Chapter

Treatment of Gestational Diabetes

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Abstract

Management of gestational diabetes mellitus (GDM) should consider both the maternal, fetal, and neonatal effects of the disease, line of treatment, and physiological changes during pregnancy. Women with GDM are classified into two categories according to their fasting blood glucose levels. Dietary control is mandatory in both classes, and the addition of pharmacological agents in those with fasting and 2-h postprandial plasma glucose levels <95 and 120 mg/dL is controversial (American College of Obstetricians and Gynecologists, 2013). Individualization of the diet in GDM according to women weight and height is recommended by the American Diabetes Association (ADA), and restriction of carbohydrate to a level that maintains normal glucose level is mandatory with individualization of the caloric intake according to women BMI and weight gain during pregnancy.

Keywords: gestational diabetes, management, diabetic diet, insulin, exercise, oral hypoglycemic

1. Introduction

The main aim of treatment of gestational diabetes is to prevent fetal, maternal, and neonatal complications. A randomized controlled trial which involved 1000 women with GDM showed that treatment of GDM is associated with the reduction of all neonatal complications, namely, birth injuries, shoulder dystocia, and perinatal morbidity and mortality. Treatment also reduced the rate of development of preeclampsia from 18 to 12% and the rate of large for gestational age (LGA) from 22 to 13% [1]. Even in women with mild GDM, treatment reduced the rate of LGA, the mass of neonatal fat, shoulder dystocia, cesarean section, and hypertensive disorders associating pregnancy [2, 3].

Improving the pregnancy outcome in women with GDM can be achieved through maintenance of fasting blood sugar levels <95 mg/dl (5.3 mmol/L), 1-h postprandial blood sugar <140 mg/dl (7.8 mmol/L), and 2-h postprandial blood sugar <120 mg/dl as recommended by both the American College of Obstetricians and Gynecologists (ACOG) and American Diabetes Association [4].

The treatment of GDM starts with dietary modifications along with particular nutritional approaches [5–7] combined with exercise [8, 9]. If this combination failed to maintain the needed glucose levels, pharmacological treatment starts, regardless of the lines used for treatment, proper monitoring of maternal health, fetal condition, and blood sugar levels.

1.1 Dietary modifications

Dietary counseling should be individualized according to women weight and height [10] through a registered dietitian [11].

JSOG committee on nutrient and metabolism problems described a caloric intake of 25–30 kcal/kg (+150 Kcal for the first half and + 350 kcal for the second half of pregnancy) [12].

The Ministry of Health and Welfare recommended a caloric intake of 25–30 kcal/kg (+ 50,250 and 450 kcal for the first, second, and third trimester, respectively) [13].

The ideal diet components are not yet determined. However excessive weight gain with postprandial hyperglycemia is commonly associated with diet that included 50–60% of carbohydrate. ACOG recommended the limitation of carbohydrate to 33–40% of the required calories and the remaining 60% to be gained from proteins (20%) and fats (40%) [4].

The complex form of carbohydrates is preferable over simple ones as they are absorbed slower without producing significant hyperglycemia. Complex carbohydrates also decrease insulin resistance [6].

If the routine three meals daily failed to achieve the target blood sugar, each meal should be divided in 2:1 or 1:1 ratio to eat 4–6 meals per day [14].

The ADA recommended "MyPlate" as a healthy guide for each meal which consists of 25% protein, 25% starch, and 50% non-starchy foods as vegetables especially steamed ones. Creating MyPlate is a simple and effective method allowing proper control of the blood glucose levels and losing weight (http://www.diabetes.org/food-and-fitness/food/planning-meals/create-your-plate/).

Some foods to be avoided include highly processed foods as white bread, fast foods, alcohol, baked products as muffins and cakes, sugary drinks, candy, and high starch foods as white rice and white potatoes.

2. Exercise

Although there are many randomized studies done to evaluate the effects of physical exercise and lifestyle modifications in adults with diabetes, only few ones evaluated these effects in pregnant women with GDM. These studies proved that exercise improves the blood glucose [8, 15–18]. These beneficial effects may occur as a result of the increase of lean muscle mass with subsequent increase in insulin sensitivity. So a moderate exercise program is highly recommended for women with GDM [11]. A moderate intensity aerobic exercise for at least 150 minutes weekly [19] or simple exercise as walking after each meal for 10–15 minutes [20] is recommended.

The Finnish GDM prevention trial (RADIEL)—a multicenter randomized controlled study—evaluated the efficacy of combined dietary and physical activity modifications in prevention of GDM and obesity-related perinatal complications [21]. Counseling was achieved through three visits to the study nurse at 13, 23, and 35 weeks of pregnancy. Dietary modification was done according to Nordic Nutrition Recommendations encouraging the intake of vegetables, fruits and berries, high-fiber whole-grain products, low-fat dairy products, vegetable fats high in unsaturated fatty acids, and fish and low-fat meat products with lower intake of sugar- and saturated fatty acid-rich foods. [22]. Physical moderate exercise for 150 minutes at least per week is recommended [23]. They found that these modifications had no effects on either the incidence of GDM or perinatal complications [24].

2.1 Pharmacologic treatment

Pharmacologic treatment is indicated when dietary management and exercise failed to achieve the target glucose levels.

Basically, insulin is the standard treatment for GDM [11]. Insulin has the advantage of non-crossing of the placenta. It is given according to the timing of the occurrence of hyperglycemia. If hyperglycemia is present throughout the day both in the fasting and postprandial state, a divided dose of combination of either long or intermediate acting insulin with the short acting one is recommended. The typical total starting dose is 0.7–1 unit/ kg of body weight. If hyperglycemia is detected only at a specific times, focusing the insulin dose at that specific time of hyperglycemia is done, e.g., high fasting blood sugar is treated using a nighttime intermediate-acting insulin, while elevated post-breakfast blood sugar is treated by short-acting insulin before breakfast. The maintenance dose is then adjusted according to the monitored blood glucose [4].

The insulin analogs as insulin aspart and lispro are preferred over the regular insulin as a short-acting type. They do not cross the placenta, and their main advantage is their faster onset of action allowing the women to receive their injection at the time of the meal not 10–15 minutes before it as needed in the regular type. This advantage provides better control of the glucose level, and less attacks of hypoglycemia resulted from timing error [25, 26]. Intermediate- and long-acting insulin include the basic isophane insulin (NPH) and recent insulin glargine and detemir (**Table 1**) [27–29].

2.1.1 Oral antidiabetic medications

Historically oral hypoglycemics should be avoided as early agents cross the placenta, resulting in fetal hyperinsulinemia with subsequent macrosomia and congenital malformations (most commonly in the ear) and severe neonatal hypoglycemia. Now their use in GDM is increasing despite them not approved by the US Food and Drug Administration [31] and the recommendation of ADA that insulin is the first-line therapy for GDM [11] as these products have advantages as ease of tablet intake, ease of storage, and safe needle disposal.

Oral antidiabetic medications include biguanides, sulfonylurea, acarbose, Guar gum, and thiazolidinedione.

Metformin is a biguanide that decreases intestinal glucose absorption and hepatic gluconeogenesis and increases peripheral glucose uptake. Historically, it was given to women used in pregestational diabetic women and women with polycystic ovary syndrome who suffer from infertility. In the latter group, it was continued until completion of the first trimester, despite the limited evidence of its ability to improve pregnancy outcome [32].

Type	Onset (min)	Peak (h)	Duration (h)
Insulin lispro	1–15	1–2	4–5
Insulin aspart	1–15	1–2	4–5
Regular insulin	30–60	2–4	6–8
Isophane insulin suspension (NPH)	60–180	5–7	13–18
Insulin glargine	60–120	No peak	24
Insulin detemir	60–180	Minimal at 8–10	18–26

Modified from Gabbe and Graves [30].

Table 1.
Describes the onset, peak, and duration of action of the commonly used insulins.

Although metformin can cross the placenta, its long-term metabolic effects on the growing fetus are not known [33]. One study showed the absence of any developmental effects till the age of 2 years of life [34].

In a randomized controlled trial, 751 pregnant women having GDM were assigned to treatment with insulin or metformin ± insulin. The perinatal outcome was similar among the two groups [35].

Another smaller trial showed that women assigned to metformin had lower blood glucose, lower maternal weight gain during pregnancy, and lower incidence of neonatal hypoglycemia [36].

In a network meta-analysis that included unpublished trials, there was a difference between insulin and metformin treatments regarding neonatal birth weight, hypoglycemia, or mode of delivery [37].

Therefore, women with GDM are carefully counseled about the use of metformin. They should know that it is not superior to insulin, there are no definitive data about its long-term effects of the growing fetus, and 26–46% of women on metformin will need to add insulin to replace it or to potentiate its effects for better glucose control [35, 36].

Metformin starting dose is usually 500 mg once daily at nighttime for 1 week, and then the dose is increased according to the response. The maximum daily dose is 2500–3000 mg daily in two–three divided doses.

Contraindications to metformin include impaired kidney function, and serum creatinine should be evaluated before the start of treatment.

Side effects of metformin occur in 2.5–45.7% of cases [38], and the commonest is GIT upset in the form of abdominal pain and diarrhea. Its use may be associated with higher rate of lactic acidosis, preeclampsia, and neonatal jaundice. So the drug is instructed to be administered with meals and to increase the needed dose gradually.

A systematic review stated that metformin use during pregnancy is safe and effective regarding the short-term pregnancy outcomes. There are no solid guidelines about the duration of metformin use during pregnancy, so it is based on clinical experience on a case-by-case basis [39].

Sulfonylurea used in GDM includes glyburide, tolbutamide, glibenclamide, and gliclazide. Chlorpropamide crosses, while glibenclamide does not cross the placenta.

Glyburide augments insulin secretion by pancreas (through binding adenosine triphosphate potassium channel receptors of the beta cells) and extrapancreatic tissues. It also increases insulin sensitivity of peripheral tissues. It should not be used as a first-line treatment as most studies showed inferior results when compared to insulin or metformin [31].

The dose of glyburide is 2.5–20 mg per day in divided doses. The maximum dose is 30 mg daily [40]. Even with these high doses, 4–16% of patients will need the addition of insulin for adequate glycemic control [41–44].

Contraindications include allergy to sulfa, and side effects include mild infrequent GIT side effects as nausea, vomiting, and diarrhea.

Although some individual trials showed no difference regarding blood glucose control between glyburide and insulin [41–46], meta-analyses reported higher incidence of macrosomia, maternal, and neonatal hypoglycemia [35, 36, 47]. Other trials found that women used glyburide and had higher incidence of hypertension, hyperbilirubinemia, and still birth than those on insulin therapy [31, 42, 48–52].

Other sulfonylurea include Thiazolidinedione as Pioglitazone & Rosiglitazone which decrease insulin resistance by reducing RESISTIN hormone released from adipose tissue. Their use during pregnancy cannot be recommended as no enough reports to support their use.

A Cochrane meta-analysis evaluated 7381 women with GDM and reported similar pregnancy outcomes when insulin therapy is compared with oral antidiabetic agents (metformin, glyburide, both, and acarbose) [53]. However these oral antidiabetic agents have different safety and efficacy, so pooling all of them together against insulin weakens that meta-analysis.

To sum up, the current available data show the absence of short-term hazards, but the long-term effects are still unknown. So, the women should be counseled about the unknown proven safety of the oral antidiabetic agents and the high rate of need for adding insulin before describing it.

ACOG considers insulin as the first-line treatment for GDM and describes oral agents (mainly metformin and rarely glyburide) as an alternative in women who decline insulin use (for financial issues or non-availability of safe administration) after proper consultation.

3. Other medications used in GDM

As there are many evidences that link oxidative stress and development of complications of diabetes with pregnancy, the use of antioxidants was suggested to improve pregnancy outcome [54]. Oxygen free radicals released during aerobic metabolism cause cellular damage [55, 56]. Many authors reported the participation of reactive oxygen species in diabetes associated with pregnancy [57, 58].

An interesting randomized controlled trial was conducted that involved 200 women with GDM who were assigned to receive antioxidant (1 gram L-ascorbic acid daily) or placebo. Maged and colleagues found that antioxidants significantly decreased the required insulin dose to control blood sugar and oxidative markers (glutathione, malondialdehyde, superoxide dismutase). In placental tissue homogenate, maternal blood and neonatal blood were significantly different between the two groups. In the antioxidant group, the neonatal blood sugar was more stable within 2 h of delivery, and the neonatal ICU admission was lower than other women. They concluded that the use of antioxidant administration during pregnancy in women with GDM reverses the oxidative stresses resulting in the improvement of neonatal outcome [59].

4. Glucose monitoring

Monitoring of glucose control is through blood testing urine analysis for glucose and ketone bodies and glycosylated hemoglobin.

The optimal frequency of blood glucose testing in women with GDM is not known. However, four evaluations daily seem to be satisfactory (fasting and after each meal) [4].

Fasting blood sugar is predictive of neonatal fat mass and subsequent development of childhood obesity and diabetes [60], and 1-h postprandial level was predictive of better blood sugar control and subsequent development of LGA and cesarean delivery [61], so both should be measured. The postprandial measurement can be after 1 or 2 h as the peak glucose level occurs almost 90 min after meals [62]. Measurement neither at 1 h nor at 2 h is superior to the other [63–65].

After stabilization of the blood sugar, individualization of the frequency of glucose measurement according to the gestational age, adherence of the patient to treatment and the needs of further adjustment is recommended. However the minimum is two measurements per day [4].

Women under self-monitoring of blood glucose daily had significantly lower incidence of fetal macrosomia and less weight gain than those under intermittent measurement of fasting glucose during semi-weekly antenatal visits [66].

de Veciana and colleagues randomly assigned 66 women with GDM for preprandial or 1-h postprandial measurement of blood sugar. They found that postprandial group had better blood glucose control with less macrosomia, cesarean delivery for cephalopelvic disproportion, and neonatal hypoglycemia [61].

A review included 10 trials of 538 women (468 and 70 women with type 1 and type 2 diabetes). Different glucose monitoring methods were compared without clear advantage of one method over the others. Two trials (43 women) comparing **self-monitoring versus standard care** proved no difference for cesarean section or glycemic control. One study (100 women) compared **self-monitoring versus hospitalization** and found no clear difference for hypertensive disorders, cesarean section, or preterm birth. Another study (61 women) which compared **preprandial versus postprandial glucose monitoring** proved no clear difference regarding cesarean section, macrosomia, or glycemic control. Three studies (84 women) which compared **automated telemedicine monitoring versus conventional system** found no clear difference for cesarean section and mortality or morbidity. **CGM was compared to intermittent monitoring** in two studies (225 women), and there was no difference for preeclampsia and cesarean section and large for gestational age. One trial (25 women) compared **constant CGM versus intermittent CGM** and found no clear difference between groups for cesarean section, glycemic control, or preterm birth [67].

4.1 Glycosylated hemoglobin

Hemoglobin (Hb) A forms about 90% of hemoglobin in adults, and its glycosylation occurs due to irreversible nonenzymatic binding of glucose to N-terminal of β chain. Hb A_1 is divided into Hb $A_{1\,a1}$, Hb $A_{1\,a2}$, Hb $A_{1\,b}$, and Hb $A_{1\,C}$ (the most important). The mean plasma glucose over the erythrocyte life span is correlated with the degree of glycosylation. Its advantages include that it is a single, non-fluctuating blood test that reflects the glucose levels over the last 4–8 weeks. So, HbA1c is an attractive test that can be added to routine investigations done in the first antenatal evaluation as it serves as a diagnostic tool for women with undiagnosed diabetes or at risk of its development [68]. If measured during the first trimester, it gives an idea about blood glucose control in the periconceptional period and during organogenesis. Its main disadvantage is its affection by red blood cell turnover [6] which results in the absence of clear recommendations for its use to diagnose GDM [69–71]. HbA1C increases also in cases of non-hemolytic anemias and chronic renal failure [72]. Women with A1c of 10–12% have up to a 25% risk of major malformations.

4.2 Fetal assessment

Like women with pregestational diabetes, women with GDM should follow antenatal fetal assessment especially those with poor glycemic control and women under medical treatment with insulin or oral antidiabetic agents [73]. It should start at 32 weeks of gestational age and earlier in women with GDM associated with other factors that may adversely affect fetal outcome as hypertensive disorders [74].

There is no consensus about antepartum fetal monitoring in properly controlled women without medical treatment, and if done it usually starts to alter at 32 weeks. The specific test used and its frequency are dependent on the regional practice, but

amniotic fluid measurement is probably included as polyhydramnios is commonly associated with fetal hyperglycemia [4].

At Parkland Hospital, women with GDM are routinely asked to count daily fetal kick especially during the third trimester, and women on insulin treatment are offered for hospital admission and CTG monitoring three times weekly [74].

5. Obstetrical management

Timing and management of delivery of women with GDM are dependent on glycemic control, fetal condition, and associated complications. Women with proper glycemic control without associated medical problems are followed up till term [75, 76].

A comparison was done between women with GDM who were subjected to labor induction at 38 weeks and those who were followed up till 41 weeks of gestation, which revealed similar CS rate and all other outcomes except the higher occurrence of neonatal hyperbilirubinemia in one study [77], lower incidence of LGA in another study [78], and lower incidence of shoulder dystocia in a third one [79] in the induction group. A more recent study found a lower rate of CS in the induction group [80]. So women with GDM using medications with proper control of blood sugar delivered better during the 39 weeks of gestation [4].

In women with poor control of their blood sugar, timing of delivery is determined by balancing the risk of prematurity and the ongoing risk of intrauterine fetal death. In general earlier delivery in women with good glycemic control is recommended [75, 76], but the clear guides for glycemic control and timing of delivery are absent [81]. In general delivery between the start of 37 weeks and the completion of 38 weeks appears appropriate, while delivery at 34 weeks till the completed 36 weeks should be attempted only in women with abnormal fetal well-being assessment and those with failed hospital control of blood sugar [4].

Ultrasound assessment of fetal size should be done in all women with GDM. However only 22% of fetuses diagnosed as LGA by ultrasound had macrosomia after birth [82]. To prevent one case of permanent brachial plexus injury, 588 and 962 CS should be performed for ultrasonographic estimated fetal weight of 4500 and 4000 gm, respectively [83, 84]. So women with GDM and macrosomic fetus should be counseled about the elective CS risks and benefits [85].

6. Postpartum evaluation

Women with GDM should be evaluated postpartum as 15–70% will develop diabetes later in life [86–90]. These women were estimated to have sevenfold increased risk of developing type 2 DM when compared to controls [91]. So, screening after 4–12 weeks of delivery is recommended to identify those with diabetes, impaired fasting glucose levels, or impaired glucose tolerance [11] (**Figure 1**).

ACOG practice bulletin No. 190: Gestational diabetes mellitus [4].

The Fifth International Workshop-Conference on Gestational Diabetes recommended that women with GDM undergo evaluation with a 75-g oral glucose tolerance test at 6–12 weeks postpartum [92]. These recommendations are shown in **Table 2**.

Women with GDM are at an increased risk for cardiovascular complications associated with dyslipidemia, hypertension, and abdominal obesity—the *metabolic syndrome* [74].

Kessous and colleagues found that women with GDM were 2.6 times more likely to be hospitalized for cardiovascular morbidity [93].

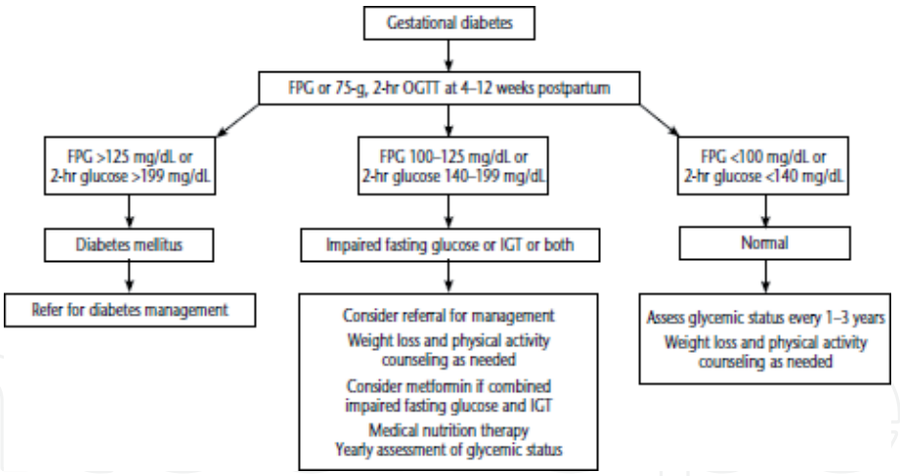

Figure 1.
Management of postpartum screening results. Abbreviations: FPG, fasting plasma glucose, OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Time	Test	Purpose
Post-delivery 1–3 days	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (6–12 week)	75 g, 2-h OGTT	Postpartum classification of glucose metabolism
1-year postpartum	75 g, 2-h OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Triannually	75 g, 2-h OGTT	Assess glucose metabolism
Prepregnancy	75 g, 2-h OGTT	Classify glucose metabolism

Metzger et al. [92].

Table 2.
Fifth international workshop-conference: Metabolic assessments recommended after pregnancy with gestational diabetes.

Shah and coworkers also reported excessive cardiovascular disease by 10 years in women with GDM [94].

7. Recurrent gestational diabetes

The risk of recurrence of GDM is estimated to be 40% in primiparous women [95]. Women with higher body mass index are more likely to have impaired glucose tolerance in subsequent pregnancies. Therefore, lifestyle modifications, including weight control and exercise between pregnancies, may prevent the recurrence of GDM [96]. Overweight and obese women in their first pregnancy will lower the risk of GDM, if they lose 2 or more units of their body mass index [97]. The risk of GDM in second pregnancy was 4.2% in women without GDM in their first pregnancy against 41.3 percent in those with a history of gestational diabetes in their first pregnancy [98].

8. Contraception

Women with recent GDM can use low-dose hormonal contraceptives safely as the rate of developing of diabetes is similar in oral contraceptive users and nonusers

of any hormonal contraception [99]. Care should be taken in women at risk of cardiovascular diseases as obese, hypertensive, and dyslipidemic women with direction of the contraceptive choice toward a method without potential cardiovascular consequences as intrauterine device.

Studies were reviewed and evaluated for quality according to the method outlined by the US Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

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References

[1] Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. The New England Journal of Medicine. 2005;**352**:2477-2486

[2] Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The New England Journal of Medicine. 2009;**361**:1339-1348

[3] 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. Annals of Internal Medicine. 2013;**159**:123-129

[4] Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin No. 190: Gestational diabetes mellitus. Obstetrics and Gynecology. 2018;**131**(2):e49-e64. DOI: 10.1097/AOG.0000000000002501

[5] Han S, Middleton P, Shepherd E, Van Ryswyk E, Crowther CA. Different types of dietary advice for women with gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2017;(2):CD009275. (Meta-analysis)

[6] Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial. Diabetes Care. 2009;**32**:996-1000

[7] Louie JC, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, et al. Diabetes Care. 2011;**34**:2341-2346

[8] Ceysens G, Rouiller D, Boulvain M. Exercise for diabetic pregnant women. Cochrane Database of Systematic Reviews. 2006;(3):CD004225. (Meta-analysis)

[9] Barakat R, Pelaez M, Lopez C, Lucia A, Ruiz JR. Exercise during pregnancy and gestational diabetes related adverse effects: A randomised controlled trial. British Journal of Sports Medicine. 2013;**47**:630-636

[10] Bantle JP, Wylie-Rosett J, Albright AL, et al. Nutrition recommendations and interventions for diabetes. Diabetes Care. 2008;**31**(1 Suppl):S61

[11] American Diabetes Association. Management of diabetes in pregnancy. Diabetes Care. 2017;**40**:S114-S119

[12] Sugawa T. Proposed committee report on nutrient and metabolism problems: Management policy for gestational diabetes mellitus and pregnant women with diabetes complications. Acta Obstetrica et Gynaecologica Japonica. 1985;**37**:473-477. (in Japanese)

[13] Ministry of Health, Labour and Welfare. Dietary Reference Intakes for Japanese (2010 Edition). 2nd ed. Tokyo: First Printing; 2010. (in Japanese)

[14] Sugiyama T. Management of Gestational Diabetes Mellitus. JMAJ. 2011;**54**(5):293-300

[15] Jovanovic-Peterson L, Durak EP, Peterson CM. Randomized trial of diet versus diet plus cardiovascular

conditioning on glucose levels in gestational diabetes. American Journal of Obstetrics and Gynecology. 1989;**161**:415-419

[16] Bung P, Bung C, Artal R, Khodiguian N, Fallenstein F, Spatling L. Therapeutic exercise for insulin-requiring gestational diabetics: Effects on the fetus—Results of a randomized prospective longitudinal study. Journal of Perinatal Medicine. 1993;**21**:125-137

[17] Halse RE, Wallman KE, Newnham JP, Guelfi KJ. Homebased exercise training improves capillary glucose profile in women with gestational diabetes. Medicine and Science in Sports and Exercise. 2014;**46**:1702-1709

[18] Anjana RM, Sudha V, Lakshmipriya N, Anitha C, Unnikrishnan R, Bhavadharini B, et al. Physical activity patterns and gestational diabetes outcomes – The wings project. Diabetes Research and Clinical Practice. 2016;**116**:253-262

[19] American Diabetes Association. Standards of medical care in diabetes—2011. Diabetes Care. 2011;**34**(Suppl. 1):S11-S61

[20] Davenport MH, Mottola MF, McManus R, Gratton R. A walking intervention improves capillary glucose control in women with gestational diabetes mellitus: A pilot study. Applied Physiology, Nutrition, and Metabolism. 2008;**33**:511-517

[21] Rönö K, Stach-Lempinen B, Klemetti MM, Kaaja RJ, Pöyhönen-Alho M, Eriksson JG, et al. Prevention of gestational diabetes through lifestyle intervention: Study design and methods of a Finnish randomized controlled multicenter trial (RADIEL). BMC Pregnancy and Childbirth. 2014;**14**:70

[22] Becker W, Lyhne N, Pedersen A, Aro A, Fogelholm M, Þhórsdottir I, et al. Nordic nutrition recommendations 2004 – Integrating nutrition and physical activity. Scandinavian Journal of Nutrition. 2004;**48**:178-187

[23] ACOG Committee on Obstetric Practice. ACOG committee opinion. Exercise during pregnancy and the postpartum period. Number 267, January 2002. American College of Obstetricians and Gynecologists. International Journal of Gynecology & Obstetrics. 2002;**77**:79-81

[24] Rönö K, Grotenfelt NE, Klemetti MM, Stach-Lempinen B, Huvinen E, Meinilä J, et al. Effect of a lifestyle intervention during pregnancy-findings from the Finnish gestational diabetes prevention trial (RADIEL). Journal of Perinatology. 2018;**38**:1157-1164. DOI: 10.1038/s41372-018-0178-8

[25] Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T. Insulin lispro in CSII: Results of a double-blind crossover study [published erratum appears in Diabetes 1997;46:1239]. Diabetes. 1997;**46**:440-443

[26] Anderson JH Jr, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter insulin Lispro study group. Diabetes. 1997;**46**:265-270

[27] Herrera KM, Rosenn BM, Foroutan J, Bimson BE, Al Ibraheemi Z, Moshier EL, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. American Journal of Obstetrics and Gynecology. 2015;**213**:426.e1-426.e7

[28] Koren R, Toledano Y, Hod M. The use of insulin detemir during pregnancy: A safety evaluation. Expert Opinion on Drug Safety. 2015;**14**:593-599

[29] Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: A meta-analysis. Archives of Gynecology and Obstetrics. 2015;**292**:749-756

[30] Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstetrics and Gynecology. 2003;**102**:857-868

[31] Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK Jr, Jonsson FM. Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000-2011. Obstetrics and Gynecology. 2014;**123**:1177-1184

[32] De Leo V, Musacchio MC, Piomboni P, Di Sabatino A, Morgante G. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2011;**157**:63-66

[33] Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GD, et al. Pharmacokinetics of metformin during pregnancy. Drug Metabolism and Disposition. 2010;**38**:833-840

[34] Wouldes TA, Battin M, Coat S, Rush EC, Hague WM, Rowan JA. Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2016;**101**:F488-F493

[35] Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. MiG trial investigators [published erratum appears in N Engl J Med 2008;359:106]. The New England Journal of Medicine. 2008;**358**:2003-2015

[36] Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RP. Randomized trial of metformin vs insulin in the management of gestational diabetes. American Journal of Obstetrics and Gynecology. 2013;**209**:34.e1-7

[37] Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Treatments for gestational diabetes: A systematic review and meta-analysis. BMJ Open. 2017;7:e015557. (Systematic Review and Meta-analysis)

[38] Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: A systematic review and meta-analysis. BMJ. 2015;**350**:h102. (Meta-analysis)

[39] Lautatzis ME, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: A systematic review. Metabolism. 2013 Nov;**62**(11):1522-1534. DOI: 10.1016/j.metabol.2013.06.006 Epub 2013 Jul 23

[40] Hebert MF, Ma X, Naraharisetti SB, Krudys KM, Umans JG, Hankins GD, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Obstetric-Fetal pharmacology research unit network. Clinical Pharmacology and Therapeutics. 2009;**85**:607-614

[41] Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. The New England Journal of Medicine. 2000;**343**:1134-1138

[42] Jacobson GF, Ramos GA, Ching JY, Kirby RS, Ferrara A, Field DR. Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. American Journal of Obstetrics and Gynecology. 2005;**193**:118-124

[43] Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: A randomized controlled trial. Obstetrics and Gynecology. 2010;**115**:55-59

[44] Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK Jr, Jonsson FM. Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. JAMA Pediatrics. 2015;**169**:452-458

[45] Anjalakshi C, Balaji V, Balaji MS, Seshiah V. A prospective study comparing insulin and glibenclamide in gestational diabetes mellitus in Asian Indian women. Diabetes Research and Clinical Practice. 2007;**76**:474-475

[46] Lain KY, Garabedian MJ, Daftary A, Jeyabalan A. Neonatal adiposity following maternal treatment of gestational diabetes with glyburide compared with insulin. American Journal of Obstetrics and Gynecology. 2009;**200**:501. e.16

[47] Song R, Chen L, Chen Y, Si X, Liu Y, Liu Y, et al. Comparison of glyburide and insulin in the management of gestational diabetes: A meta-analysis. PLoS One. 2017;**12**:e0182488. (Meta-analysis)

[48] Langer O, Yogev Y, Xenakis EM, Rosenn B. Insulin and glyburide therapy: Dosage, severity level of gestational diabetes, and pregnancy outcome. American Journal of Obstetrics and Gynecology. 2005;**192**:134-139

[49] Chmait R, Dinise T, Moore T. Prospective observational study to establish predictors of glyburide success in women with gestational diabetes mellitus. Journal of Perinatology. 2004;**24**:617-622

[50] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. ADOPT study group [published erratum appears in N Engl J Med 2007;356:1387-8]. The New England Journal of Medicine. 2006;**355**:2427-2443

[51] Rochon M, Rand L, Roth L, Gaddipati S. Glyburide for the management of gestational diabetes: Risk factors predictive of failure and associated pregnancy outcomes. American Journal of Obstetrics and Gynecology. 2006;**195**:1090-1094

[52] Cheng YW, Chung JH, Block-Kurbisch I, Inturrisi M, Caughey AB. Treatment of gestational diabetes mellitus: Glyburide compared to subcutaneous insulin therapy and associated perinatal outcomes. The Journal of Maternal-Fetal & Neonatal Medicine. 2012;**25**:379-384

[53] Brown J, Grzeskowiak L, Williamson K, Downie MR, Crowther CA. Insulin for the treatment of women with gestational diabetes. Cochrane Database of Systematic Reviews. 2017;(11):CD012037. (Systematic Review)

[54] Min J, Park B, Kim YJ, et al. Effect of oxidative stress on birth sizes: Consideration of window from mid pregnancy to delivery. Placenta. 2009;**30**:418-423

[55] Saugstad OD. Mechanisms of tissue injury by oxygen radicals: Implications for neonatal disease. Acta Paediatrica. 1996;**85**:1-4

[56] Halliwell B. Free radicals and antioxidants: A personal view. Nutrition Reviews. 1994;**52**:253-265

[57] Damasceno DC, Volpato GT, de MattosParanhos CI, Cunha Rudge MV. Oxidative stress and diabetes in pregnant rats. Animal Reproduction Science. 2002;**72**:235-244

[58] Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes. 2005;**54**:1615-1625

[59] Maged AM, Torky H, Fouad MA, GadAllah SH, Waked NM, Gayed AS, et al. Role of antioxidants in gestational diabetes mellitus and relation to fetal outcome: A randomized controlled trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;**29**(24):4049-4054. DOI: 10.3109/14767058.2016.1154526

[60] Durnwald CP, Mele L, Spong CY, Ramin SM, Varner MW, Rouse DJ, et al. Glycemic characteristics and neonatal outcomes of women treated for mild gestational diabetes. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) maternal-Fetal medicine units network (MFMU). Obstetrics and Gynecology. 2011;**117**:819-827

[61] de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. The New England Journal of Medicine. 1995;**333**:1237-1241

[62] Ben-Haroush A, Yogev Y, Chen R, Rosenn B, Hod M, Langer O. The postprandial glucose profile in the diabetic pregnancy. American Journal of Obstetrics and Gynecology. 2004;**191**:576-581

[63] Weisz B, Shrim A, Homko CJ, Schiff E, Epstein GS, Sivan E. One hour versus two hours postprandial glucose measurement in gestational diabetes: A prospective study. Journal of Perinatology. 2005;**25**:241-244

[64] Moses RG, Lucas EM, Knights S. Gestational diabetes mellitus. At what time should the postprandial glucose level be monitored? The Australian & New Zealand Journal of Obstetrics & Gynaecology. 1999;**39**:457-460

[65] Sivan E, Weisz B, Homko CJ, Reece EA, Schiff E. One or two hours postprandial glucose measurements: Are they the same? American Journal of Obstetrics and Gynecology. 2001;**185**:604-607

[66] Hawkins JS, Lo JY, Casey BM, et al. Diet-treated gestational diabetes: Comparison of early versus routine diagnosis. American Journal of Obstetrics and Gynecology. 2008;**198**:287

[67] Moy FM, Ray A, Buckley BS, West HM. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. Cochrane Database of Systematic Reviews 11 Jun 2017;(6):CD009613. DOI: 10.1002/14651858.CD009613.pub3.

[68] Malkani S, Mordes JP. Implications of using hemoglobin A1C for diagnosing diabetes mellitus. The American Journal of Medicine. 2011;**124**:395-401

[69] Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Journal of Diabetes Investigation. 2010;**1**:212-228

[70] Mosca A, Paleari R, Dalfra MG, Di Cianni G, Cuccuru I, Pellegrini G, et al. Reference intervals for hemoglobin A1c in pregnant women: Data from an Italian multicenter study. Clinical Chemistry. 2006;**52**:1138-1143

[71] Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care. 2012;**35**:574-580

[72] Benaiges D, Flores-Le Roux JA, Marcelo I, Mane L, Rodriguez M, Navarro X, et al. Is first-trimester HbA1c useful in the diagnosis of gestational diabetes? Diabetes Research and Clinical Practice. 2017;**133**:85-91

[73] Wu K, Cheng Y, Li T, Ma Z, Liu J, Zhang Q, et al. The utility of HbA1c combined with haematocrit for early screening of gestational diabetes mellitus. Diabetology and Metabolic Syndrome. *2018*;***10***:14 https://doi.org/10.1186/s13098-018-0314-9

[74] American College of Obstetricians and Gynecologists. Antepartum fetal surveillance. Practice bulletin No. 145. Obstetrics and Gynecology. 2014;**124**:182-192

[75] Cunningham FG, Leveno KJ, Bloom SL, et al. Diabetes mellitus. In: Cunningham FG, Williams JW, editors. William's Obstetrics. 24th ed. New York (NY): McGraw-Hill; 2014. pp. 1125-1146 [Chapter 57]

[76] Spong CY, Mercer BM, D'alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. Obstetrics and Gynecology. 2011;**118**:323-333

[77] American College of Obstetricians and Gynecologists. Medically indicated late-preterm and early-term deliveries. Committee opinion No. 560. Obstetrics and Gynecology. 2013;**121**:908-910

[78] Alberico S, Erenbourg A, Hod M, Yogev Y, Hadar E, Neri F, et al. Immediate delivery or expectant management in gestational diabetes at term: The GINEXMAL randomised controlled trial. GINEXMAL group. BJOG. 2017;**124**:669-677

[79] Lurie S, Insler V, Hagay ZJ. Induction of labor at 38 to 39 weeks of gestation reduces the incidence of shoulder dystocia in gestational diabetic patients class A2. American Journal of Perinatology. 1996;**13**:293-296

[80] Witkop CT, Neale D, Wilson LM, Bass EB, Nicholson WK. Active compared with expectant delivery management in women with gestational diabetes: A systematic review. Obstetrics and Gynecology. 2009;**113**:206-217. (Systematic Review)

[81] Melamed N, Ray JG, Geary M, Bedard D, Yang C, Sprague A, et al. Induction of labor before 40 weeks is associated with lower rate of cesarean delivery in women with gestational diabetes mellitus. American Journal of Obstetrics and Gynecology. 2016;**214**:364.e1-8

[82] Caughey AB, Valent AM. When to deliver women with diabetes in pregnancy? American Journal of Perinatology. 2016;**33**:1250-1254

[83] Scifres CM, Feghali M, Dumont T, Althouse AD, Speer P, Caritis SN, et al. Large-for-gestational-age ultrasound diagnosis and risk for cesarean delivery in women with gestational diabetes mellitus. Obstetrics and Gynecology. 2015;**126**:978-986

[84] Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. JAMA. 1996;**276**:1480-1486

[85] Garabedian C, Deruelle P. Delivery (timing, route, peripartum glycemic control) in women with gestational diabetes mellitus. Diabetes & Metabolism. 2010;**36**:515-521

[86] American College of Obstetricians and Gynecologists. Fetal macrosomia. Practice bulletin No. 173. Obstetrics and Gynecology. 2016;**128**:e195-e209

[87] Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: A systematic review.

Diabetes Care. 2002;**25**:1862-1868. (Systematic Review)

[88] Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. JAMA. 2005;**294**:2751-2757

[89] Buchanan TA, Xiang AH. Gestational diabetes mellitus. The Journal of Clinical Investigation. 2005;**115**:485-491

[90] Russell MA, Phipps MG, Olson CL, Welch HG, Carpenter MW. Rates of postpartum glucose testing after gestational diabetes mellitus. Obstetrics and Gynecology. 2006;**108**:1456-1462

[91] Chodick G, Elchalal U, Sella T, Heymann AD, Porath A, Kokia E, et al. The risk of overt diabetes mellitus among women with gestational diabetes: A population-based study. Diabetic Medicine. 2010;**27**:779-785

[92] Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. Lancet. 2009;**373**:1773-1779. (Meta-analysis)

[93] Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes. Diabetes Care. 2007;**30**(Suppl 2):S251

[94] Kessous R, Shoham-Vardi I, Pariente G, et al. An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity. Heart. 2013;**99**:1118

[95] Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes. Diabetes Care. 2008;**31**(8):1668

[96] Holmes HJ, Casey BM, Lo JY, et al. Likelihood of diabetes recurrence in women with mild gestational diabetes (GDM). American Journal of Obstetrics and Gynecology. 2003;**189**(6):161

[97] Kim C, Cheng YJ, Beckles GL. Cardiovascular disease risk profiles in women with histories of gestational diabetes but without current diabetes. Obstetrics and Gynecology. 2008;**112**(4):875

[98] Ehrlich SF, Hedderson MM, Feng J, et al. Change in body mass index between pregnancies and the risk of gestational diabetes in a second pregnancy. Obstetrics and Gynecology. 2011;**117**(6):1323

[99] Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: Risk of recurrence in subsequent pregnancies. American Journal of Obstetrics and Gynecology. 2010;**203**:467