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Medical Sciences

MANAGEMENT OF GESTATIONAL DIABETES- A REVIEW OF CURRENT LITERATURE

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ABSTRACT:
GESTATIONAL DIABETES MELLITUS (GDM) IS DEFINED AS GLUCOSE INTOLERANCE WHICH LEAD TO HYPERGLYCAEMIA OF VARIABLE DEGREES OF SEVERITY WITH FIRST ONSET OR FIRST RECOGNITION DURING PREGNANCY[55,59]. GDM IS ONE OF THE MOST COMMON MEDICAL DISORDERS OF PREGNANCY WITH AN SIGNIFICANT IMPACT ON THE MATERNAL–FETAL HEALTH. DUE TO THE EPIDEMY OF OBESITY, INCREASING MATERNAL AGE AND DECREASING PHYSICAL ACTIVITY, GDM'S PREVALENCE INCREASED BY 10–100% OVER THE PAST 30 YEARS. THE INTERNATIONAL DIABETES FEDERATION (IDF) REPORTS THAT ONE IN SIX (16.8%) PREGNANCIES ARE AFFECTED BY DIABETES GLOBALLY AND 86.4% OF CASES ARE DIAGNOSED WITH GDM[27]. HYPERGLYCEMIA DURING PREGNANCY INCREASES PERINATAL MORBIDITY AND MORTALITY IN MOTHERS AND CHILDREN WITH A HIGH RISK OF DEVELOPMENT OBESITY, METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS (T2DM) LATER IN LIFE.[9] THERE IS A NEED TO FOCUS ON PREVENTION, SCREENING, EARLY DIAGNOSIS AND MANAGEMENT OF GDM IN ORDER TO AVOID THIS TRANSGENERATIONAL VICIOUS CIRCLE. THE AIM OF THIS REVIEW IS TO SUMMARIZE THE LAST DATA ABOUT THE MANAGEMENT OF GESTATIONAL DIABETES.

KEY WORDS: GESTATIONAL DIABETES, PREVALENCE, SCREENING, DIAGNOSE, MANAGEMENT OF GESTATIONAL DIABETES

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I. INTRODUCTION

Gestational diabetes (GDM) is defined as glucose intolerance with first recognition and onset during pregnancy. During pregnancy, maternal insulin resistance increases in order to ensure an adequate nutrient supply to the developing foetus. Hyperglycaemia develops if there is an insufficient insulin synthesis and secretion[7]. Nutrition management is an important key in the medical care of the patient diagnosed with GDM in order to control blood glucose throughout the pregnancy[8]. It is necessary to complete a nutrition assessment of mother in order to obtain the medical and obstetrical history, anthropometric and laboratory data, lifestyle, and food preferences. In order to reduce the risk of developing diabetes later in life, it is of great importance to have lifestyle changes[9]. A meal plan should be realized in order to assure adequate nutrients and promote an optimal weight gain, normoglycemia with a specific amount of carbohydrate per day and the absence of ketonuria. Follow-up visits are necessary in order to evaluate nutrient intake and parameters such as weight gain, blood glucose control, prevention of ketosis and compliance.

A. Prevalence

Prevalence of GDM is estimated to be around 7% of all pregnancies worldwide. It is difficult to have a clear estimation because the prevalence is reported differently due to the lack of an universal diagnostic criteria and screening procedures. GDM is associated with important maternal and fetal complications such preeclampsia, shoulder dystocia and birth injury, macrosomia, primary caesarean delivery, preterm delivery and foetal and neonatal mortality. Women whith a history of GDM have a seven fold increased risk of type 2 diabetes mellitus compared to women who have not had GDM. Rates of type 2 diabetes mellitus after a diagnosis of GDM vary depending on the population and length of follow up, but the greatest risk is in the first five years and it have been reported to be as high as 70%[10]. Research has shown that lifestyle changes can prevent or delay progression to type 2 diabetes mellitus for these women[11]. An early diagnosis of GDM represents an opportunity for intervention to reduce the development of type 2 diabetes mellitus because the prevalence of type 2 diabetes mellitus is increasing rapidly.

B. Risk Factors

During the first prenatal visit it is important to determine risk of developing GDM. The risk can be classified as low, average, or high. Low risk implies the following characteristics and does not require a routine screening[12].

- Without history of family diabetes (first degree relatives- parents, siblings)
- Normal pre-pregancy body mass index

[7] Powe CE, Allard C, Battista MC, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. Diabetes Care 2016;39(6):1052-1055.
[8] Brand-Miller J., Hayne S., Petocz P., Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2003;26:2261–2267.
[9] Egan AM, Simmons D. Lessons learned from lifestyle prevention trials in gestational diabetes mellitus.Diabet Med 2019;36(2):142-150.
[10] Eades, C. E., Cameron, D. M., & Evans, J. M. M. (2017). Prevalence of gestational diabetes mellitus in Europe: A meta-analysis. Diabetes Research and Clinical Practice, 129, 173–181
[11] Egan AM, Simmons D. Lessons learned from lifestyle prevention trials in gestational diabetes mellitus.Diabet Med 2019;36(2):142-150.
[12] Zhang C., Rawal S., Chong Y.S. Risk factors for gestational diabetes: is prevention possible? Diabetologia. 2016;59:1385–1390.

- No previous history of abnormal glucose tolerance
- No history of adverse pregnancy outcomes associated with GDM
- Not a member of an ethnic group with a higher prevalence of GDM

Average risk implies the following characteristics. The presence of one ore more of them recommend screening for GDM between the 24th and 28th weeks of gestation:

- <25 years of age and obese
- Family history of diabetes in first degree relatives
- Member of an ethnic/racial group of high prevalence (Hispanic American, Native American, Asian American, African American, Pacific Islander)

High risk implies the following characteristics and the presence of any of them recommend a screening for GDM as soon as possible:

- Significant obesity
- Family history of diabetes
- GDM in previous pregnancy and history of adverse outcomes History of glucose intolerance
- glucosuria

If GDM is not diagnosed, blood glucose testing should be repeated at 24-28 weeks or at any time the patient has symptoms or signs that are suggestive for hyperglicemia.

II. SCREENING AND DIAGNOSIS

The tests utilized for diagnosis are the 75g 2-hour OGTT (recommendations of National Institute for Health and Care Excellence (NICE), American Diabetes Association (ADA)) and the 100g 3-hour OGTT (recommendation of American Association of Obstetricians and Gynecologists (ACOG))[13]. Using a 75 g 2-hour OGTT, gestational diabetes is diagnosed if one or more values is equal, or exceeds the cut off values: FPG (5.1 mmol/l [92 mg/dl]), 1-h plasma glucose (10 mmol/l [180 mg/dl]), and 2-h plasma glucose (8.5 mmol/l [153 mg/dl]). These cut-off values were chosen arbitrary by the IADPSG [an international consensus group with representatives from multiple obstetrical and diabetes organizations including the American Diabetes Association (ADA)] based on the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. The aim of HAPO study was to clarify risks of adverse outcomes associated with a degree of hyperglycaemia. In this study 25,505 pregnant women were enroled and tested by a 75g 2-hour OGTT within 24 to 32 weeks. It was noted the association between glucose values and the likelihood of large for gestational age, primary caesarean delivery, fetal insulin levels and neonatal adiposity. An odds ratio of 1.75 times the mean for the outcomes of increased neonatal body fat, large for gestational age and cord serum C-peptide greater than the 90 th percentile was arbitrarily chosen for the proposed new diagnostic criteria by the IADPSG. The OGTT should be performed after fasting overnight for 8-14 hours, and not reducing the usual carbohydrate intake for the preceding several days. In 2010, IADPSG published new recommendations for the screening and diagnosis of GDM and their recommendation was an universal screening for gestational diabetes. They state that at the first antenatal visit, pregnant women should be screened for GDM using standard criteria to diagnose diabetes in non pregnant state. In this way we identify the women with overt diabetes (“pre-existing diabetes”) based on any of the following criteria: fasting plasma glucose level (FPG) ≥7.0 mmol/l (126 mg/dl), a casual plasma glucose of 11.1 mmol/l (≥200 mg/dl), or HbA1c ≥6.5. Confirmation of the diagnosis

[13] ACOG Practice Bulletin No. 190 summary: gestational diabetes mellitus. Obstet Gynecol 2018;131(2): 406-408

need an OGTT. If early screening is negative, the IADPSG recommends that at 24–28 weeks of gestation perform a 2-hour (h), 75-g OGTT "one-step approach"[14].

III. COMPLICATIONS

Women with GDM are predisposed to develop pre-eclampsia and experience perineal trauma or caesarean delivery. Although in majority of cases glucose homeostasis return to normal postpartum, GDM is a strong risk factor for type 2 diabetes in later life. Offspring of women with GDM are more likely to have a higher birth weight with associated complications such as neonatal hypoglycaemia, jaundice, birth trauma and even stillbirth. Long term complications can be intellectual impairment, metabolic syndrome, obesity and diabetes[15].

IV. NUTRITION MANAGEMENT

Nutrition management represents the key of treatment during GDM for blood glucose control. During nutrition management of GDM, specific caloric and nutrient recommendations are determined and adapted to individual assessment and self monitoring of blood glucose. Plasma glucose monitoring and daily food journal provide information for insulin and meal plan adjustments[16]. According to the American Diabetes Asssociations, all women with GDM should receive nutritional counselling, individualization of medical nutrition therapy (MNT) depending on maternal weight and height. MNT should include an adequate calories and nutrients intake according to the needs of pregnancy and maternal blood glucose goals[17]. The most important complication correlated to maternal hyperglicemia, specially maternal postprandial hyperglicemia is fetal macrosomia. Studies has shown that a control of postprandial glucose levels reduces macrosomia, neonatal hypoglicemia, and cesarean delivery as compared to managing preprandial glucose levels alone. Therapy for pregnant women with GDM should be targeted to treat 1-2h postprandial glucose. ACOG and ADA recommendations are: fasting glucose < 95 mg/dl, 1-hour postprandial glucose< 140 mg/dl, 2 h- postprandial glucose < 120 mg/dl.

A. Weight gain recommendations

Lifestyle modification is the first strategy of prevention and management of GDM, which includes nutrition therapy and physical activity. It should be implemented prior to pregnancy, during pregnancy, and postpartum. Nutritional therapy is an individualized food plan that limits the amount of carbohydrate and offers adequate nutrition to maintain an adequate weight gain. Through nutritional education, women can understand the quantity and quality of food needed. Carbohydrate, protein, and fat intakes should account for 50–

[14] Benhalima K, Mathieu C, Van Assche A, et al. Survey by the European Board and College of Obstetrics and Gynaecology on screening for gestational diabetes in Europe. Eur J Obstet Gynecol Reprod Biol 2016;201:197–202; Di Cianni G., Volpe L., Casadidio I. Universal screening and intensive metabolic management of gestational diabetes: cost-effectiveness in Italy. Acta Diabetol. 2002;39:69–73.

[15] Mitanchez D., Yzydorczyk C., Siddeek B., Boubred F., Benahmed M., Simeoni U. The offspring of the diabetic mother–short- and long-term implications. Best Pract Res Clin Obstet Gynaecol. 2015;29:256–269.

[16] Brand-Miller J., Hayne S., Petocz P., Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2003;26:2261–2267.

[17] Kgosidialwa O, Egan AM, Carmody L, et al. Treatment with diet and exercise for women with gestational diabetes mellitus diagnosed using IADPSG criteria. J Clin Endocrinol Metab 2015;100(12):4629-4636.

60%, 15–20%, and 25–30% of the daily dietary total energy, respectively[18]. Potential beneficial factors for dietary structure include fruit, green leafy vegetables, poultry and fish, nuts, fiber, or a Mediterranean diet[19]. Fiber intake per day needs to be ≥28 g. Food with a high GI (glycemic index) lead to higher postprandial values, while food with a low GI may reduce postmeal glycemic excursion, birth weight, and the frequency of insulin use[20]. Total weight gain during pregnancy varies widely among women but the current weight gain recommendations according to the Institute of Medicine are based on pre-pregnacy BMI[21].

Pre-pregnacy BMI Category	Total Weight Gain (kg)	First Trimster Total (kg)	Second Trimester (kg/week)	Third Trimester (kg/week)
Low (BMI<18.5)	12,5-18	2.3	0.49	0.49
Normal (BMI 18.5-24.9)	11.5-16	1.6	0.44	0.44
High (BMI 25-29.9)	7-11.5	0.9	0.30	0.30
Obese (BMI>29)	<7			

Source: Institute of Medicine „Nutrition during Pregnacy. Part 1: Weight Gain Part 2: Nutrient supliments" National Academy Of Sciences, Washington DC. 1990

B. Caloric Requirements

The ideal calorie intake per day is 1800–2000 kcal and should not be <1500 kcal because it will increase the risk of ketonemia who affect the development of the offspring's nervous system[22]. The caloric requirements are different for each trimester. During the first trimester the energy needs are the same as for nonpregnant women, 30 kcal/kg of ideal pre-pregnant body weight. Thomas- Dobersen recommendations are 36 kcal/kgc for the second trimester and 38 kcal/kgc of ideal body weight or prepreganant body weight for third trimester. Jovanic- Peterson recommendations (using a euglycemic diet with 40 % of calories from carbohidrates) are a calorie intake of 30 kcal/kg of current weight recommended for normal pre-pregnant weight, 24 kcal/kgc of current weight for overweight, 12-15 kcal/kgc for obese women during their second and third trimester. It has been documented that women with GDM who followed an euglycemic diet, in 75 % cases obtained normal glycemia.

[18] Bider-Canfield Z, Martinez MP, Wang X, et al. Maternal obesity, gestational diabetes, breastfeeding and childhood overweight at age 2 years [published online ahead of print March 8, 2016]. Pediatr Obes. doi:10.1111/ijpo.12125.
[19] Brand-Miller J., Hayne S., Petocz P., Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2003;26:2261–2267.
[20] Kgosidialwa O, Egan AM, Carmody L, et al. Treatment with diet and exercise for women with gestational diabetes mellitus diagnosed using IADPSG criteria. J Clin Endocrinol Metab 2015;100(12):4629-4636.
[21] Zhang C., Rawal S., Chong Y.S. Risk factors for gestational diabetes: is prevention possible? Diabetologia. 2016;59:1385–1390.
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C. Carbohydrate

An optimal macronutrient composition for dietary management of gestational diabetes mellitus(GDM) is essential to improve perinatal outcomes. It is important to provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate gestational weight gain. The guidelines recommendation is a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber. Carbohydrate (CHO) is the primary nutrient which affect the postprandial glucose levels and the amount and type of carbohydrate are essential for optim blood glucose levels. A glycemic control reduce the need for insulin and control weight gain and infant birth weight[23]. Data reported that a low CHO diet could minimize postprandial glucose excursions and decrease the need for insulin therapy[24]. This diet lead to an increase in dietary fat when protein intake is constant. Data has shown that outside of pregnancy, diets high in fat, particularly saturated fat, promote insulin resistance. An increasing of maternal insulin resistance during pregnancy leat to an increased substrate delivery to the fetus and worse fetal hyperinsulinemia. Studies have shown that maternal triglycerides (TG) and free fatty acids (FFA) can be used by the placenta and may be a stronger predictor of excess fetal fat adevelopment than maternal glucose. There is a focus in literature on diet in and outside of pregnancy, particularly on the quality of CHO in terms of its glycemic index or ability to increase blood glucose. CHOs that are digested more slowly and attenuate postprandial hyperglycemia can be an option for diet therapy in GDM that avoids the need for CHO restriction. Moses et al. demonstrated that women who consume LGI carbohydrates require less insulin compared to those who consume HGI (high glycemic index) carbohydrates.

D. Fat

Fat content in the diet of a pregnant women usually ranges from 30 % to 40 % of total calories, but large amounts of fat should be avoided to prevent excessive weight gain, which can lead to insulin resistance. The acceptable macronutrient distribution range for fat is 20-35% of total energy, the same as for nonpregnant women. The type of fat in the diet play an important role in the glucose response to a meal, independent of the carbohydrate content. The guidelines recommend 7-10% of total energy intake should come from saturated fat, trans fat should be reduced and cholesterol intake should be less than 200 mg/day[25].

E. Protein

The diet of well nourished women in the preconception period and throughout most of pregnancy has a significant effect on birth weight. High intakes of protein and fat during pregnancy may impair development of the fetal pancreatic beta cells and lead to insulin deficiency in the offspring[26]. Data has shown that moderate protein intake is optimal during pregnancy. Proteic meals and snacks do not have important consequences on blood glucose

[23] Brand-Miller J., Hayne S., Petocz P., Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2003;26:2261–2267; Kgosidialwa O, Egan AM, Carmody L, et al. Treatment with diet and exercise for women with gestational diabetes mellitus diagnosed using IADPSG criteria. J Clin Endocrinol Metab 2015;100(12):4629-4636.

[24] Powe CE, Allard C, Battista MC, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. Diabetes Care 2016;39(6):1052-1055.

[25] Zhang C., Tobias D.K., Chavarro J.E. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. BMJ. 2014;349:g5450. [PMC free article

[26] Powe CE, Allard C, Battista MC, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. Diabetes Care 2016;39(6):1052-1055.

excursions and can be added for additional calories in place of carbohydrate foods. The recommendations for protein intake are 1,1 g/kgc/day or 15-20% of total daily calories.

V. CLINICAL OUTCOMES

Nutrition management in combination with intensive monitoring represent a key to delivery a healthy infant[27].

A. Blood glucose monitoring

The use of self-monitoring blood glucose (SMBG) allows to evaluate the nutrition management recommended and emphasize the importance of an appropriate amount and type of food that are likely to produce normoglycemia. For women treated with insulin, evidence indicates that postprandial monitoring is superior to preprandial monitoring. The targets of glucose monitoring recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus are:

- Fasting glucose <95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial glucose <120 mg/dL (6.7 mmol/L).

B. Food records

Detailed food journals are useful to make adjustments to the meal plan or to the insulin regimen and also help the patient to become aware of individual blood glucose response to particular types and amounts of food. These also indicate the patient's level of understanding and compliance with the recommended meal plan.

C. Urinary ketone testing

Testing urinary ketone on the first morning specimen may be useful in detecting insufficient caloric or carbohydrate intake in women treated with caloric restriction[28].

D. Glycosylated haemoglobin

In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were associated with worsening outcomes Observational studies has shown the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation. Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy. Because HbA1C represents an integrated measure of glucose, it may not express accurate postprandial hyperglycemia, which lead to macrosomia. HbA1C may be useful but it should be used as a secondary measure of glycemic control in pregnancy, after self-monitoring of blood glucose. In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age (LGA) infants, preterm delivery, and preeclampsia. In conclusion, a target of <6% (42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. A1C levels may need to be monitored more frequently than usual (e.g., monthly) due the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters.

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[27] Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358(19):1991-2002.

[28] Buhling KJ, Elze L, Henrich W, et al. The usefulness of glycosuria and the influence of maternal blood pressure in screening for gestational diabetes. Eur J Obstet Gynecol Reprod Biol 2004;113(2): 145-148.

VI. PHARMACOLOGICAL THERAPY

When lifestyle modification is insufficient to maintain normoglycemia in women with GDM, it is necessary to introduce drug treatment[29]. Current medication treatments of hyperglycemia during pregnancy include insulin therapy and oral antidiabetic agents (OADs) and they are added when women with GDM are unable to achieve or maintain blood glucose levels and/or when fetal growth rate is above normal. Insulin is the first-line agent recommended for treatment of GDM in the U.S. OADs are not recommended as first-line treatment for GDM because they are known to cross the placenta and there are no sufficient[30] data on long-term safety for offspring.

A. Insulin therapy

While the majority of women with GDM will reach their glycaemic targets with lifestyle changes, 15–30% women will require additional intervention. This intensification of treatment should occur if glycaemic goals are not reached in 1–2 weeks, or at diagnosis if the plasma fasting glucose level is ≥7.0 mmol/L. In pregnancy complicated by GDM can be used either multiple daily injections or insulin pump technology. The physiology of pregnancy necessitates frequent titration of insulin in order to match with the changing requirements. It is important to have daily and frequent self-monitoring of blood glucose. Literature has shown that none of the currently available human insulin preparations do not cross the placenta. Insulin is a traditional, safe, and effective medication treatment of GDM. Many kinds of insulin preparations are available, such as rapid-acting insulin (e.g., regular human insulin), intermediate insulin (e.g., neutral protamine hagedorn), and long-acting insulin (e.g., insulin detemir). Rapid-acting insulin usually works from 30-min or 1-h post subcutaneous injection, reaching its peak effectiveness between 2 and 4 h, and the effect can last for about 6–8 h. Intermediate insulin works for 1–2 h post subcutaneous injection, reaching its peak effectiveness between 4 and 8 h, and its effect can last for about 12–18 h. Long-acting insulin works for 3–4 h post subcutaneous injection, reaching its peak effectiveness between 8 and 10 h, and its effect can last as long as 20 h. Thus, it is beneficial to combine these insulin preparations to simulate the daily physiological insulin secretion. Insulin administration should start with a small dose, which should be gradually increased, and the insulin type and regimens should be individualized. Therapy is associated with an increased risk of hypoglycaemia is important to educate the patient before initiating. Two key randomized, controlled trials, which identified women with GDM from 24 to 28 weeks of gestation reduces analised the frequency of adverse outcomes. Firstly, the Australian Carbohydrate intolerance Study in Pregnant Women (ACHOIS) trial group found that treating GDM reduces serious perinatal morbidity and may also improve the woman's health-related quality of life. Subsequently, Landon et al. in a randomized controlled trial noted that treatment of GDM reduced the risk of foetal overgrowth, shoulder dystocia, caesarean delivery and hypertensive disorders which were pre-specified secondary outcomes. There was no effect on the primary outcome, a composite of stillbirth or perinatal death and neonatal complications, including hyperbilirubinemia, hypoglycaemia, hyperinsulinemia and birth trauma[31].

[29] Egan AM, Simmons D. Lessons learned from lifestyle prevention trials in gestational diabetes mellitus.Diabet Med 2019;36(2):142-150.

[30] Zhang C., Tobias D.K., Chavarro J.E. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. BMJ. 2014;349:g5450. [PMC free article

[31] Dornhorst A. A comparison of glyburide and insulin in women with gestational diabetes mellitus. Diabet Med. 2001;Suppl 3:12–14; Rowan J.A., Hague W.M., Gao W., Battin M.R., Moore M.P., MiG Trial

B. Oral Hypoglicemic agents

The choice of pharmacologic therapy is also under debate. Study has shown that compared with insulin, glibenclamide was associated with higher birth weights and neonatal hypoglycaemia. Compared with insulin, treatment with metformin resulted in less maternal weight gain but a lower gestational age at delivery. Another study reported a high probability that metformin use is associated with reduced risk of pregnancy-induced hypertension compared with insulin. In the Metformin in Gestational Diabetes (MiG) trial, metformin was not associated with an increase in neonatal complications compared with insulin, and rates of severe neonatal hypoglycaemia were lower in those women receiving metformin. However, follow-up on data from the MiG trial participants revealed that children of mothers who received metformin had higher skinfold measurements but no difference in body fat percent by body composition measures or neurodevelopmental outcomes at 2 years old compared with offspring of those randomized to insulin. It should be noted that almost half the women randomised to metformin also received insulin to manage hyperglycaemia. A smaller proportion of infants have been followed up to age 9 years and those exposed to metformin were larger by multiple measures including weight, arm and waist circumferences and waist:height. These data suggest that metformin may interact with foetal environmental factors to influence offspring outcomes in the long term. There are no data regarding longterm outcomes for those treated with glibenclamide during pregnancy[32]. There are some women with GDM who need medical therapy and who, due to cost, language barriers, comprehension, or cultural influences, are not be able to use insulin safely or effectively in pregnancy. Oral agents may be an alternative in these women after a discussion of the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in women with hypertension, preeclampsia, or at risk for intrauterine growth restriction[33].

B1. Metformin

Metformin is a biguanide which inhibit hepatic gluconeogenesis and stimulate glucose uptake in the peripheries[34]. Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews but it crosses the placenta so in umbilical cord blood levels of metformin are as high or higher than simultaneous maternal levels. In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin in the Auckland cohort for the treatment of GDM were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to

Investigators Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–2015.

[32] Balsells M., García-Patterson A., Solà I., Roqué 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; SMFM Statement: Pharmacological treatment of gestational diabetes. Am J Obstet Gynecol 2018;218(5): B2-B4. 37. Dashora U, Rafique S, Tharayil G, et al. The feasibility and impact of implementing NICE guidance on diabetes control during delivery. Br J Diabetes2017;17(3).

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[34] Benhalima K, Mathieu C, Damm P, et al. A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). Diabetologia 2015;58(7): 1422-1429.

insulin[35]. This was not found in the Adelaide cohort. In two randomized control trials of metformin use in pregnancy for polycystic ovary syndrome, a follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin. A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass.

B2. Sulfonylureas

It is known that sulfonylureas cross the placenta and are associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels. Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin in a 2015 meta-analysis and systematic review. Studies has shown that glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia but long-term safety data for offspring exposed to glyburide are not available. Glibenclamide is a sulfonylurea that binds to pancreatic beta-cell adenosine triphosphate potassium channel receptors and increases insulin secretion and may be used at 2.5-20 mg per day in divided doses, although the dose–response relationship in pregnancy is not clear.

VII. PHYSICAL ACTIVITY

An important adjuvant therapy in management of diabetes in pregnancy, particularly in GDM, could be the practice of moderate exercise because is effective in controlling weight gain and improving glucose homeostasis by increasing insulin sensitivity. Women with GDM should be advised to take regular exercise to improve glucose control. Studies reported that exercise intervention reduced the incidence of GDM by 28% [95% *CI*: 9–42%; relative risk (*RR*) = 0.72, *P* = 0.005] compared with the control. Halse et al. showed that exercise during pregnancy may help to maintain daily postprandial normoglycemia in women with diet-controlled GDM. Unfortunately there is no unified and clear guideline for physical activity during pregnancy. Many organizations such as the American College of Obstetricians and Gynecologists, the Canadian Diabetes Association, and the Sports Medicine Australia recommend that for women without contraindications to exercise, an accumulated time for moderate exercise of ≥30 min on most, if not all, days of the week (at least 150 min/week) is needed during pregnancy and the postpartum period. Pregnant women need to undergo a comprehensive physical assessment, and obtain professional and individualized exercise guidance, before start a exercise therapy. Aerobic activities and strengthening exercises involving large muscle groups are recommended. It should be avoided sports with risks of falling, trauma or collisions. Women need to monitor fetal activity and their blood glucose levels before and after exercise to ensure the safety of exercise and prevent the occurrence of hypoglycemia. Healthy eating and exercise habits should continue after delivery[36].

[35] Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care 2018; 6(1):e000456.

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VIII. POSTPARTUM FOLLOW-UP

The postpartum period is also important in the management of GDM because both the mother and the offspring are at increased risk of future obesity, T2DM, hypertension, and metabolic syndrome. The guidelines recommend to have a postpartum follow-up at 4–12 weeks after childbirth and all women with hyperglycemia during pregnancy should have a 75-g OGTT in order to evaluate their blood glucose levels. If the diagnostic criteria for diabetes or pre-diabetes are met at this point, the mother should be advised to see an endocrinologist and make follow-up visits every 1–3 years. Women with a history of GDM should ideally have an intrapartum interval more than 1 year and plan to get pregnant. They need also to undergo the 75-g OGTT prior to or at least in the early stage of next pregnancy. Lifestyle intervention is also the most fundamental and effective method for postpartum management. Ratner et al. randomized 350 women with recently diagnosed GDM to standard lifestyle and placebo or metformin therapy, or to lifestyle intervention group, and found that in the fourth year after childbirth, lifestyle intervention and metformin therapy can both reduce the incidence of diabetes by approximately 50% from that with the standard lifestyle and placebo. The data also has shown that breastfeeding can also reduce the risk of type 2 diabetes in women with GDM. Gunderson et al. conducted a prospective, observational cohort study of women with a history of GDM to evaluate lactation and the 2-year incidence of diabetes after GDM pregnancy. In their study, the incidence of diabetes after GDM pregnancy was inversely associated with lactation intensity. The conclusions was that the longer the breastfeeding is, the lower is the 2-year incidence of diabetes after GDM pregnancy. Bider-Canfield et al. indicated in a study that breastfeeding for ≥6 months is associated with a decreased risk of childhood overweight at age 2 years[37].

IX. PREVENTION

Current recommendations for women with GDM to prevent the onset of type 2 diabetes include diet, weight reduction or weight maintenance and participating in regular physical activity[38]. Data has shown that lifestyle modification reduce diabetes development by 50 % or more. It has been documented that dietary modifications of lowering fat and carbohydrate intake in combination with physical activity can reduce the risk of developing GDM in subsequent pregnancies. It is important to plan and prepare before pregnancy because usually women of reproductive age do not have regular physical examination or know their blood glucose levels. Thus, sometimes, hyperglycemia is already present at conception and studies have shown that hyperglycemia during organogenesis increase the risk of spontaneous abortions and congenital anomalies. All women are encouraged to adopt good dietary and lifestyle habits before pregnancy, especially those who are underweight or overweight/obese. As a woman's body mass index (BMI) prior to pregnancy is of high importance, both low and high BMIs are closely related to poor pregnancy outcomes. Zhang et al. found that adherence to a low-risk lifestyle (healthy body weight, healthy diet, regular exercise, and non-smoking) before pregnancy is associated with a low risk of GDM .

Kgosidialwa O, Egan AM, Carmody L, et al. Treatment with diet and exercise for women with gestational diabetes mellitus diagnosed using IADPSG criteria. J Clin Endocrinol Metab 2015;100(12):4629-4636.

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X. CONCLUSION

In conclusion, GDM is associated with a higher risk of adverse health outcomes for both mothers and offspring, during the perinatal phase and also in the long term. It is important to give importance to the prevention and management of GDM throughout pregnancy, prior to pregnancy and postpartum. Nutrition intervention and physical activity should be the primary and major strategies. If lifestyle modification alone fails to maintain normoglycemia, insulin should be considered. Postpartum care plays also a critical role in the prevention of future chronic non-communicable diseases.

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