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Chapter 3

Body Mass Index and Insulin Sensitivity/Resistance: Cross Talks in Gestational Diabetes, Normal Pregnancy and Beyond

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Abstract

Pregnancy is a complex of metabolic, physiological, biochemical, and immunological changes in women's body, usually reversible after delivery in normal pregnancy. Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during the current pregnancy." The etiology of the GDM is multifactorial and not sufficiently elucidated. The overweight and obesity during prepregnancy and pregnancy are one of the main modifiable risk factors of GDM. Maternal obesity increases the risk of a number of pregnancy complications, adverse pregnancy outcome for mother and child, and related chronic conditions in women. The obesity prevalence is the greatest among children of obese mothers, and an independent association between maternal body mass index and offspring adiposity and insulin resistance exists. Although the underlying mechanism remains unclear, available evidence suggests that GDM pathogenesis is based on relatively diminished insulin secretion coupled with pregnancy-induced insulin resistance. Recent findings provide data that higher BMI leads to decreased insulin sensitivity and higher degree of insulin resistance and contributes to GDM development.

Keywords: gestational diabetes mellitus, pregnancy, body mass index, homeostasis model assessment, quantitative insulin sensitivity check index

1. Introduction

Normal pregnancy has typical significant changes in maternal insulin resistance and hyperinsulinemia together with progressively increasing insulin secretion during gestation. The

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glucose metabolism regulation during pregnancy has a complex characteristic. The placenta plays a critical role in the delivery of nutrients and the regulation of normal fetal growth. It has a metabolic and endocrine function, and produces cytokines that influence on the fetal growth. Gestational diabetes mellitus (GDM) is a serious complication of normal pregnancy. It is defined as "any degree of glucose intolerance with onset or first recognition during the current pregnancy." The global prevalence ranges between 1 and 14%, depending on the population studied and the diagnostic tests applied. GDM represents nearly 90% of all pregnancies with diabetes [1] and is one of the most common complications with risks for the mother and fetus. GDM is not only associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia, stillbirth, hypertension, and other obstetric complications [2, 3], but is also a strong predictor of impaired glucose tolerance and transitioning to overt type 2 diabetes mellitus (T2DM) postpartum [4]. Although most of the women with previous GDM return to normal glucose tolerance after delivery, both GDM patients and their offspring are at a greater risk of developing T2DM later [5]. The exact cellular mechanisms involved in GDM development are not yet completely understood. Growing data provide evidence for common pathogenesis of different diabetes forms as a result of a progressive β-cell dysfunction, inadequacy to secrete insulin, and insulin resistance in peripheral tissues leading to hyperglycemia. Pancreatic β-cell dysfunction is one of the main pathogenetic GDM mechanisms [6, 7]. Although this defect likely precedes the pregnancy [8], first it is detected clinically as insufficient β-cell compensation of insulin resistance in late pregnancy. GDM occurs if pancreatic β-cells are unable to face the increased insulin demand during pregnancy with elevated glucagon-like peptide 1 (GLP-1) confirming the abnormal insulin secretion [9]. The β-cell defect in GDM women is still present in the postpartum period [10]. Pregnancy is a diabetogenic condition. Many causes are suggestive for insulin resistance or decreased maternal insulin sensitivity. Pregnancy is normally characterized by progressive insulin resistance with beginning near mid-pregnancy and progression during the third trimester to levels approximating the insulin resistance typical for type 2 diabetes mellitus (T2DM) [11]. Firstly, Ryan et al. [12], using the euglycemic clamp technique, demonstrate decrease in insulin sensitivity with a state of insulin resistance in pregnancy being more marked in gestational-onset diabetic women in comparison of non-diabetic control group in late pregnancy. These alterations could be due to placental factors, progesterone, and estrogen, having insulin-antagonistic effects [12]. It seems that gestational diabetes and T2DM are the faces of one and the same disease. Women who develop GDM probably have reduced insulin secretion and/or chronic insulin resistance before pregnancy [13, 14] with a substantially increased risk of developing T2DM later [15]. GDM is the most common pregnancy metabolic disorder with an increasing prevalence ranging from less than 1 to 28% [16–18] that parallels the worldwide epidemic of T2DM [19]. The frequency of occurrence depends on diagnostic methods, ethnicity, and body composition [20]. Some ethnic groups have been long associated with an increased risk of GDM, and the prevalence seems particularly higher among women from South Asia and South East Asia than from Caucasian, African-American, and Hispanic communities [21]. Several pathophysiological mechanisms for GDM development have been proposed as metabolic, inflammatory, autoimmune, and genetic ones with various biologic and molecular pathways for regulation of glucose levels involved. During pregnancy, fine balance between pro -and anti-inflammatory cytokines, necessary for the normal development, exists [22]. In particular, GDM seems to be linked to downregulation of adiponectin and anti-inflammatory cytokines, and to upregulation of adipokines as leptin and pro-inflammatory cytokines, implicated in insulin resistance [22].

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2. Obesity and risk of GDM

2.1. Obesity before pregnancy

The etiology of GDM is multifactorial and not sufficiently elucidated. The overweight, obesity during prepregnancy and pregnancy, excessive gestational weight gain, excessive central body fat deposition, are among the main modifiable risk factors of GDM and contribute significantly to risk of pregnancy complications. Obesity and diabetes constitute worldwide threats to the public health [23] and health care systems and economies [24]. Obesity is a chronic inflammatory state. Pregnancy and especially GDM are associated with elevation in inflammatory markers thus the heightened inflammatory response may play a substantial role in pregnancy complications [22]. Obesity prevalence has been continuously grown, particularly in lower and middle-income countries, but in both, developed and developing countries, more women are obese at conception, and young women at fertile age are at high risk of excess weight gain driving obesity and related reproductive and metabolic complications [25]. The obesity in worldwide is epidemic. The number of individuals with obesity doubled between 1980 and 2014. Moreover, in 2014, over 1.9 billion adults (18+ years) were overweight, with over 600 million being obese [26]. Accumulating epidemiological data confirm that maternal obesity has short- and long-term implications for women and babies, with a threefold increased risk of GDM [27], large for gestational age babies [28], also increased probability of macrosomia and childhood obesity [29–31], and even of fetal death, stillbirth, and infant death [32]. GDM brings a sevenfold higher risk for future development of T2DM [15]. Excessive adiposity and weight gain are well-documented risk factors of type 2 diabetes in the general population [33–35]. Women who develop GDM are more likely to be overweight or obese at the time of the diagnosis in comparison to the general population. A larger part of them develop incident of overweight or obesity in later life. Women with a history of GDM are usually advised to control their weight after delivery [36].

2.2. Excessive gestational weight gain as risk factor for GDM

An excess body weight is a major health issue worldwide as the sixth significant risk factor contributing to disease, and the increased obesity level may result in a decline of life expectancy in the future [37]. The body mass index (BMI), or Quetelet index, is used to assess the degree of obesity/human body fat based on an individual's weight and height [38]. However, BMI values may have different connotations in individuals with diverse ethnic background, short/tall stature, or varied muscle mass, and do not reflect the regional distribution of fat in the body, i.e., subcutaneous versus visceral/central [39]. Both prepregnancy BMI and weight gain during pregnancy are positively associated with gestational insulin resistance [40, 41], with obesity being a risk factor for GDM [42] and increased risk of adverse maternal and perinatal outcomes [43]. In addition to high risk of GDM, excessive gestational weight gain (EGWG) and obesity in prepregnancy have further adverse risks of preeclampsia, eclampsia, cesarean delivery, macrosomia, etc. [44–48]. Because of increasing living standards, EGWG prevalence is higher than ever before with approximately 40% of pregnant women gaining more weight than is recommended [48]. These two factors—high prepregnancy BMI and EGWG—have been reported as well-established risk for adverse pregnancy outcomes [49–54]. Large studies, including different ethnic women in western countries, determine

increased risk for macrosomia in parallel with increasing EGWG in all prepregnancy BMI categories, and the risk varies in relation to degree of BMI [55–58]. Moreover, more underlined risk of macrosomia in overweight and obese before pregnancy women and in those who gain excessive weight during pregnancy has been proved [59]. Women with previous pregnancies complicated by GDM are at an increased risk of developing T2DM in the postpartum [15]. A meta-analysis evaluates 28 studies including women with previous GDM, with follow-up ranging between 6 weeks and 28 years after the end of pregnancy, and it reveals rates of T2DM between 2.6 and 70%, depending on ethnicity, diagnostic criteria, and the follow-up period [60]. Prepregnancy obesity and excessive weight gain from prepregnancy to postpartum increase postpartum diabetes and prediabetes risks among GDM women [61]. Women, failing to lose weight postpartum, are with a higher risk of subsequent long-term obesity [62]. The recent meta-analysis shows 18% increase in risk of diabetes per unit increase in BMI [63], and every kilogram of weight gain increases by 7% the risk of diabetes [64]. Several studies have indicated that body fat distribution, dependent on ethnicity, has a larger effect than general obesity in predicting the risk of diabetes [65, 66]. Asians are with smaller frames and lower body fat distribution than white Europeans for the same BMI [67]. In comparison to Europeans, Chinese, and South Asians have more abdominal adipose tissue, especially visceral adipose tissue [68]. In this regard, waist circumference (WC) is a simple and valid index to assess abdominal fat and has been proved to be an independent predictor of T2DM [69, 70]. In Caucasian women, WC is also an important predictor of GDM [71].

2.3. Obesity and adipose tissue

In the last decade, abundant data have indicated that adipose tissue is not just an energy storage depot but rather a metabolically active tissue [72]. Adipose tissue is considered to be an important and active organ for maintenance of systemic homeostasis through a complex network of auto-, para-, and endocrine cross talks to other tissues and organs [73] mediating the development of obesity and related diseases. During obesity, the number and size of adipocytes are increased [74]. Studies of adipocytes from women in different trimesters reveal alterations in lipolytic activity that promote maternal fat accumulation in early pregnancy and enhance fat mobilization in late pregnancy [75]. Hypertrophy of adipocytes can impair the functions of adipose tissue in association with excess amount of adiposity and leading to a dysregulated secretory profile [76]. Obesity in pregnancy has intense effects, causing systemic inflammation. Maternal obesity and GDM may be associated with a state of chronic, low-grade inflammation, referred as "meta-inflammation," opposite to an acute inflammatory response [77], or metabolically induced inflammation. Meta-inflammation is distinct from an acute pro-inflammatory response and is triggered primarily by metabolites and nutrients, leading to systemic insulin resistance [78]. The base of this chronic low-grade inflammation is a production of pro-inflammatory cytokines by adipocytes in obesity [79]. This elevation of circulating pro-inflammatory cytokines, originated from adipose tissue, may induce increased inflammatory cytokine secretion by the placenta and alter placental function [80]. During pregnancy, similar to gestational age, the size of the placenta is also in progress. The levels of pregnancy-associated hormones estrogen, progesterone, cortisol, and placental lactogen in the maternal circulation are elevated [81, 82] accompanied by an increasing insulin resistance. A healthy pregnancy outcome is highly reliant on tight physiological regulation

largely orchestrated by the placenta, an extremely complex and multifunctional materno-fetal organ [83]. The placenta like a transient endocrine organ with a secretion of various hormones and cytokines, affecting both maternal and fetal metabolism, plays a major role in the initiation and preservation of pregnancy. Maternal obesity significantly impacts the endocrine function of the placenta. Obese pregnancies have a dysregulated maternal cytokine profile with considerable rise in pro-inflammatory cytokines [84, 85]. Furthermore, such over expression of pro-inflammatory cytokines is also observable in GDM placenta. This alteration in normal secretion of adipocytokines is involved as an essential factor in GDM development [86–89].

2.4. Adipose tissue and adipokines in normal pregnancy and in pregnancy with GDM

Adipokines, secreted from adipose tissue, are involved in a wide spectrum of biological processes, including regulation of energy homeostasis, adipocyte proliferation and differentiation, inflammation, angiogenesis and regulation of coagulation, and vascular function [90–92]. Adipokines act locally in adipose tissue (auto- and paracrine manners), but they also mediate via the circulation the cross talks between adipose tissue and other key metabolic organs (endocrine manner). Some adipokines, such as leptin and adiponectin, are adipocyte specific, while others, like pro-inflammatory cytokines, to a higher degree are secreted by the nonfat cells in adipose tissue [76]. In obesity, dysregulation of pro- and anti-inflammatory cytokines released from adipose tissue is in the base of the chronic low-grade systemic inflammation as that leads to development of metabolic and cardiovascular disorders [93, 94] and promotes insulin resistance or GDM. Adipose tissue produces adipocytokines, including leptin, adiponectin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), as well as the recently discovered resistin, visfatin, and apelin [95, 96]. A study finds the circulatory levels of IL-6, interleukin-8 (IL-8), interleukin-1β (IL-1β), TNFα, and C-reactive protein (CRP) are higher in overweight and obese pregnant women, relatively to normal weight women during pregnancy and postpartum [97]. The expression of pro-inflammatory cytokines has also been reported to be dysregulated in the development of GDM introducing an altered cytokine profile in hyperglycemic pregnancies [98, 99]. These effects are all related to regulation of insulin resistance. Higher circulatory levels of CRP, IL-6, monocyte chemoattractant protein-1 (MCP-1), and interleukin-1 (IL-1) receptor antagonist (IL-1Ra) are significantly associated with maternal adiposity [100]. Increased circulation levels of pro-inflammatory cytokines, IL-6, TNFα, leptin, and decreased levels of adiponectin and anti-inflammatory markers such as interleukin-4 (IL-4) and interleukin-10 (IL-10) are seen in GDM pregnancies in comparison to normal pregnancies, regardless of BMI [99]. The elevated circulating levels of IL-6 and TNFα in maternal blood are consistently observed in maternal obesity as well as in GDM, in the presence or absence of obesity [101–103]. TNFα and leptin have been suggested as the strongest predictors of pregnancy-associated insulin resistance [104, 105]. Together with increased levels of serum cortisol, interleukins, and other factors, they can interrupt the insulin signaling pathway and lead to insulin resistance during normal pregnancy [104]. Additionally, TNFα has been established as the most significant predictor of pregnancy-induced insulin resistance, with higher synthesis and releasing by the placenta in comparison to IL-6 or IL-8 [106]. Hence, TNF-α is more likely to exert crucial effects on IR during pregnancy. Although the leptin is produced mainly by adipocytes, there is strong evidence that the placenta, rather than maternal

adipose tissue, contributes to the rise in maternal leptin concentrations during pregnancy [107]. Pregnancy is considered as a leptin-resistant state, but the results on circulating leptin levels in GDM are controversial. However, most studies have shown increased leptin in GDM [108–110]. Adiponectin, anti-inflammatory factor, is considered to have beneficial effects on insulin sensitivity and anti-inflammatory activities [99]. TNF-α, leptin, and adiponectin are produced by placenta [111, 112] and releasing into the maternal circulation contributes to the rise in maternal TNF-α and leptin concentrations during pregnancy [104], more pronounced in GDM than in normal pregnancy [99]. Increased circulating concentrations of TNF-α enhance leptin production, opposite, leptin increases the production of TNF-α and IL-6 by monocytes [113] and stimulates the production of CC chemokine ligands (CCL) [114]. Except this, TNF-α and other pro-inflammatory mediators suppress the production of adiponectin by adipocytes [115]. Something more, some studies find a significant positive correlation between BMI values and levels of TNF-α and leptin, and an inverse correlation between BMI and adiponectin levels in GDM [108, 116–118]. The increased secretion of pro-inflammatory cytokines, the relative hypoxia, and cell death due to hypertrophic adipocytes promote a high infiltration rate of monocytes into visceral adipose tissue and activation of macrophages [119]. In general, the increase in release of pro-inflammatory cytokines, infiltration of macrophages, as well as relationship between hypertrophic growth of adipose tissue and inflammation lead to the development of insulin resistance [120] and β-cell failure [121, 122].

2.5. Interaction between iron and adipocytes

Several recent studies have attempted to illuminate the effect of iron overload on adipocyte function. Although inflammatory cytokines can influence iron storage in various cell types, studies have shown that the link between elevated iron and obesity/diabetes is independent of inflammation [123, 124]. No central mechanism for the impact of iron on adipocytes is known; however, iron is known to influence adipocytes' mitochondrial function and adiponectin production [125]. Alterations in adipocyte mitochondrial iron content affect adipocyte differentiation and insulin sensitivity [126, 127]. Some studies have suggested that adipose tissue may be a primary target organ for the metabolic effects of iron. The results propose that stores of body iron and/or iron metabolism may be involved in the development of insulin resistance not only in liver or muscle but also in adipocytes [128]. Adipocytes require iron for normal function and differentiation. They also express specialized proteins involved in iron metabolism and this fact is well suited to possible adipocyte action as an iron sensor. Evidence that adipocyte iron levels regulate adiponectin transcription and serum protein levels is present. These data further highlight the role of the adipocyte as a key regulator of metabolism in all tissues, based on integrated sensing of nutritional stores and iron availability [129]. The hypothesis that adiponectin links iron and insulin resistance is attractive as decreased adiponectin levels are associated with insulin resistance during GDM, a relationship between its reduced concentration and β-cell dysfunction in GDM women [130]. Moreover, studies in mice, human, and cell culture have demonstrated that iron lowers adiponectin production and increases diabetes risk [129]. Serum ferritin levels, as indicator for tissue iron stores, reflect insulin resistance during diabetic pregnancy [131], with a higher level in GDM women in comparison to normal pregnant [132], and also with a risk of subsequent development of postpartum impaired glucose tolerance and overt T2DM [131]. Furthermore, intracellular iron excess

catalyzes the formation of reactive oxygen species (ROS), promoting oxidative stress [133, 134] thus leading to increased β-cells apoptosis, hepatic dysfunction, and insulin resistance, and in consequence, promoting the T2DM progression [135]. Research data verify that serum ferritin concentrations are among the best predictors of serum leptin under physiological conditions. More importantly, the relationship is causal, reflecting regulation of leptin transcription by iron [136]. Studies on relationship between ferritin and leptin have suggested a possible link which is independent of relationship with BMI and inflammation. Iron overload may lead to a decrease in leptin serum level [137] along with the destruction of the fat cell membrane and the dysfunction in adipose tissue [138]. Opposite to this suggestion—leptin with other stimuli, such as pro-inflammatory cytokines, can be added to the list of adipose-derived factors that may contribute to hypoferremia observed in the overweight and obese population [139]. The functional significance of iron accumulation in adipocytes and the reduced leptin level is not yet clear. One possible explanation is that while iron regulates the serum leptin level, at the same time, it could have an effect on leptin signaling to a change in leptin sensitivity [140]. This interplay between iron, leptin, and adiponectin is an intriguing subject for study in various population groups, including pregnant women with gestational diabetes.

Deficiency of vitamin D is associated with impaired glucose homeostasis during pregnancy [141]. New studies underline the key role of vitamin D in glucose homeostasis and insulin resistance: 1,25(OH)2D3, the active form of vitamin D, regulates circulating glucose levels by binding to vitamin D receptor of pancreatic β-cell and modulating insulin secretion [142, 143]; it promotes insulin sensitivity by stimulating the expression of insulin receptors and enhancing insulin responsiveness for glucose transport [144]; regulates the balance between the extracellular and intracellular calcium pools in pancreatic β-cell, [145]; it is responsible for the presence of vitamin response element in the human insulin gene promoter with stimulation of the expression of insulin receptor and for the effects on systemic inflammation by modulating the effects of cytokines on β-cell function [146], since insulin resistance and β-cell apoptosis could be induced by systemic inflammation. Vitamin D has a direct effect on pancreatic β-cells and is a prerequisite for the normal insulin secretion function of the endocrine pancreas [147, 148]. Probably, the active form of vitamin D decreases expression of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α involved in insulin resistance [149]. Some studies report a negative relationship between serum 25(OH) D levels, BMI [150–152], and HOMA-IR [147, 152]. Maternal overweight and obesity are among the highest modifiable risk factors. The prevalence of obesity is increasing, especially in women at reproductive age. In America, according to the data from Pregnancy Risk Assessment Monitoring System (PRAMS), one in five women is obese when they become pregnant, which presents the increase of the obesity prevalence by 70% compared to the previous decade [153]. Obesity is a risk factor for the development of GDM [154], and increased BMI is associated with a greater frequency of complications in pregnancy, at birth and postpartum [155, 156]. The most commonly studied index, body mass index, calculated by formula BMI = weight (kg)/height (m^2) [37], is for measure of total body fat [157]. BMI is derived from easy measurements of height and weight and it is not expensive. Usually, women are classified as underweight (BMI less than 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), class I obese (BMI 30.0–34.9), class II obese (BMI 35–39.9), or class III obese (BMI 40.0 or greater), according to Institute of Medicine (IOM) [158]. There are some limitations maybe even more important when attempting to compare individuals from

different ethnic groups. The proposed BMI cut-off points ranging from 18·3 to 29·7 kg/m^2 for children and adolescents aged 5–19 years, which correspond to the adult obesity threshold of 30 kg/m^2.These cut-offs are on the base of data from the USA population [159]. The use of these global cut-off points to define overweight and obesity remains contentious. Given the marked variations in different world regions, countries, and populations within countries, the use of these values may underestimate the health hazards of adult obesity [160]. Current studies show that maybe visceral fat mass is a novel risk factor for predicting gestational diabetes in obese pregnant women [161]. Central obesity as assessed by early pregnancy waist-hip ratio (WHR) and visceral fat mass (VFM) measured by bioimpedance is an independent predictor of GDM in addition to classical risk factors [162]. In a prospective study of 485 women cohort in Canada, elevated first trimester visceral and total adipose tissue depth independently predict the risk of subsequent dysglycemia in pregnancy [163]. Measures of central/abdominal obesity such as WC and WHR have been compared to BMI for their association with adverse cardiovascular and metabolic consequences [164]. BMI and WHR are significant risk factors for development of gestational diabetes and IR, but this association varies among different ethnicities [165]. Results of meta-analysis of 20 studies show that the risk of developing GDM is about two, four, and eight times higher among overweight, obese, or severely obese compared with normal-weight women at the beginning of their pregnancies [166].

For every 1 kg/m^2 increase in BMI, the prevalence of GDM increases by 0.92% [42]. The increasing BMI index with 1 kg/m^2 increased the risk of GDM developing with 9.9% [167] Increasing trend in the risk of severe adverse obstetric outcomes, rising along with increasing maternal BMI, exists [168]. Maternal overweight and obesity, diabetes, and excessive gestational weight gain are associated with fetal overgrowth and large for gestational age (LGA), which then can lead to an increased risk in the offspring for later obesity and diabetes [169, 170]. It has been found that in Finnish obstetric population, the maternal morbidity rises markedly when comparing overweight (BMI ≥26–29 kg/m^2) vs. obese (BMI ≥ 30 kg/m^2) women: the incidence of maternal diabetes, hypertension, and other chronic diseases [171].

3. Insulin resistance and insulin sensitivity in normal and GDM pregnancy

Pregnancy is a normal physiological state of insulin resistance, and it presents a physiological stress model of pancreatic β-cells [172, 173]. It is associated with a decrease in insulin sensitivity of an approximate 50–60% by the latter half of pregnancy and a 200–250% increase in insulin secretion with purpose to maintain euglycemia in the mother [10]. The increased resistance is caused by post-insulin receptor events and is brought about by the cellular effects of the increased levels of some pregnancy-associated hormones [174]. In gestational diabetes, insulin resistance is not adequately compensated by insulin hypersecretion because of defective β-cell function. Insulin resistance during pregnancy reveals limitations in insulin secretion; on the other hand, increasing insulin resistance and subsequent insulin hypersecretion may worsen the level of β-cell failure [174]. As a result, pregnant women with GDM have a higher level of insulin resistance compared to healthy pregnant women.

Some studies demonstrate that the insulin secretion and sensitivity capacities of Asian women are different from those of women in Western countries. Since even in Asians, the pancreatic β-cell mass is relatively smaller than in Westerners, and insulin secretion capacity is also lower on the background of abdominal obesity is more common in Asians than in Westerners with similar body weights [175]. A study assesses the change in insulin resistance and β-cell function in a multiethnic population-based cohort of pregnant women. Pregnant women from East Asia and South Asia are more insulin resistant and show poorer β-cell function (HOMA-β) than Western Europeans [176]. The mechanisms leading to increased insulin secretion in pregnancy, primary or compensatory to resistance, are not entirely elucidated yet. They are partly related to metabolic effects of several hormones and cytokines which are elevated in maternal circulation during pregnancy [177]. Decreased insulin sensitivity or increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g., liver, muscle, or adipose tissue. Obesity is the most common risk factor related to decreased insulin sensitivity. During the pregnancy, it is related with maternal energy metabolism, and visceral fat accumulation has important biological meaning. In this relation, the influence of visceral fat, respectfully BMI, and insulin sensitivity are too important [178].

In healthy pregnant women, pancreatic β-cells increase their insulin production through hyperplasia, hypertrophy, and hyperfunction to compensate for the pregnancy-induced insulin resistance [176]. Maternal islets adapt to this increased demand mainly through enhanced insulin secretion per β-cell and increased β-cell proliferation [179]. Like other forms of hyperglycemia, GDM is characterized by pancreatic β-cell dysfunction that is insufficient to meet the body's insulin needs. Available data suggest that β-cell defects in GDM are a result from the same spectrum of causes that underlie hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance [180]. In normal pregnancies, the dynamic changes in glucose homeostasis and insulin sensitivity are in connection with alterations in lipid and protein metabolism. Longitudinal studies of glucose tolerance during gestation demonstrate an increased insulin response to oral glucose in the first trimester relative to prepregnancy values [10], with a subsequent progressive increased insulin responses in consistent with progressive IR [10]. Remarkably, there is an independent effect of pregnancy on β-cell function independent of the observed changes in insulin; but the etiology of this effect is at present unknown, although may include the role of incretins [181, 182]. The impact of obesity on these changes is significant; in particular, the decline in fasting glucose at early gestation is reduced, but not reduced at all in severely obese women [183]. In late gestation, the normal reduction in peripheral insulin sensitivity of 50% is reduced in obese women [10]. In addition to significant peripheral and hepatic insulin resistance, which manifests as reduced insulin-mediated glucose disposal, there is a large reduction in insulin-stimulated carbohydrate oxidation and a reduction in insulin suppression of endogenous glucose production, all of which are reversed in the postpartum period [184]. Importantly, the overall effects of this impaired insulin resistance are not influenced only on the glucose. In the postprandial state, this obesity-related insulin resistance overacts the normal circulatory increases in metabolic fuels, i.e., glucose, lipids, and amino acids. The fasting, postprandial, and integrated 24-h plasma concentrations of all basic macronutrients are affected by enhanced insulin resistance in obese pregnant women [185].

3.1. Homeostasis model assessment of insulin resistance (HOMA-IR)

The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and β-cell function, based on a single measurement of fasting glucose and insulin or C-peptide concentrations in the blood [186]. The easiest and most popular assessment of β-cell function is the homeostatic index HOMA-B. It is widely used because of its simplicity and it reflects the release of insulin under nonstimulated conditions [187]. HOMA model is considered as a structural model of the underlying physiological basis for the feedback loop between the liver and the β-cell in fasting [188]. HOMA-IR has been observed to have a linear correlation with the glucose clamp and considered as minimal model for estimations of insulin sensitivity/resistance in various studies [188, 189]. HOMA-IR determines the relationship between the liver and pancreas. This index reflects more the liver insulin resistance in comparison to peripheral insulin resistance [190], and it is a good indicator of overall insulin sensitivity during pregnancy. Although surrogate marker HOMA-B is less evaluated as an index, it provides high reliability in the measurement of β-cell function. Both indices, HOMA-B and HOMA-IR, submit better overall picture of the essential metabolic disorder [191]. Disadvantage of HOMA model is related to the fact that it underlines the lack of linearity at deepening of insulin resistance [192]. This model is a widely used and well correlates with the insulin sensitivity, as measured by the venous clamp technique in various studies [188, 189].

3.2. Assessment of insulin sensitivity by using quantitative insulin sensitivity check index (QUICKI) and HOMA2 variant insulin sensitivity (HOMA %S)

The quantitative insulin sensitivity check index (QUICKI) is an empirically derived mathematical transformation of fasting blood glucose and plasma insulin concentrations [193, 194]. QUICKI is a simple, robust, accurate, and reproducible method that appropriately predicts changes in insulin sensitivity after therapeutic interventions as well as the onset of diabetes [195]. QUICKI has been seen to have a significantly better linear correlation with glucose clamp determinations of insulin sensitivity than minimal-model estimates [196]. Its calculation is used to evaluate the insulin sensitivity [197] including during early and late pregnancy [190]. The index assumes that the circulating glucose and insulin are determined by a feedback loop between the liver and pancreatic β-cells [198]. Insulin sensitivity has been modeled by proportionately decreasing the effect of plasma insulin concentrations at both the liver and the periphery [199]. Other parameter to assess insulin sensitivity is HOMA-S%. The computer model can be used to determine insulin sensitivity (HOMA–S%) from paired fasting plasma glucose and insulin concentrations. The data from individual subjects determine unique combinations of insulin sensitivity (HOMA %S) and beta cell function (HOMA %B) from steady-state conditions [200]. HOMA can be used to track changes in insulin sensitivity and β-cell function in individuals. Also, it can be used in individuals to indicate whether reduced insulin sensitivity or β-cell failure predominates. Determination of HOMA-%S is used to establish the prevailing normal over a normoglycemic population in each comparative group [188]. Maternal obesity is associated with higher maternal glucose and GDM risk; its association with newborn size at birth is, in part, independent of maternal glycemia [201–204]. BMI is an indicator of the tissue quantity (weight) over the skeletal frame (height), including adipose tissue and muscle. BMI is known to increase blood volume and to reduce the concentration

of serum metal ions, such as, iron and zinc [205]. Maternal overweight (BMI ≥ 25 kg/m^2) has been shown to be the strongest risk factor for GDM. Two meta-regression analyses show that the odds ratios for developing GDM are 1.97–2.14 in overweight (BMI ≥ 25 kg/m^2), 3.01–3.56 in obese (most studies BMI ≥ 30 kg/m^2), and 5.55–8.56 in severely obese (BMI ≥ 35–45 kg/m^2) women compared with normal weight women [154].

3.3. The effect of BMI on insulin sensitivity indices

In late gestation, the normal reduction in peripheral insulin sensitivity of 50% [206] is reduced in obese women as determined by the quantitative insulin sensitivity check index and that insulin sensitivity in women with GDM worsened as gestation progressed [207]. The indexes of insulin sensitivity QUICKI and HOMA significantly correlated with a direct measurement of insulin sensitivity using the euglycemic-hyperinsulinemic clamp during pregnancy [208]. The mechanism for the decrease in insulin sensitivity in pregnancy is not fully understood and is part of the natural process during pregnancy, although the insulin signaling pathway can be interrupted by several factors, such as increased levels of serum cortisol, TNF α, and some interleukin cytokines, leading to insulin resistance, during normal pregnancy [104]. In this connection, it would appear that preconceptual fat mass is one of a major determinant, because lean women exhibit an inverse correlation between changes in insulin sensitivity and fat mass, which is not seen in obese women [209]. Obese women exhibit a negative relationship between the decrease in insulin sensitivity and accretion of fat mass from prepregnancy to late gestation [210]. Visceral fat volume in human body has important biological meaning, which is well expressed during the pregnancy. In this relation, the influence of visceral fat, respectfully BMI, on the insulin sensitivity is too important. A study has announced diminished insulin sensitivity in pregnant women with GDM compared to healthy pregnant women for BMI ($P > 0.05$) with significantly higher body fat percentage, expressed by connection QUICKI index-BMI ($r = -0.384$, $P < 0.01$) [211]. These results are similar to other author's results—lower level of insulin sensitivity index QUICKI in pregnant women with GDM in comparison to NGT $P = 0.001$, a reverse correlation between QUICKI index and BMI in the both of group ($r = -0.458$ for NGT and $r = -0.603$ for GDM) [167]. Insulin sensitivity measured during the clamp was higher during pregnancy in the NGT group than in the GDM group ($P < 0.05$) [208]. Values of QUICKI index in overweight women with normal glucose tolerance (NGT) and in women with GDM have been significantly lower ($P < 0.01$) than those in normal-weight women with NGT, and QUICKI in women with GDM has been decreased significantly ($P < 0.05$) during pregnancy, according to Endo et al. [207]. Furthermore, other authors have reported significant interaction between race and BMI (under/normal weight, overweight/obese) for glucose, insulin, and HOMA-IR at or above the 75th percentile and QUICKI less than the 25th percentile in mid-trimester [212]. Other authors have detected lower levels of QUICKI index in overweight compared to normal-weight women at third trimester of pregnancy [199]. Changes in insulin sensitivity are a hallmark of pregnancy and contribute to the metabolic changes, while nutrient transfer to the fetus impacts maternal metabolite levels [213, 214]. Studies show that values for HOMA-S% between pregnant with GDM and matched control NGT subject are highly significant different ($P < 0.001$) [215, 216]. Some authors found lower level for HOMA S% in GDM pregnant with prepregnancy BMI ≥ 25 kg/m^2 in comparison to GDM with prepregnancy BMI <25 kg/m^2 ($P < 0.001$) [217].

These values are not markedly different from those obtained in the other study [167]. In this study, there are statistically significant differences in HOMA-S% between the NGT and GDM groups (P = 0.002). It is found a reverse correlation between HOMA-S% and BMI in the both NGT and GDM patient groups (r = −0.467 and r = −0.679, respectively). The authors' hypothesis is that as higher is a BMI, stronger is its influence on insulin sensitivity, expressed by HOMA-S% index [167]. The current studies confirm that GDM is associated with increased insulin resistance and β-cell dysfunction, as well as reduced insulin sensitivity and secretion.

BMI, glucose, and insulin sensitivity are interrelated and alter maternal metabolism. A novel aspect of studies is identification of metabolic signatures uniquely associated with maternal BMI and glycemia, including differences in metabolites most strongly associated with these phenotypes [218]. The association of several plasma metabolites with maternal prepregnancy BMI across gestation in a cohort of 167 non-Hispanic and Hispanic ancestry women was reported [219]. Some of these metabolites have been found to have a role in aspects of metabolism such as insulin sensitivity and pancreatic β-cell function. A limited number of GDM metabolomics studies have been performed, evidence suggests that the metabolic signatures of T2D and GDM overlap [220]. Metabolomic studies of maternal metabolism during pregnancy are focused largely on normal pregnancy and GDM [221–227]. It is important to examine the associations of maternal BMI on the maternal metabolome, to consider estimated maternal insulin sensitivity as a predictor of the maternal metabolome. Furthermore, maternal BMI and insulin sensitivity impact a broad array of metabolites and have shared independent associations with the maternal metabolome [228].

3.4. The effect of BMI on homeostasis model assessment of insulin resistance (HOMA-IR)

Insulin resistance is, by definition, a disorder in the signal transduction of several known hormones [229]. Insulin resistance in peripheral tissues in women with GDM is exacerbated, but few studies have examined the extent of insulin resistance in placenta in this disease. It is possible that this insulin resistance could contribute to alter the placental transport of nutrients [230–232]. The degree of maternal insulin resistance manifested during pregnancy is theoretically associated with the degree of glucose flux from mother to fetus. Excessive insulin resistance during pregnancy is also observed in obese subjects without abnormal glucose tolerance [10]. Different studies found HOMA-IR values in the GDM group are significantly higher than in NGT patients, which indicated a significant insulin resistance [167, 215, 233–239]. Some studies report controversial results. They found that the HOMA-IR values are similar in GDM patients and healthy NGT controls [240–243]. Women with GDM in early pregnancy had significantly higher HOMA-IR values than those with GDM in later pregnancy or those with NGT [244] and results are similar to other from prior work [245]. Probably, higher BMIs among women with early-onset GDM are detected to at least partially explain this phenomenon [246]. An important goal is to identifying women with GDM during early pregnancy to minimize maternal and neonatal morbidity. One study reported that first trimester HOMA-IR values are independent predictors for the development of GDM in logistic regression analysis, and the HOMA-IR value is found to be a better marker (AUC ¼ 0.75; 95% CI, 0.67e0.83) than the other factors [247]. Another study detects borderline significance for risk of subsequent GDM for increased HOMA-IR values at gestational weeks 16–18, independent of other variables that

are associated with GDM [248]. Some researchers determined the predictability of GDM with a 90% sensitivity and 61% specificity by ROC analysis in patients whose HOMA-IR scores are >2.08 in the first trimester [249]. A study reports that HOMA-IR at 21–28 gestational weeks is reliable risky factor to development of IR (OR = 0.677, 95% CI = 0.573–0.781, P = 0.002, sensitivity 54.7%, and specificity 24.5%). HOMA-IR is found with statistically significant impact on developing of GDM-OR = 2.039 (95% CI = 1.427–2.914, P < 0.0001). The increasing HOMA-IR index with unit increases the risk of GDM developing about two times. The predictive threshold values for developing insulin resistance in gestational pregnant at 21–28 gestational weeks are HOMA–IR > 1.8 [250]. According to the International Diabetes Federation (IDF) criteria, the HOMA-IR cut-off point to differentiate low and high value of insulin resistance is 2.38. Several previous studies performed on smaller populations have demonstrated that HOMA-IR index assessed at diagnosis of GDM is ranged from 1.6 to 25 [130, 176, 251, 252]. HOMA-IR values of ≥1.29 at diagnosis may indicate insulin resistance in the studied population of women and are associated with a higher value of the prepregnancy BMI [177]. Maternal obesity-prepregnancy at the time of GDM diagnosis is in connection to enhance insulin resistance. A positive correlation between BMI and HOMA-IR in NGT group r = 0.485 and in GDM pregnant r = 0.594 has been established without statistical difference between two pregnant groups in second to third trimester [250]. The results are similar to those of others studies [253–255]. Other study obtains no significant correlations between BMI and markers of insulin resistance, indicating that BMI is not a confounder in the elevated insulin resistance among the enrolled GDM subjects [256]. The correctness requires to be noted some authors refer to BMI, especially in pregnancy, to be a poor index of fat mass, and it could be superseded in the statistical models by other anthropometric measures, three of which were independent predictors of GDM. These simple measures (age, fasting blood glucose, and subcutaneous fat), while are recognized in a few earlier reports, they are largely ignored in assessment of GDM risk [257–259]. Other study finds trimester-specific strongly positive association between HOMA-IR and prepregnancy BMI in each trimester (P < 0.001 in trimester 1 and 2, P = 0.004 in trimester 3). Also, the results from these analyses support the notion that the maternal metabolome is predominantly influenced by obesity and less by dietary intake during pregnancy [219]. However, it appears that beginning of the pregnancy in the obese state disturbs normal anabolic activity through early-gestational insulin resistance [260]. This may suggest that the obesity induces various metabolic and hormone fluctuations, rather than insulin resistance alone. This study demonstrates for the first time an association between prepregnancy BMI and a pattern of metabolites related to obesity, which differs from nonpregnant cohorts [219].

4. Conclusions

Undoubtedly, in recent years, the frequency of GDM is increasing in tandem with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age, assessing by BMI. Another risk factor for GDM is the excessive weight gain during the pregnancy, assessing by use of BMI. The optimal weight increase in pregnancy is well established on the base of studies, and is different depending on BMI prior to pregnancy. Some studies show, that excessive weight gain is a significant risk factor for GDM in all categories of BMI, but the relationship is more stringent in obese individuals. Most of studies observed that higher BMI decreases the

insulin sensitivity, increases the IR and contributes to development of GDM. New guidelines into the mechanisms underlying maternal metabolism during pregnancy are being gained through the use of new technologies. Future studies on the base of integrated data from multiple technologies will allow a systems biology approach to maternal metabolism during pregnancy.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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