin or glyburide [68].

There is no consensus on the threshold values for which these two oral medications should be initiated. Different approaches have been used. One approach is to start therapy if more than two values on the same meal during a 2-week period are above target by more than 10 mg/dL [80]. Another approach would be to start medications if 50% of the values in a given week are above target levels [51]. Between 15% and 40% of women who are prescribed oral medications for GDM will ultimately require insulin [42]. Glyburide may be associated with lower failure rates than metformin [80]. Nearly half of the women with GDM treated with metformin monotherapy have glycemic control failure rates requiring conversion to insulin therapy [81]. Other than that, glycemic control, maternal and neonatal outcomes, and adverse effects are similar among patients treated with oral agents versus insulin [82, 83].

Labor and Delivery

As the placenta is delivered, there is a considerable reduction in pregnancy-related insulin resistance. Most women with GDM will not require insulin once active labor begins and rarely require insulin after delivery. Blood glucose needs to be obtained on the day after delivery to make sure hyperglycemia is resolved.

There is no data to support delivery of women with GDM before 38 weeks gestation if evidence of maternal or fetal compromise is absent. There is a lack of information on the risk of perinatal morbidity and mortality in the infants of women with well-controlled GDM if pregnancy proceeds beyond 40 weeks of gestation. However, it is prudent to intensify fetal surveillance when pregnancy continues beyond this point [30].

Postpartum Management

According to the Fifth International Workshop, there is evidence that suggest that breastfeeding

might have a beneficial effect on the development of postpartum diabetes in women with GDM. Therefore, breastfeeding is encouraged [30].

Since insulin is degraded in the digestive tract of the infant, women who are breastfeeding can safely use any type of insulin. Glyburide and glipizide may also be utilized [82].

There is some data to suggest that metformin is excreted into breast milk in small amounts. However, this seems not to have any deleterious effects on the infant [84]. At present, larger studies are needed to determine safety of metformin in breastfeeding mothers (see Fig. 2).

Fetal Surveillance

The intensity of fetal monitoring is determined by the severity of GDM. At a minimum, patients treated with diet alone should be taught to measure fetal movements during the last 8–10 weeks of pregnancy. Patients who are being treated with insulin should undergo nonstress testing beginning at 32 weeks of gestation. Fetal ultrasound may be used to assess fetal size at 29–33 weeks and should be used for detection of fetal anomalies in patients who had GDM diagnosed during the first trimester or who have fasting plasma glucose of >120 mg/dL [58]. Recent evidence suggests the use of fetal ultrasound rather than strict glycemic parameters as a guide for initiation of insulin therapy. This approach would minimize glucose testing and insulin utilization in low-risk pregnancies [85].

Pre-gestational Diabetes

Both pre-existing T1DM and T2DM significantly represent a greater maternal and fetal risk than GDM. Among them, spontaneous abortion, fetal

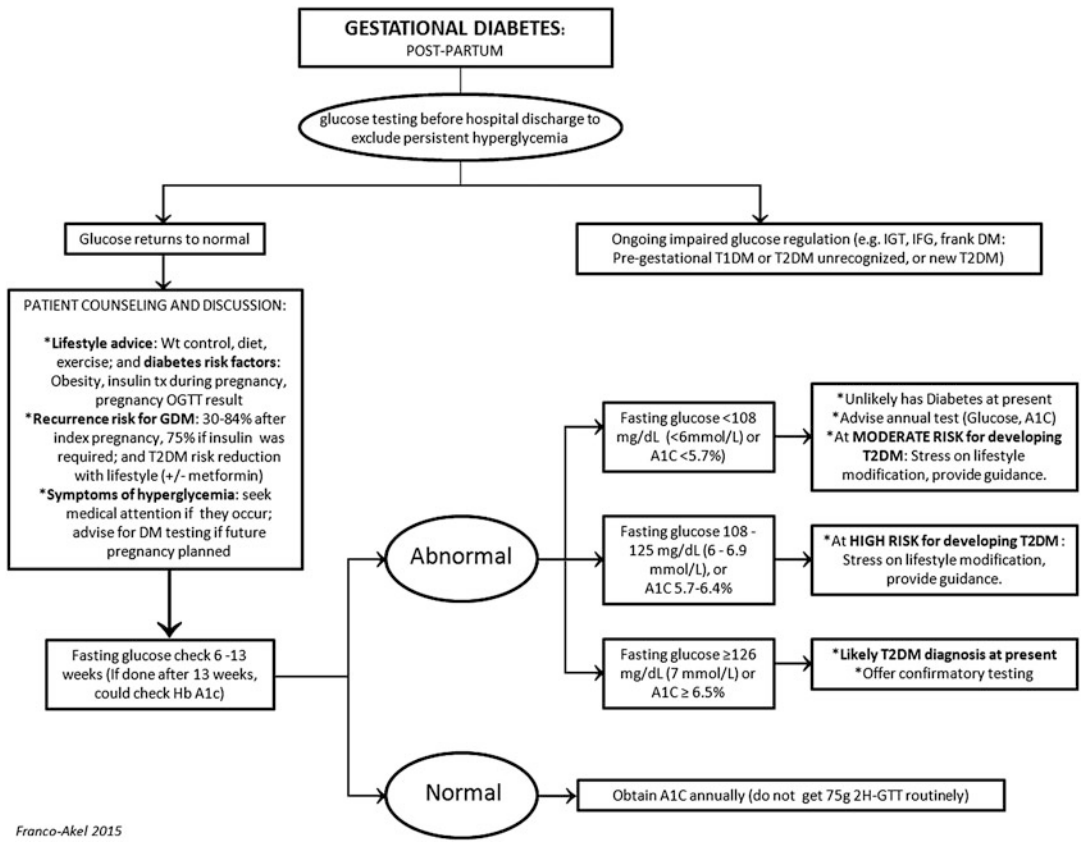

Fig. 2 Postpartum follow-up in gestational diabetes women

anomalies, preeclampsia, intrauterine fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia are the most clinically important. In addition, diabetes in pregnancy may increase the risk of obesity and T2DM in the offspring later in life [86, 87]. Therefore, it is imperative that all efforts are directed toward the achievement of glucose control before conception.

Congenital Malformations

Before the introduction of insulin, diabetic women were rarely able to produce viable offspring. The level of glycemic control early in organogenesis has been shown to impact rates of malformations. Miller et al. showed that a hemoglobin A1C in the first trimester of >8.5% was associated with a malformation rate of 22.4%, a hemoglobin A1C 7–8.4% was associated with a rate of 5%, while a hemoglobin A1C <6.9% was associated with no excessive malformations [88]. The duration of diabetes and the presence of vasculopathy have also been shown to be associated with an increased risk of anomalies [89].

Pre-conception Care

Pregnancy must be a planned event for women with T1DM and T2DM. It has been pointed out that women with T2DM are less likely to receive pre-conception care because the disease has often gone undiagnosed [90]. In addition, T2DM is also more prevalent in minority groups who may have limited access to care.

Family planning should be discussed, and an effective plan for contraception should be prescribed and used until a woman is ready to become pregnant [53]. Pre-conception counseling should be provided, addressing the importance of glycemic control as close to normal, and as safely possible, ideally with a hemoglobin A1C <6.5% (48 mmol/mol) to reduce the risk of congenital anomalies [53].

Women with pre-existing diabetes who desire pregnancy or who have become pregnant should receive extensive counseling on the risk of development and/or progression of diabetic retinopathy [53]. If no such counseling takes place and a woman with pre-existing diabetes presents to the office at the beginning of her pregnancy, it is imperative to establish glycemic control as soon as possible, only after an ophthalmologic evaluation by a specialist is performed, since the rapid normalization of glycemia is known to play a role in the progression of diabetic retinopathy [6]. (see section "Diabetic Retinopathy").

Evaluation of renal function and thyroid function is essential component of the initial visit. Hypertensive women should be treated with agents which have been shown to be safe in pregnancy. ACE inhibitors, diuretics, and beta blockers should be avoided because of the associated risk of congenital malformations [91]. Also, statin drugs need to be discontinued in anticipation of conception due to potential teratogenic effects [92] (see Table 2).

Table 2 Pre-conception care – initial visit

Hemoglobin A1C
Blood glucose record
24-h urine microalbumin/creat
TSH
Blood pressure/medication reconciliation
Retinal exam
Cardiovascular evaluation/medication reconciliation
Neurological exam
Nutritional evaluation
Counseling on risks of pregnancy

Diabetic Retinopathy

The association of pregnancy with rapidly progressing diabetic retinopathy has been well established [93, 94]. This progression can lead to sight-threatening damage, which can occur during pregnancy and up to 1 year after delivery [95–97]. The absence of diabetic retinopathy before conception confers a very small risk to develop severe retinal disease during pregnancy; although, even if not identified before conception, important retinopathy can develop during pregnancy [96]. Therefore, it is reasonable that women

with diabetes not known to have retinopathy get an eye evaluation soon after pregnancy is achieved [68].

There is a direct relationship between the severity of pre-conception retinopathy and the risk for progression of retinopathy during gestation [96]. For this reason, women with a diagnosis of pre-gestational T1DM or T2DM and who plan to become pregnant, or are already pregnant, should receive counseling on this risk [68, 98]. These women should have a detailed ocular evaluation by a qualified ophthalmologist [68].

Risk factors associated with progression of retinopathy in pregnant women are pre-conception hypertension [99], uncontrolled hypertension during pregnancy [100], preeclampsia [101], and poorly controlled glycemia at the beginning or during pregnancy [97]. Paradoxically, rapid establishment of tight glycemic control in women with diabetic retinopathy has been associated with worsening of retinal disease [95].

The main goal of screening for diabetic retinopathy is preventing and/or reversing vision loss by means of treatment of retinopathy [98]. If retinopathy has been identified and it is severe enough to warrant therapy, it is strongly recommended to defer conception until retinopathy is treated appropriately and stabilized [98]. In addition, once women with established background retinopathy get pregnant, they should be followed by their ophthalmologist every trimester, then within 3 months of giving birth, and then as needed [68].

Women with GDM do not need retinal examination during pregnancy, as they appear to lack an increased risk for retinopathy during pregnancy, in contrast to those with pre-existing diabetes [102].

Diabetic Kidney Disease

Women with diabetes who plan pregnancies should receive pre-conception kidney function evaluation, by means of creatinine and urinary albumin-to a -creatinine ratio testing [53], as well as estimated glomerular filtration rate (eGFR) [68].

Mild degree of diabetic kidney disease may worsen during pregnancy. Mild renal dysfunction is usually both modest and reversible once pregnancy is completed [103]. Mild renal dysfunction, however, can result in more significant degrees of proteinuria and renal impairment when blood pressure and blood glucose are not well controlled during pregnancy [104]. Therefore, all women with diabetes and any degree of pre-conceptional renal dysfunction should be monitored regularly during pregnancy [68].

In women with more severe pre-conceptional renal dysfunction (e.g., reduced GFR and elevated serum creatinine), renal function can further deteriorate during pregnancy and may be irreversible [105, 106]. These women should be assessed by a nephrologist before pregnancy [68].

Angiotensin-converting enzyme inhibitors (ACEI) are the first-line medical therapy for diabetic kidney disease, although these are contraindicated during pregnancy. Alpha methyldopa is considered safe during early pregnancy. Diltiazem, which is a more effective agent in preventing progression of nephropathy, can be used at the end of the first trimester [107]. Preeclampsia is the most common complication in patients with overt nephropathy; other maternal complications include anemia and nephrotic syndrome. Fetal complications include fetal distress, intrauterine growth retardation, preterm delivery, and stillbirth. Diabetic kidney disease, in the absence of hypertension, impacts fetal outcome when renal function is impaired by at least 50% [90]. With improved control of pre-conception and perinatal glycemia, and blood pressure, perinatal mortality has decreased to 5% [90].

Treatment: Pharmacologic Therapy and Monitoring

Close follow-up by a diabetes team is required throughout gestation to assure maintenance of strict glycemic control. Office visits every 2–3 weeks are usually necessary with more frequent telephone contact as needed (see Table 3).

Multiple blood glucose measurements and insulin injections are often required to achieve

Table 3 Plan of care in diabetic pregnancy

Five to nine blood glucose measurements/day
Hemoglobin A1C every 4–6 weeks
Office visits every 2–3 weeks
Telephone contact (as needed)
Fetal surveillance

tight glycemic control. As noted previously, postprandial monitoring seems to result in improved fetal outcome. Indeed, postprandial blood glucose levels are the most important predictor of fetal macrosomia [108]. Hemoglobin A1C should be monitored to confirm the level of control. The usual insulin requirements in women with pre-existing T1DM are similar to those in women with GDM who required insulin, as outlined above. Insulin pump therapy can achieve glucose control and perinatal outcomes equal to multiple injection regimens [109]. As discussed for women with GDM, women with T2DM must be treated with insulin during pregnancy. Again, insulin requirements in these patients are often high due to obesity and insulin resistance.

Diet and Exercise

As discussed for women with GDM, the patients with pre-gestational diabetes should receive appropriate dietary counseling by a nutritionist or other professional and followed closely. Exercise may be beneficial for pregnant patients with T2DM. Exercise in pregnant women with T1DM may lead to increased hypoglycemic episodes and is only permitted in women who participated in an exercise program prior to becoming pregnant [90].

Hypoglycemia

Hypoglycemia is an important complication of tight glucose control during pregnancy. Early pregnancy is associated with decreased fasting glucose levels due to increased glucose uptake by the placental fetal unit and decreased hepatic glucose production. The majority of hypoglycemic episodes occur during the first trimester. Recurrent episodes of hypoglycemia may be associated with small-for-gestational-age infants [58], and severe prolonged episodes of hypoglycemia can result in intrauterine fetal demise [110].

Diabetic Ketoacidosis

Although the frequency of diabetic ketoacidosis (DKA) has decreased markedly, it remains a serious emergency in a pregnant woman with T1DM, and it is associated with increased fetal morbidity and mortality. Ketogenesis appears to be accelerated during the third trimester. The mechanism by which DKA results in poor fetal outcome is not clear but is hypothesized to involve fetal hypoxia. Another possibility is that the fetus develops acidosis and hypokalemia with subsequent cardiac arrest [111]. The fetal heart rate should be continuously monitored while the mother is undergoing intensive treatment for DKA. It is also prudent to alert a neonatologist. In a retrospective, matched control study of 90 patients, there was an increased risk of maternal DKA when subcutaneous insulin infusion was used versus multiple insulin injections during pregnancy in women with overt diabetes [112].

Labor and Delivery

Women with diabetes, regardless of type (e.g., T1DM, T2DM, and GDM), experience rapid changes in serum levels of placental hormones in the postpartum period; thus, maternal hypoglycemia is a concern. It has been described that elevated glucose levels in the maternal serum in the peripartum period increase the risk for neonatal hypoglycemia and fetal academia [113, 114], birth asphyxia, and abnormal fetal heart rate [115], potentially causing fetal distress. Although these associations have been demonstrated mostly in observational studies of women with T1DM, it is reasonable to consider that avoidance of maternal hyperglycemia is a crucial aspect in the management in this period [113].

Women with GDM receiving insulin therapy, commonly will not require it once labor begins. Blood glucose levels should be monitored closely during labor to determine the patient's insulin requirements [116].

Several factors are implicated in determining insulin requirement in the intrapartum period. The most important of those is the type of maternal diabetes (e.g., T1DM, T2DM, or GDM). In addition, insulin requirements are influenced by the specific phase of labor. Usually these remain stable during the latent phase of labor and decrease significantly in the active phase. In addition, it has been observed that the degree of glucose control during gestation may impact the requirements of insulin during the peripartum period [116, 117].

Women with poorly controlled glucose levels throughout pregnancy may require higher doses of insulin in the peripartum period. Also, infants born from mothers with uncontrolled diabetes are at risk for severe neonatal hypoglycemia due to hyperinsulinemia from secondary hyperplasia of the pancreas. This becomes a challenging situation, since even with tight glycemic control in the peripartum period, neonatal hypoglycemia becomes difficult to prevent [118]. An ideal strategy to maintaining target glycemia in these phases has not been determined. The management strategy should be implemented by the individual provider in order to achieve safe glucose levels. A target glycemia of 72–126 mg/dL (4.0–7.0 mmol/L) during labor and delivery in women with overt or GDM has been recommended [68] (see Fig. 3).

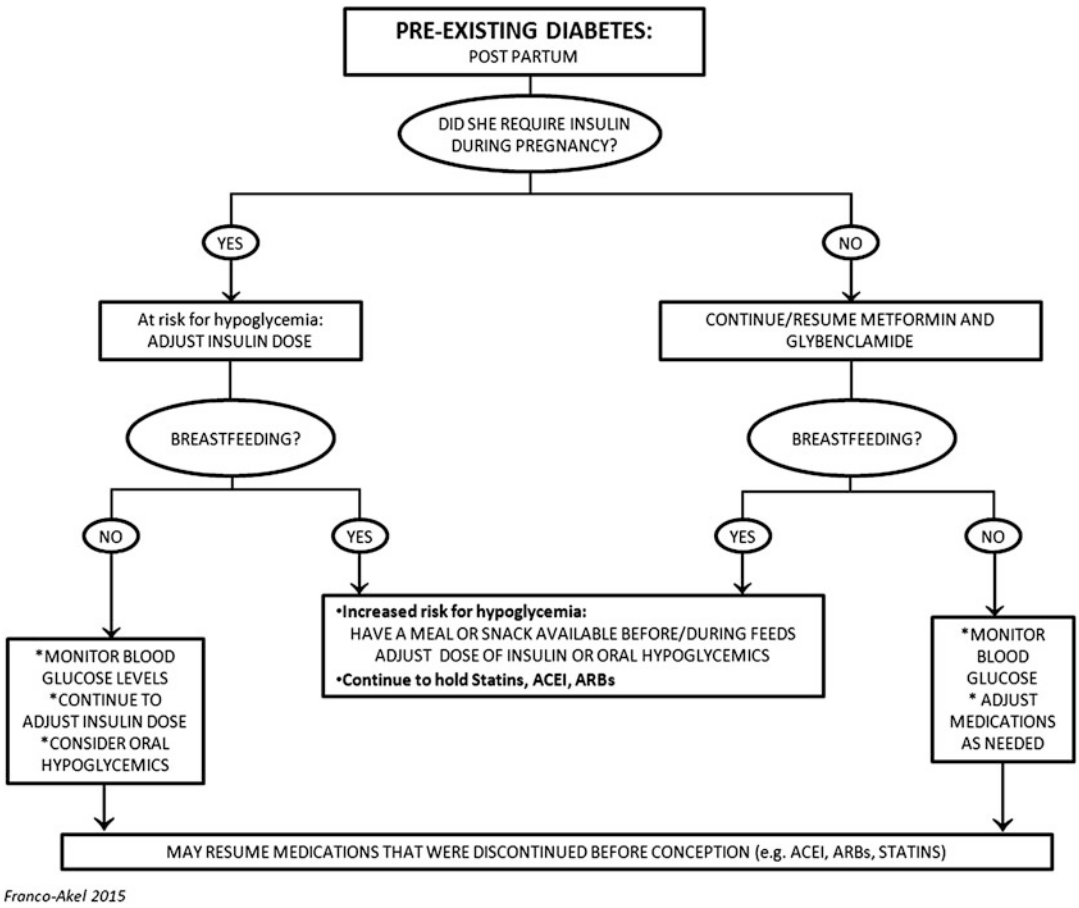

Fig. 3 Postpartum follow-up in women with pre-existing diabetes

Fetal Surveillance

Fetal surveillance may be deferred until the 35th week in patients with pre-gestational diabetes who have been under strict metabolic control. Those patients with poor control, nephropathy, hypertension, or vascular disease should begin surveillance at week 26. The best method of surveillance is via fetal ultrasound, which can estimate gestational age, screen for anomalies, determine amniotic fluid volume, and assess fetus status through Doppler and biophysical profiles [90].

Summary

The presence of diabetes in a pregnant woman can result in serious maternal and neonatal morbidity and mortality if not treated appropriately. Screening pregnant women for gestational diabetes and attainment of euglycemia, either by diet or insulin therapy, clearly prevents potentially catastrophic maternal and fetal events. Pregnancies that suffer from hyperglycemia early in gestation are at high risk for fetal loss and malformations. Thus, pre-conception care is essential for all women with diabetes type 1 and type 2. Diabetic women of reproductive age must be continuously reminded of the need to plan their pregnancies. Maintenance of strict glycemic control requires tremendous effort on the part of the patient and the health-care team. This should be considered an achievable goal in all pregnant women with diabetes.

Acknowledgments We would like to thank Amanda Busta, undergraduate student at NYU, for her invaluable assistance in the preparation and editing of this manuscript, and to Jill Gregory, CMI, FAMI for the designing an illustration of figure 1.

References

1. American diabetes association. Diabetes care. Diagnosis and classification of diabetes mellitus. 2006;29 (Suppl 1):S43–8.
2. Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33:676–82.
3. Falavigna M. Effectiveness of gestational diabetes treatment: a systematic review with quality of evidence assessment. Diabetes Res Clin Pract. 2012;98:396–405.
4. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2002. Natl Vital Stat Rep. 2003;52:1.
5. Martin J. et al. Births: final data for 2013. NVSR. 64 (1):20. (PHS) 2014–1120. Supplemental table I–6.
6. Jovanovic L, Nakai Y. Successful pregnancy in women with type 1 diabetes: from preconception through postpartum care. Endocrinol Metab Clin North Am. 2006;35:79–97.
7. American diabetes association. Diabetes care. Management of diabetes in pregnancy. 2015;38 (Suppl 1): S77–9.
8. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am. 2007;34(2):173–99.
9. Mauricio D, Balsells M, Morales J, Corcoy R, Puig-Domingo M, de Leiva A. Islet cell autoimmunity in women with gestational diabetes and risk of progression to insulin-dependent diabetes mellitus. Diabetes Metab Rev. 1996;12(4):275–85.
10. Dunne F, Brydon P, Smith K, Gee H. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990–2002. Diabet Med. 2003;20:743–8.
11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477–86.
12. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361:1339–48.
13. Krall LP, Levine R, Barnett D. The history of diabetes. In: Khan R, Weir GC, editors. Joslin's diabetes mellitus. Malvern: Lee & Febiger; 1994.
14. LeCorché E. Du diabete dans ses rapports avec la vie uterine. La menstruation et la grossesse. Ann Gynecol Obstet. 1885;24:257.
15. Feig DS, Palda VA. Type 2 diabetes in pregnancy: a growing concern. Lancet. 2002;359:1690–2.
16. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. Obstet Gynecol Surv. 1986;41:325–35.
17. Reece EA, Homko CJ, Wu YK, Wiznitzer A. Metabolic fuel mixtures and diabetic embryopathy. Clin Perinatol. 1993;20:517–32.
18. Duncan JM. On puerperal diabetes. Trans Obstet Soc Lond. 1882;24:256.
19. Joslin EP. Treatment of diabetes mellitus. Philadelphia: Lea and Febiger; 1923.

20. Pedersen J. The pregnant diabetic and her newborn: problems and management. Baltimore: Williams and Wilkins; 1977.
21. Rubin A, Murphy DP. Studies in human reproduction. III. The frequency of congenital malformations in the offspring of nondiabetic and diabetic individuals. J Pediatr. 1958;53:579–85.
22. Desoye G, Hauguel-de Mouzon S, Shafrir E. The placenta in diabetic pregnancy. In: Hod M, Jovanovic L, Di Renzo G, de Leiva A, Langer O, editors. Textbook of diabetes and pregnancy. New York: Martin Dunitz; 2003. p. 126–49.
23. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. J Nutr. 2003;133(5 Suppl 2):1674S–83.
24. Handwerger S, Freemark M. The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. J Pediatr Endocrinol Metab. 2000;13:343.
25. Boden G. Fuel metabolism in pregnancy and gestational diabetes mellitus. Obstet Gynecol Clin North Am. 1996;23:1–10.
26. Yogev Y, Ben-Haroush A, Hod M. Pathogenesis of gestational diabetes mellitus. In: Hod M, Jovanovic L, Di Renzo G, de Leiva A, Langer O, editors. Textbook of diabetes and pregnancy. New York: Martin Dunitz; 2003. p. 39–49.
27. Lain K, Catalano P. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50(4):938–48.
28. Kirwan JP, Haugel-De Mouzon S, Lepercq J, et al. TNF-alpha is a predictor of insulin resistance in human pregnancy. Diabetes. 2002;51:2207–13.
29. Xiang AH, Peters RK, Trigo E, Kjos SL, Lee WP, Buchanan TA. Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes. Diabetes. 1999;48:848–54.
30. Metzger B, Buchanan T, Coustan D, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 2007;30 Suppl 2:S251–60.
31. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. Am J Obstet Gynecol. 2010;203(5):467.e1–e6.
32. http://www.idf.org/gestational-diabetes
33. American diabetes association. Diabetes care. Classification and diagnosis of diabetes. 2016;39 (Suppl 1): S13–22.
34. American diabetes association. Diabetes care. Position statement. 2014;37 (Suppl 1):S14–80.
35. American diabetes association. Diabetes care. Management of diabetes in pregnancy. 2015;38(Suppl): S77–9.
36. Danilenko-Dixon DR, Van Winter JT, Nelson RL, Ogburn Jr PL. Universal versus selective gestational diabetes screening: application of 1997 American Diabetes Association recommendations. Am J Obstet Gynecol. 1999;181(4):798–802.
37. Chevalier N, Fénichel P, Giaume V, Loizeau S, Bongain A, Daideri G, Brucker-Davis F, Hiéronimus S. Universal two-step screening strategy for gestational diabetes has weak relevance in French Mediterranean women: should we simplify the screening strategy for gestational diabetes in France? Diabetes Metab. 2011;37(5):419–25.
38. Avalos GE, Owens LA, Dunne F, ATLANTIC DIP Collaborators. Applying current screening tools for gestational diabetes mellitus to a European population: is it time for change? Diabetes Care. 2013;36 (10):3040–4.
39. American diabetes association. Diabetes care. Classification and diagnosis of diabetes. 2015;38 (Suppl 1): S8–16.
40. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and American college of endocrinology – clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015. Endocr Pract. 2015;21 Suppl 1:1–87.
41. Vandorsten JP, Dodson WC, Espeland MA, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements. 2013;29:1–31.
42. Committee on Practice Bulletins–Obstetrics. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol. 2013;122:406–16.
43. Duran A, S'aenz S, Torrej'on MJ, et al. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: gestational Diabetes Study. Diabetes Care. 2014;37:2442–50.
44. Ethridge Jr JK, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the International Association of the Diabetes and Pregnancy Study Groups criteria. Obstet Gynecol. 2014;124:571–8.
45. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ. 2010;340:c1395.
46. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2001.
47. Lindsay MK, Graves W, Klein L. The relationship of one abnormal glucose tolerance test value and pregnancy complications. Obstet Gynecol. 1989;73 (1):103–6.
48. Langer O, Anyaegbunam A, Brustman L, Divon M. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. Am J Obstet Gynecol. 1989;161 (3):593–9.
49. Langer O, Yogev Y, Most O, et al. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol. 2005;192:989–97.

50. Refuerzo JS. Oral hypoglycemic agents in pregnancy. Obstet Gynecol Clin North Am. 2011;38:227–34. ix.
51. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp Jr JM, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB, Eunice Kennedy Shriver National Institute of Child Health, Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361(14):1339–48.
52. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352(24):2477–86.
53. American diabetes association. Diabetes care. Management of diabetes in pregnancy. 2016;39 (Suppl 1): S94–8.
54. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25(10):1862–8.
55. Lee-Parritz A. Contemporary management of gestational diabetes. Curr Opin Endocrinol Diabetes Obes. 2011;18:395–400.
56. Crume TL, Ogden L, West NA, et al. Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. Diabetologia. 2011;54:87–92.
57. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med. 2013;159(2):123–9.
58. Metzger B, Coustan D. Summary and recommendations of the fourth international workshop – conference on gestational diabetes mellitus. Diabetes Care. 1998;21 Suppl 2:B161.
59. Ceysens G, Rouiller D, Boulvain M. Exercise for diabetic pregnant women. Cochrane Database Syst Rev. 2006;3:CD004225.
60. Barakat R, Pelaez M, Lopez C, Lucia A, Ruiz JR. Exercise during pregnancy and gestational diabetes-related adverse effects: a randomised controlled trial. Br J Sports Med. 2013;47(10):630–6.
61. Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care. 2013;36(1):56–62.
62. American College of Obstetricians and Gynecologists Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 30, Sept 2001.
63. Grant SH, Wolever TMS, O'Connor DL, et al. Effect of low glycaemic index diet on blood glucose in women with gestational hyperglycaemia. Diabetes Res Clin Pract. 2011;91:15–22.
64. Shirazian T, Monteith S, Friedman F, Rebarber A. Lifestyle modification program decreases pregnancy weight gain in obese women. Am J Perinatol. 2010;27:411–4.
65. De Barros MC, Lopes MAB, Francisco RPV, et al. Resistance exercise and glycemic control in women with gestational diabetes mellitus. Am J Obstet Gynecol. 2010;203:e1–6.
66. Kahn BF, Davies JK, Lynch AM, Reynolds RM, Barbour LA. Predictors of glyburide failure in the treatment of gestational diabetes. Obstet Gynecol. 2006;107:1303–9.
67. Conway DL, Gonzalez O, Skiver D. Use of glyburide for treatment of gestational diabetes: the San Antonio experience. J Matern Fetal Neonatal Med. 2004;15:51–5.
68. Blumer I, Hadar E, Hadden DR, Jovanovic L, Mestman JH, Murad MH, Yogev Y. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98 (11):4227–49.
69. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. Fertil Steril. 2006;86(3):658–63.
70. Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. Ann Pharmacother. 2011;45 (1):9–16.
71. Mathiesen ER, Hod M, Ivanisevic M, et al. Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35 (10):2012–7.
72. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to neutral protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med. 2008;25:442–9.
73. Lepercq J, Jacqueminet S, Hieronimus S, Timsit J, Grimaldi A. Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes. Diabetes Metab. 2010;36:209–12.
74. Negrato CA, Rafacho A, Negrato G, et al. Glargine vs. NPH insulin therapy in pregnancies complicated by diabetes: an observational cohort study. Diabetes Res Clin Pract. 2010;89:46–51.
75. Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in

type 1 diabetes in the UK. Diabet Med. 2009;26:803–14.
76. Loukovaara S, Immonen I, Teramo KA, Kaaja R. Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. Diabetes Care. 2003;26:1193–8.
77. Durnwald CP, Landon MB. A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy. J Matern Fetal Neonatal Med. 2008;21:309–13.
78. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician. 2015;91(7):460–7.
79. Langer O, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med. 2000;343:1134–8.
80. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010;115(1):55–9.
81. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. MiG trial investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–15.
82. Dhulkotia JS, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010;203 (5):457.e1–e9.
83. Feig DS, Briggs GG, Kraemer JM, et al. Transfer of glyburide and glipizide into breast milk. Diabetes Care. 2005;28:1851–5.
84. Hale TW, Kristensin JH, Hackett LP, et al. Transfer of metformin into human milk. Diabetologia. 2004;45:1509–14.
85. Schaefer-Graf UM, Kjos SL, Fauzan OH, et al. A randomized trial evaluating a predominately fetal growth-based strategy to guide management of gestational diabetes in Caucasian women. Diabetes Care. 2004;27:297–302.
86. Holmes VA, Young IS, Patterson CC, et al. Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, preeclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. Diabetes Care. 2011;34:1683–8.
87. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000;49:2208–11.
88. Miller E, Hare JW, Cloherty JP, et al. Elevated maternal Hb A1C and major congenital anomalies in infants of diabetic mothers. N Engl J Med. 1998;304:1331–4.
89. Karlsson K, Kjeller I. The outcome of diabetic pregnancies in relation to the mother's blood glucose level. Am J Obstet Gynecol. 1972;112:213–20.
90. Jovanovic L. Medical emergencies in the patient with diabetes during pregnancy. Endocrinol Metab Clin North Am. 2000;29(4):771–87.
91. American Diabetes Association. ADA position statement: preconception care of women with diabetes. Diabetes Care. 2001;24 Suppl 1:S66–8.
92. Kusters DM, Hassani Lahsinoui H, van de Post JA, Wiegman A, Wijburg FA, Kastelein JJ, Hutten BA. Statin use during pregnancy: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther. 2012;10(3):363–78.
93. Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. Ophthalmology. 1996;103:1815–9.
94. Best RM, Chakravarthy U. Diabetic retinopathy in pregnancy. Br J Ophthalmol. 1997;81:249–51.
95. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care. 2000;23:1084–91.
96. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Diabetes Care. 1995;18:631–7.
97. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with type 1 diabetes. Diabet Med. 2010;27:431–5.
98. American diabetes association. Diabetes care. Microvascular complications and foot care. 2016; 39 (Suppl 1):S72–80.
99. Cundy T, Slee F, Gamble G, Neale L. Hypertensive disorders of pregnancy in women with type 1 and type 2 diabetes. Diabet Med. 2002;19:482–9.
100. Rosenn B, Miodovnik M, Kranias G, et al. Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. Am J Obstet Gynecol. 1992;166:1214–8.
101. Lövestam-Adrian M, Agardh CD, Aberg A, Agardh E. Pre-eclampsia is a potent risk factor for deterioration of retinopathy during pregnancy in type 1 diabetic patients. Diabet Med. 1997;14:1059–65.
102. Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Diabetes. 2007;56:2990–6.
103. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Mølvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetes Care. 2001;24:1739–44.
104. Leguizamon G, Reece EA. Effect of medical therapy on progressive nephropathy: influence of pregnancy, diabetes and hypertension. J Matern Fetal Med. 2000;9:70–8.

105. Biesenbach G, Grafinger P, Stöger H, Zazgornik J. How pregnancy influences renal function in nephropathic type 1 diabetic women depends on their pre-conceptional creatinine clearance. J Nephrol. 1999;12:41–6.
106. Gordon M, Landon MB, Samuels P, Hissrich S, Gabbe SG. Perinatal outcome and long-term follow-up associated with modern management of diabetic nephropathy. Obstet Gynecol. 1996;87:401–9.
107. Kitzmiller JL, Combs CA. Diabetic nephropathy and pregnancy. Obstet Gynecol Clin North Am. 1996;23:173.
108. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels predict birth weight: the diabetes in early pregnancy study. Am J Obstet Gynecol. 1991;164:103–11.
109. Gabbe S. New concepts and applications in the use of the insulin pump during pregnancy. J Matern Fetal Med. 2000;9:42–5.
110. Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic ketoacidosis in pregnancy. Obstet Gynecol Clin North Am. 1996;23:87–107.
111. Kitzmiller JL. Diabetic ketoacidosis and pregnancy. Contemp Obstet Gynecol. 1982;20:141–8.
112. Chen R, Ben-Haroush A, Weissmann-Brenner A, Melamed N, Hod M, Yogev Y. Level of glycemic control and pregnancy outcome in type 1 diabetes: a comparison between multiple daily insulin injections and continuous subcutaneous insulin infusions. Am J Obstet Gynecol. 2007;197:404. e1–e5.
113. Kalra P, Anakal M. Peripartum management of diabetes. Indian J Endocrinol Metab. 2013;17 Suppl 1: S72–6.
114. Miodovnik M, Mimouni F, Tsang RC. Management of the insulin-dependent diabetic during labor and delivery. Influences on neonatal outcome. Am J Perinatol. 1987;4:106–14.
115. Feldberg D, Dicker D, Samuel N, Peleg D, Karp M, Goldman JA. Intrapartum management of insulin-dependent diabetes mellitus (IDDM) gestants. A comparative study of constant intravenous insulin infusion and continuous subcutaneous insulin infusion pump (CSIIP). Acta Obstet Gynecol Scand. 1988;67:333–8.
116. Castorino K, Jovanovic L. Pregnancy and diabetes management: advances and controversies. Clin Chem. 2011;57:221–30.
117. Garabedian C, Deruelle P. Delivery (timing, route, peripartum glycemic control) in women with gestational diabetes mellitus. Diabetes Metab. 2010;36:515–21.
118. Kline GA, Edwards A. Antepartum and intra-partum insulin management of type 1 and type 2 diabetic women: impact on clinically significant neonatal hypoglycemia. Diabetes Res Clin Pract. 2007;77: 223–30.