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GESTATIONAL DIABETES – A REVIEW OF CURRENT LITERATURE

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Gestational diabetes mellitus (GDM) is a complication of pregnancy whose prevalence is increasing due to the dramatic increase of obesity's prevalence in women of childbearing age. Gestational diabetes has been defined as any degree of glucose intolerance with onset, or first recognition during pregnancy which can lead to maternal and neonatal adverse outcomes without an optimal control of blood glucose levels[13]. Globally there is a lack of uniform strategies for screening and diagnosing GDM.[2,3,67] Pregnancy is associated with insulin resistance(IR)[4,5] and hyperinsulinemia that may predispose some women to develop gestational diabetes but in the majority of cases β-cell dysfunction appears on a background of chronic insulin resistance present before pregnancy. In less than 10% of GDM patients, defects of β-cell function appear due to an autoimmune destruction of pancreatic β-cells, as in type 1 diabetes, or caused by monogenic mutations, as in several MODY subtypes. This review has the purpose to overview literature related to GDM, the challenges of screening and diagnosis, the pathophysiology of GDM, the long and short term consequences of gestational diabetes for both mother and offspring and the management of GDM.

Keywords: gestational diabetes, screening, diagnose, pathophysiology, management.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a variable severity of glucose intolerance with onset or first recognition during pregnancy[13].

Epidemiological studies estimate that globally at least 1 out of 10 pregnant woman is affected by GDM.[93] Women with GDM represent a heterogeneous group, either unrecognized pre-existing non-insulin-dependent diabetes (type 2), or type 1 diabetes with onset during pregnancy. Prevalence of gestational diabetes mellitus (GDM) vary depending upon the demographic characteristics of the population and the criteria used.[9,27]

This condition might determine several adverse perinatal outcomes including macrosomia, fetal hypoglycemia and neonatal mortality. GDM is also associated with elevated risk for long-term complication such as cardiovascular disease, obesity and diabetes.[12,35,41] The explanation consist in the fact that hyperglycemia generates an adaptive response in the fetus in order to control the glucose level, expressed as hyperinsulinemia. This adaptative response include also the elevation in the placental consumption of glucose and increase of the feto-placental blood flow.

Due to lack of innervation in the placenta, the vascular tone is under the control of various vasoactive substances synthetised or realeased from the endothelium like nitric oxide, adenosine, prostaglandin etc.[7,20]. These vasoactive molecules may also regulate endothelial proliferation, migration and angiogenesis.[24]

Several studies have shown that placenta from GDM is characterized by hypervascularization and elevation in the pro-angiogenic signals including the secretion and activity of the vascular endothelial growth factor (VEGF).[21]

It is important to pay rigorous attention to GDM and the purpose of this review is to cover various data related to GDM, including epidemiology, diagnostic criteria and screening, the pathophysiology of GDM, the treatment and the long and short term consequences of GDM for both mother and child.

DEFINITION OF GDM

Pregnancy is a physiological state when a series of complex anatomical and functional adaptation occurs in the mother's organism in oder to assure the development of fetus.

During the normal pregnancy a "physiological" insulin resistance is necessary in order to provide the glucose necessary to the growing fetus.[4,5] If this normal adaptation is no longer occurring it generates a pathological state of insulin resistance, which is called Gestational Diabetes Mellitus (GDM).[13] Therefore, GDM has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy.

PREVALENCE

The prevalence of GDM varies from 1–20% with increasing values worldwide due to the epidemy of obesity and type 2 diabetes mellitus (T2DM). Epidemiologically speaking, it has been estimated that near to 90% of the diagnosis of diabetes in pregnancy is actually GDM.[93]

This dramatic rise in the GDM prevalence will have a major impact on health care systems.[34]

Ethnicity seems to play an important role.[42,78] Studies reported that the United States Native Americans, Asians, Hispanics, and African-American women have a higher risk of GDM compared to non-Hispanic white women. Studies have also shown that women from Asia are at very high risk of developing GDM and the increased insulin resistance is observed at much lower BMI levels when compared to European women.[81]

SCREENING OF GDM

GDM is an asymptomatic condition and because a large proportion of patients had no classic risk factors, guidelines recommend the universal screening for GDM.[67]

There were controverses about the timing of screening but data show that there are no benefits to screen before 24 weeks of gestation. Because insulin resistance rise from the second trimester screening before this period might miss GDM so widely, adopted timing was between 24–28 weeks. The screening of GDM can be performed to the whole obstetric population (universal screening) or target at the high risk groups (risk factor screening).

2005 ADA's recommendations were that all obstetric patients should be classified into low, average and high risk. Patients were classified with low risk if they had all of the following criteria and with the recommendation not to be screened for GDM: less than 25 years old, no history of abnormal glucose metabolism and no history of poor obstetric outcome, ethnic group with a low prevalence of GDM, no known diabetes in first-degree relatives, normal pre-pregnancy weight. Patient at high risk would be tested as soon as possible. They present the following criteria: severe obesity, strong family history of type 2 diabetes, previous history of GDM, impaired glucose metabolism, or glucosuria. The remaining patients were average risk.

The ADA's recommendations were reafirmed in 2008 by National Institute for Health and Clinical Excellence (NICE) and in 2011 by American College of Obstetricians and Gynecologist (ACOG) and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).

Guidelines for the supervision of pregnancy with regard to gestational diabetes mellitus (GDM) recommend that pregnant women (except for those at very low risk) should be screened for GDM in gestational week 24–28. Early oral glucose tolerance test (OGTT) should be carried out in gestational weeks 12–16 in cases of existing risk factors. If GDM is diagnosed, treatment should be carried out based on fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) values. Insulin and/or oral antidiabetic therapy in addition to intensive control of plasma glucose and delivery planning should be considered in cases of high FPG and 1h PPG.

There were proposed two strategies to screen the target population.[1–3] The "one-step" approach referred to diagnosing GDM with diagnostic OGTT without prior plasma or serum glucose screening. The "two-step" approach was to perform a diagnostic OGTT only if the first screening test was positive. ACOG recommended a "two-step" test which all pregnant women should be screened by patient history, clinical risk factors, or a 50g OGTT. RANCZOG accepted either approach.

ADA recommended "one-step" test using 75 g, 2-hour OGTT at 24–28 weeks of gestation.

There is necessary a postpartum follow-up examinations which should include OGTT, body mass index (BMI), waist circumference, blood pressure (BP) and serum lipids due to the high risk of developing diabetes. The examinations should take place early if the treatment of GDM during pregnancy was intensive. If the woman has been treated with diet, insulin or antidiabetic agents

during pregnancy, she should be examined at 4–12 weeks postpartum. If the first follow-up was normal, subsequent follow-ups should take place in 1–3 years intervals.[1–3]

DIAGNOSE OF GDM

The tests utilized for diagnosis are the 75g 2-hour OGTT (NICE, ADA, RANZCOG) and the 100g 3-hour OGTT (ACOG) .

Using a 75 g 2-hour OGTT, gestational diabetes is diagnosed if one or more values 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]).[31] 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 HAPO study.[33,35] The aim of HAPO was to clarify risks of adverse outcomes associated with a lesser degree of hyperglycaemia and facilitate the development of diagnostic criterioa. 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. Their recommendation was an universal screening for gestational diabetes and 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.[61,94] 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 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".

In January 2011, the Standards of Care of ADA endorsed the IADPSG recommendations and also the Endocrine Society does. The WHO updated their recommendations in 2013, and recommended glucose cut-off values for GDM corresponding to those proposed by IADPSG.

The American Association of Obstetricians and Gynecologists (ACOG) and the National Institute of Health (NIH) have not endorsed the IADPSG recommendations, and still recommend the traditional "2-step approach", in which an initial screening between 24–28 weeks by 50 g oral glucose challenge test (GCT), and measuring the plasma glucose concentration after one hour. Afterward, a diagnostic 3-hour 100 g OGTT is recommended for those women who exceeded the glucose threshold of ≥7.2, or ≥7.8 mmol/L (130 or 140 mg/dL) in GCT.

PATOPHYSIOLOGY

GDM is characterized by a dysfunction in the pancreatic β cell, which does not produce enough insulin adequately to the increased requirements of late pregnancy.[4,5,57] The mechanisms responsible for GDM are under investigation and studies reveal at least three possibilities:

1. The presence of anti-islet cell antibodies (<10% cases);
2. Genetic variants of monogenic forms of diabetes (1–5% cases),
3. Presence of obesity and chronic insulin resistance (>80% cases).

Considering that obesity, is a condition of insulin resistance and a common risk factor to GDM, and insulin secretion during pregnancy increases according to gestational age it has been reinforced the idea that chronic deficiency is the underling cause for GDM. It has been reported that in general, hyperglycemia is resolved after birth but epidemiological evidences show that GDM constitutes a risk factor for development of diabetes mellitus type 2 (DMT2) and hypertension in both mother and offspring.[18,28] It has been estimated that about 10% of women with GDM have diabetes mellitus soon after delivery and the rest will develop diabetes mellitus at rates of 20–60% within 5–10 years after the manifestation of GDM in the absence of specific interventions to reduce their risk.[33] These evidences have suggested that metabolic defects in GDM, characterized by

hyperglycemia, and insulin deficiency (relative in GDM) are maintained after birth and represent a risk factor for metabolic and cardiovascular diseases in the mother and her sibling.[85,86]

Pregnancy is normally defined as a progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels similarly seen in individuals with type 2 diabetes. The insulin resistance appears to result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta.[7,22.57] Because the insulin resistance rapidly decrease after delivery it suggests that the major contributors to this state of resistance are placental hormones. Hormones and adipokines secreted from the placenta, include tumor necrosis factor (TNF)-α, human placental lactogen, and human placental growth hormone. In addition, increased estrogen, progesterone, and cortisol during pregnancy contribute to a disruption of the glucose insulin balance.

Pancreatic β-cells normally increase their insulin secretion to compensate the insulin resistance of pregnancy and this plasticity of β cell function is the hallmark of normal glucose regulation during pregnancy. The development of GDM occurs when a woman's pancreas does not secrete enough insulin to keep up with the metabolic stress of the IR.

In GDM women, defects in β-cell function can also be due to autoimmune destruction of pancreatic β-cells, as in type 1 diabetes. This is characterized by circulating immune markers directed against pancreatic islets (anti-islet cell antibodies) or β-cell antigens (such as glutamic acid decarboxylase, GAD, or insulin autoantibodies, IAA). These patients appear to have type 1 diabetes. This is usually diagnosed through routine glucose screening during pregnancy. Anti-islet cell or anti-GAD antibodies are present in less than 10% of GDM patients, who are not always lean. These women can rapidly develop overt diabetes after pregnancy.[2,3]

Another cause for a defective β-cell function in GDM are mutations in autosomes (autosomal dominant inheritance pattern, commonly referred to as maturity-onset diabetes of the young (MODY), with genetic subtypes denoted as MODY-1, MODY-2, etc.). Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes coding for: (a) glucokinase (MODY-2), (b) hepatocyte nuclear factor 1α (MODY-3), (c) and insulin promoter factor 1 (MODY-4). Together, these monogenic forms of GDM account for less than 10% of al GDM cases.[3]

Outcomes of pregnancy are highly reliant on a promptly physiological control of placenta, a multifunctional materno-fetal organ. The placenta is an endocrine organ and an immune barrier, where occurs the exchange of oxygen and carbon dioxide, the absorption of nutrient and the elimination of metabolic waste.[7] Placental barrier has a selective permeability, it prevents the passage of macromolecules over 700 Daltons, whereas the smallest particles can cross (for instance melatonin, catecholamines and other hormones).[20]

This anatomic and functional structure includes syncytiotrophoblasts, cytotrophoblasts, stromal core villi and fetal vascular endothelium.[10,22] The syncytiotrophoblast is a multinucleated and continuous layer of epithelial cells, formed by the fusion of cytotrophoblasts and it is in direct contact with maternal blood. Due to this position it is the area where direct exchange of oxygen, nutrient and removal of waste products occurs. Syncytiotrophoblast has also endocrine functions characterized by production of human chorionic gonadotrophin (hCG) regulated by progesterone, human placental lactogen (hPL), insulin-like growth factor I (IGF-I) and endothelial growth factor. Cytotrophoblasts (or Langhans´cells) are continually differentiating into syncytiotrophoblast and this layer also may synthesize hCG.

In the placenta, the blood vessels constitute a network coming from and going to the fetus and represent a continuous circulatory system with the fetal cardiovascular system. In the placenta, the veins are conducting oxygenated blood toward the fetus, whereas the arteries contain deoxygenated blood toward the placenta. [48] Due to its position, the placenta is exposed to various intrauterine changes and can easily be affected by any condition. Glucose is the primary placental energy substrate and materno–fetal glucose exchange is vital for fetal survival[74]. The gestational changes in maternal glucose metabolism and increased blood glucose level reflect the maternal metabolic adaptations to fulfill the nutrition requirements of the developing fetus. This phenomenon is exacerbated in GDM.

In GDM, it has been reported macroscopical and histological alterations of placenta. Placental size and placental weight are elevated in GDM, which lead to a reduced fetal/placental weight ratio, that means, the placenta growth is even higher than fetal growth.[53] Studies reported that in syncytiotrophoblast and cytotrophoblast from GDM there are functional alterations as an increase of cytotrophoblast mass observed in the number of

nuclei. There is described also high fibrin deposit over syncytiotrophoblast and hyperplasia of cytotrophoblast, which explain the increase of the thickness of syncytial basement membranes in GDM. Other alterations in the throphoblastic cells from GDM are low expression of serotonin transporter (SERT) and receptors (5-HT2A)[92] and a high expression of inducible nitric oxide synthase (iNOS). This is a phenomena observed in placentas from GDM, that may be correlated with high nitric oxide synthesis.[23].

Placental alteration in GDM includes also changes in the transport of nutrients (such as amino acid), enhanced blood formation and glucose consumption. Endothelium in the feto-placental circulation is involved in various mechanisms in order to assure the input of nutrients and oxygen to the fetus. Due to the lack of innervation of the placenta, the regulation of vascular tone is dependent on endothelial cells-mediated synthesis and release of several vasoactive substances like nitric oxide (NO), adenosine, endothelial derived hyperpolarizing factor (EDHF), prostacyclin, thromboxane, mono or di or tri monophosphate of adenosine (AMP, ADP, ATP) etc.[47,74]

Angiogenesis is a physiological process leading to growth of new blood vessels from a pre-formed one, a crucial process for placental development and fetal growth during normal and GDM.[24] Because angiogenesis in the placenta is also controlling blood flow toward the fetus, due to vasodilatation of placental vessels, this process is associated with macrosomia present in GDM. Placenta from GDM present an elevated number of redundant capillary connections per villi, compared to normal pregnancy that suggest a more intense capillary branching an increased placental capillary length, branching and surface area. [40,50,52] Associated mechanism behind increased placental angiogenesis in GDM is related to the pro-angiogenic effect of hyperglycemia, which lead to an elevation in the placental synthesis and release of VEGF, expression of VEGF receptors (VEGFR) and nitric oxide production[21,37,76]. Studies report that placenta from women with hyperglycemia present high levels of VEGF and VEGF receptor 2 (VEGFR-2) but reduced expression of VEGF receptor 1 (VEGFR-1). Vasomotor and angiogenic properties of placental's vessels modulate the fetoplacental blood flow by a cross talking between placenta and fetus.

Because in the maternal circulation in gestational diabetes mellitus (GDM) there is a hyperglicemiant status which through feto-placental circulation generate hyperglycemia, hyperinsulinemia and insulin resistance. This hyperglycemic condition affects also trans-placental glucose transport and dysregulation of GLUT activity and studies report that the expression of GLUT1 at the basal membrane is increased twofold with a 40% increase in glucose uptake and mTOR signaling.[46] These changes are associated with a 50% reduction in mitochondrial respiration in trophoblast cells isolated from GDM placenta. In GDM the high glucose uptake, due to high metabolism, may generate elevated oxygen consumption which would generate an endothelial dysfunction characterized by elevation in ROS, prostaglandin and purine concentration in the fetoplacental circulation.

The oxidative stress is inevitable present in pregnancy and is related with the metabolism of fetal and utero-placental tissues, which lead to a continue delivery of oxygen and nutrients toward the growing fetus.[23,49] This mechanism is associated with the etiology of GDM and is related with the imbalance between synthesis of reactive oxygen and nitrogen species (ROS and RNS, respectively) and the activity of antioxidant enzymes. The most relevant free radicals are superoxide (O2•-) in the ROS group and nitric oxide (NO) and peroxinitrite (ONOO-) in the RNS group. NO can diffuse from endothelial cells to smooth muscle cells, whereas O2•- and ONOO have actions in the cells where they were synthesized. The main sources of O2•- in the placenta include the mitochondrial electron transport chain, xanthine oxidase, NADPH oxidase and uncoupled endothelial NO synthase (eNOS). The main source of NO are the endothelial and inducible NO synthases (eNOS and iNOS, respectively).

In early pregnancy, in placental tissue has been discovered a higher activity of NADPH oxidase so the synthesis of O2 •- is more marked at the end of the first trimester. Studies showed that in GDM patients, in maternal plasma, umbilical cord plasma and placental tissue is an increased activity of xanthine oxidase (XO) and a decreased activity of catalase[77]. These remarks conclude that there is an impairment of antioxidant defenses in the placenta and blood from mother and newborn, which might be related with the high mortality and morbidity in both mother and newborn observed during GDM pregnancies. Placental tissues from GDM have a decreased response to oxidative stress induced by hypoxanthine plus X, reflected by a reduced levels of catalase and glutathione peroxidase (GPx) after exposition to the pro-oxidative challenge.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) [33,35] study reported that a higher pre-pregnant BMI and the BMI at 28 weeks are strongly correlated to increased insulin resistance at 28 weeks. They explain that adipose tissue produce a large amount of diabetogenic adipokines like TNF-α[56] as well as the placenta and is suspected to play an important role in insulin resistance pathways. This could explain the elevated pre-pregnant insulin resistance level seen in obese women.

The literature suggests that maternal inflammation leads to the over-production of inflammatory cytokines by the placenta that would normally be expressed at significantly lower levels in healthy pregnancies. It is proposed that this enhanced inflammation is associated with the metabolic changes seen in GDM pregnancies. [45]

OUTCOMES OF PREGNACY COMPLICATED BY GDM

GDM is associated with a significantly increased risk of macrosomia, shoulder dystocia, hyperbilirubinemia, birth injuries as well as neonatal hypoglycemia and.[12,35,41]

Women with GDM also have higher rates of caesarean sections and induced deliveries.[29] The HAPO Study Cooperative Research Group recently showed a strong and continuous correlation between maternal glucose levels and increased birth weight and cord-blood serum C-peptide levels. GDM increases the offspring's predisposition to obesity and diabetes and this condition and fetal macrosomia increase the child's risk of developing the metabolic syndrome in childhood. [33,35] Studies report that 10-30% of women with GDM develop preeclampsia (PE), and it's incidence increases with both the severity of GDM and the pre-pregnancy BMI.

Long term effects of GDM for the mother

The pathogenesis of GDM is similar to that of type 2 diabetes (T2D), with both pancreatic β-cell dysfunction and chronic insulin resistance as determinant factors. .

Up to 10% of patients with prior GDM are diagnosed with T2D soon after delivery and, and in a ten-year follow-up, the risk of developing T2D is approximately 40%. The cumulative incidence of T2D is highest in the first 5 years after pregnancy and then it decreases, reaching a plateau at ten years postpartum.[18,2859] After delivery, women with GDM often have an increased risk for metabolic syndrome, and shortly after delivery these women express markers of vascular diseases such as disturbed endothelial function and increased intima-media thickness of carotid arteries. The metabolic syndrome is characterized by several risk factors, including central obesity, hypertension, insulin resistance and dyslipidemia. These risk factors are also associated with the development of CVD and T2DM, and the metabolic syndrome has been demonstrated to increase the risk of both outcomes.[33,85,86] The risk of CVD is found to be approximately 70% higher in women with previous GDM compared with women having normoglycaemic pregnancies when followed for 11.5 years after pregnancy.

Women with GDM are at higher risk of hypertensive disorders including gestational hypertension, preeclampsia, and eclampsia.[18,25] In the HAPO study, 5.9% had gestational hypertension and 4.8% had preeclampsia.[33,35] The study showed that the glucose level at the first glucose tolerance test was positively correlated with the risk of preeclampsia. Rowan *et al.* reported that 5% had gestational hypertension and 6.3% had preeclampsia.

There is a high risk that a woman develop T2D after pregnancy complicated by GDM. Small studies have detected increased circulating levels of leptin and inflammatory markers TNF-α and C-reactive protein, as well as decreased levels of adiponectin in women with prior GDM[45,56]

The HAPO study, found a direct correlation between Cesarean section rate and maternal glycemia with an overall frequency of 23.7%.[29,33] Gorgal *et al.* reported a non-elective cesarean section rate for women with GDM of 19.5% compared to 13.5% for non-diabetic women.

Long term effects in offspring of women with GDM

Offspring of women with a history of GDM are at increased risk of developing metabolic diseases such as obesity, T2DM and the metabolic syndrome. This long-term risk depends on genetic susceptibility and depends also by the postnatal environment. Maternal glucose easily crosses the placenta and as a consequence maternal hyperglycemia leads to intrauterine hyperglycemia, which induces foetal hyperinsulinemia and possible modification of growth and future metabolism of the fetus (fuel-mediated teratogenesis). The relation between birth weight and risk of T2DM is U-shaped and therefore both infants with decreased and those with increased birth weight are at

increased risk of developing T2DM as compared to persons being born with a normal birth weight.

Macrosomia in newborns of diabetic mothers is characterized by increased body fat. The IADPSG study found that percentage of body fat in newborns, maternal glycemia and foetal insulin levels estimated by cord C-peptide level were strongly positively correlated.

Shoulder dystocia is a serious complication of childbirth and data show a clear association between increased foetal size and this risk if the birth weight exceeds 4 kg.

A Danish long-term follow-up study based primarily on a Caucasian population found a high prevalence of T2DM and pre-diabetes in adult offspring of mothers with diet-treated GDM and in offspring of mothers with type 1 diabetes compared with the background population. These findings support the hypothesis that a hyperglycemic intrauterine environment plays a role in the pathogenesis of T2DM. T2DM is characterized by both reduced insulin sensitivity and impaired B-cell function, but there are no sufficient evidence about how these precursors are changed in the offspring after an exposure to maternal hyperglycemia in pregnancy. A recent study found that offspring exposed to intrauterine hyperglycemia due to GDM, primarily have reduced insulin sensitivity, but also a significantly lower relative insulin release.

MANAGEMENT OF GDM

A team approach, comprise an obstetrician, diabetes physician, a nutritionist and a pediatrician is ideal for managing women with GDM.

Dietary therapy

The American Diabetes Association and the American College of Obstetrics and Gynecology recommend nutrition therapy as the primary therapeutic strategy for the achievement of an acceptable glycemic control in GDM. The optimal dietary therapy would be a diet that provides adequate nutrition to support fetal and maternal well-being, maintaine normoglycemia with absence of ketones. Excessive weight gain should be discouraged as it increases further the risk of delivering a large-for-gestational-age infant, adverse pregnancy outcome, and childhood obesity. The recommended weight gain during singleton pregnancy is dependent on pre-pregnancy BMI: 12.5–18 kg of weight gain for underweight women (BMI <18.5 kg/m^2); 11.5–16 kg for normal weight (BMI 18.5–24.9 kg/m^2); 7–11.5 kg for overweight (BMI 25–29.9 kg/m^2), and 5–9 kg for obese (BMI ≥30.0 kg/m^2).[17,19]

Studies report that moderate exercise has been recognized as an adjuvant therapy, with potential benefits when used together with diet or diet and insulin therapy, in the management of GDM in women without a medical or obstetric contraindication. Exercise has been shown to improve glycemic control in GDM. Daily moderate exercise for 30 minutes or more is recommended for a woman with GDM like walking briskly, or arm exercises while seated in a chair for at least 10 minutes. The exercises after each meal reduce glucose rise post-meal, and help in achieving glycemic goal.[62,66,80]

Glycemic control

Glycemic control needs to be monitored and self-monitoring of blood glucose levels is the optimal method and is well tolerated by most women. Women are instructed to carry out self monitoring of blood glucose (SMBG) 4 times a day, fasting glucose (upon awakening), and one or 2 hour post-meals (after meal). In GDM, monitoring of blood glucose after meals is preferred over pre-meal testing as the risk of macrosomia increases with increased maternal glucose levels post-meals. It is not known whether a one hour, or 2-hour PP testing is the ideal goal for the prevention of fetal risks. The glycosylated hemoglobin (HbA1C) values tend to be less in pregnant women than in non-pregnant, and this is because the average blood glucose concentration tends to be lower in pregnant women. In addition, the rise in red cell mass and the rise in red blood cell turnover during pregnancy contributes to a lower HbA1C.[43,73] For this reason, frequent monitoring of HbA1C to assess glycemic control during pregnancy in women with GDM may not be useful in those with low HbA1C levels at initial visit. This measurent may be helpful in patients with overt diabetes with an HbA1C >6.5%. The target glycemic goals for women with GDM is to keep the fasting glucose ≤5–5.3 mmol/l (90–95 mg/dl), and either one-hour post-meal ≤ 7.8 mmol/l (140 mg/dl), or 2-h post-meal ≤ 6.7 mmol/l (120 mg/dl).

Continuous glucose monitoring (CGM) may reveal high postprandial peaks which can not be observable with self-monitoring of glucose. At present CGM is not recommended for routine use in guiding GDM treatment.[54,99]

Insulin therapy

Insulin therapy should be considered if the plasma glucose goals are not met on two or more occasions during a 1 to 2 week follow-up,

particularly if there is clinical or ultrasonographic suspicion of macrosomia. The type and timing of insulin should be chosen based on the specific blood glucose elevation. If the fasting glucose is greater than 90–95 mg/dl (whole blood capillary) then basal insulin, long-acting insulin analog and 4 units for example, should be started before bedtime. If fasting glucose level is too high, then basal insulin dose can be calculated according to the patient's weight, 0.2 units/kg/day. In cases where glucose level is elevated following a meal, rapid-acting insulin, or regular insulin should be prescribed before that specific meal. If both fasting and PP glucose levels are elevated, a 4-injections-per-day regimen "basal and meal time insulin regimen" should be prescribed. Basal and meal time insulin regimen is preferred over twice dose regimen because it is more likely achieves, maintains target blood glucose, and allows more flexibility. As insulin requirement may increase with the progression of pregnancy, it is crucial to follow patients' SMBG regularly, and optimize their insulin doses.[58,83,89]

Oral hypoglycemic agents

Oral hypoglycemic agents (glyburide and metformin) have been shown to be a possible alternative to insulin in the medical treatment of GDM.[32,58,72] A systematic review of randomized controlled trials and observational studies of maternal and neonatal outcomes in women with GDM was conducted and women treated with oral hypoglycemic agents were compared with those treated with all types of insulin. Two trials compared insulin to glyburide; one trial compared insulin, glyburide, and acarbose; and one trial compared insulin to metformin. No significant differences were found in maternal glycemic control or cesarean delivery rates between the insulin and glyburide groups.

Recently two large randomized controlled trials have been carried out to prove that identification and treatment of GDM and even mild carbohydrate intolerance during pregnancy confer a benefit. Thus the Australian Carbohydrate Intolerance Study in Pregnant Women, a large, randomized trial of treatment for gestational diabetes mellitus, concluded that treatment reduces serious perinatal complications and may also improve quality of life by management of GDM in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glycemic control. [17]

A large randomized controlled trial was performed by Rowan *et al.* in which 751 women with GDM at 20 to 33 weeks of gestation were received either treatment with metformin or insulin if lifestyle intervention had failed to achieve glycemic control.[89] Three hundred and sixty-three women received metformin, 92.6% of them continued to receive Metformin until delivery and 46.3% received supplemental insulin. The authors concluded that metformin, alone or with supplemental insulin, was not associated with increased perinatal complications as compared with insulin. These data sugests that the treatment with Metformin is safe and effective and moreover, the women preferred metformin to insulin treatment.

Another randomized controlled trial included 404 women between 11 and 33 weeks of gestation with singleton pregnancies and GDM that required treatment and assigned them to either glyburide or insulin.[72] All the women received dietary advice and eight women in the glyburide group required additional insulin therapy. There were no significant differences between the glyburide and insulin groups regarding macrosomia, neonatal hypoglycemia, lung complications or foetal abnormalities and it was concluded that glyburide is a clinically effective alternative to insulin therapy.

Other studies show that both metformin and sulfonylurea can be safely used in the treatment of GDM. Both glyburide and metformin cross the placenta and the possibility that administration of drugs can affect foetal metabolism is of major concern. More studies are required to define the role of antihyperglycemic agents other than insulin in the treatment of GDM that does not respond sufficiently to lifestyle intervention.

CONCLUSIONS

Worldwide there has been a dramatic increase in the prevalence of overweight and obesity in women of childbearing age.[9,27] Overweight and obese women have an increased risk of developing GDM leading to complications during pregnancy, birth and neonatally.

There are controversese surrounding the screening and the management of GDM and this need further studies to demonstrate the benefits of a universal screening and the effects of treatment in reducing the risk of long- and short-term complications.[61,67] The diagnostic criteria for GDM vary worldwide and there are no clear-cut plasma glucose cut-off values for indicating higher risk for macrosomia or other fetal complications.

Pregnancy act as a "stress test", revealing a woman's predisposition to T2D. Prevention of

GDM by lifestyle changes should be attempted as it could offer a healthier future for the child and the mother.

Maternal metabolic characteristics are crucial determinants of insulin resistance during pregnancy and in offspring and interventions, especially in the form of exercise, weight loss and a healthy diet before, during and after pregnancy might be a key to prevent the vicious circle that contributes to the epidemic of obesity, insulin resistance and T2DM. Intrauterine exposure to diabetes has been associated with high risk of diabetes, obesity, as well as cardiovascular disease in the offspring.[12,35,41]

Several mechanisms have been proposed in order to understand the relationship between maternal GDM and the risk of metabolic and cardiovascular disease in the offspring and in this review, we showed some information regarding the potential role of placental dysfunction and particularly placental endothelial dysfunction as one of the mechanisms linking with GDM.

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