Chapter 3

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

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Additional information is available at the end of the chapter

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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
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 pathophysiologcal 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].
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 circulatory 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 hypoferrremia 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 (m²) [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/m² for children and adolescents aged 5–19 years, which correspond to the adult obesity threshold of 30 kg/m². 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/m² increase in BMI, the prevalence of GDM increases by 0.92% [42]. The increasing BMI index with 1 kg/m² 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/m²) vs. obese (BMI ≥ 30 kg/m²) 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

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of serum metal ions, such as, iron and zinc [205]. Maternal overweight (BMI ≥ 25 kg/m²) 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/m²), 3.01–3.56 in obese (most studies BMI ≥ 30 kg/m²), and 5.55–8.56 in severely obese (BMI ≥ 35–45 kg/m²) 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/m² in comparison to GDM with prepregnancy BMI <25 kg/m² (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 a 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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References

[1] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2006;29(Suppl.1):S43-S48

[2] Khatun N, Latif SA, Uddin MM. Pregnancy associated complications of mothers with gestational diabetes mellitus. Mymensingh Medical Journal. 2005;14:196-198

[3] Jawerbaum A, Gonzalez E. Diabetic pregnancies: The challenge of developing in a pro-inflammatory environment. Current Medicinal Chemistry. 2006;13:2127-2138. DOI: 10.2174/092986706777935302

[4] Kaaja R, Rönnemaa T. Gestational diabetes: Pathogenesis and consequences to mother and offspring. The Review of Diabetic Studies. 2008;5(4):194-202. DOI: 10.1900/RDS.2008.5.194
[5] Damn P. Gestational diabetes mellitus and subsequent development of overt diabetes mellitus. Danish Medical Bulletin. 1998;45:495-509

[6] Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism. 2001;86:568-573. DOI: 10.1210/jcem.86.2.7137

[7] Buchanan TA, Xiang A. Gestational diabetes mellitus. The Journal of Clinical Investigation. 2005;115(3):485-491. DOI: 10.1172/JCI200524531

[8] Basu R, Breda E, Oberg A, Powell C, Man CD, Basu A, et al. Mechanisms of age-associated determination in glucose tolerance, contribution of alterations in insulin secretion, action and clearance. Diabetes. 2003;52:1738-1748. DOI: 10.2337/diabetes.52.7.1738

[9] Reyes-Lopez R, Perez-Luque E, Malacara JM. Metabolic, hormonal characteristics and genetic variants of TCF7L2 associated with development of gestational diabetes mellitus in Mexican women. Diabetes/Metabolism Research and Reviews. 2014;30(8):701-706. DOI: 10.1002/dmrr.2538

[10] Catalano P, Huston L, Amini SB, Kalhan SC. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. American Journal of Obstetrics and Gynecology. 1999;180(4):903-916. DOI: 10.1016/S0002-9378(99)70662-9

[11] Barbour LA, CataMcCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(Suppl. 2):S112-S119. DOI: 10.2337/dc07-s202

[12] Ryan EA, O'Sullivan MJ, Skyler J. Insulin action during pregnancy. Studies with the euglycemic clamp technique. Diabetes. 1985;34(4):380-389. DOI: 10.2337/diab.34.4.380

[13] Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: Risks and management during and after pregnancy. Nature Reviews. Endocrinology. 2012;8(11):639-649. DOI: 10.1038/nrendo.2012.96

[14] Kim C. Mint: Maternal outcomes and follow-up after gestational diabetes mellitus. Diabetic Medicine. 2014;31(3):292-301. DOI: 10.1111/dme.12382

[15] Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. Lancet. 2009;373(9677):1773-1779. DOI: 10.1016/S0140-6736(09)60731-5

[16] Ferrara A, Kahn HS, Quesenberry CP, Riley C, Hedderson MM. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991-2000. Obstetrics and Gynecology. 2004;103(3):526-533. DOI: 10.1097/01.AOG.0000113623.18286.20

[17] Getahun D, Nath C, Ananth CV, Chavez MR, Smulian JC. Gestational diabetes in the United States: Temporal trends 1989 through 2004. American Journal of Obstetrics and Gynecology. 2008;198(5):525.e1-525.e5. DOI: 10.1016/j.ajog.2007.11.017
[18] Zhang F, Dong L, Zhang CP, Li B Wen J, Gao W, et al. Increasing prevalence of gestational diabetes mellitus in Chinese women from 1999 to 2008. Diabetic Medicine. 2011;28(6):652-657. DOI: 10.1111/j.1464-5491.2010.03205.x

[19] Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—Present and future perspectives. Nature Reviews. Endocrinology. 2012;8(4):228-236. DOI: 10.1038/nrendo.2011.183

[20] Schiavone M, Putoto G, Laterza F, Pizzol D. Gestational diabetes: An overview with attention for developing countries. Endocrine Regulations. 2016;50(2):62-71. DOI: 10.1515/enr-2016-0010

[21] Kim SY, Saraiva C, Curtis M, Wilson HG, Troyan J, Sharma AJ. Fraction of gestational diabetes mellitus attributable to overweight and obesity by race/ethnicity, California, 2007-2009. American Journal of Public Health. 2013;103(10):e65-e72. DOI: 10.2105/AJPH.2013.301469

[22] Abell SK, Courten BD, Boyle JA, Teede HJ. Inflammatory and other biomarkers: Role in Pathophysiology and prediction of gestational diabetes mellitus. International Journal of Molecular Sciences. 2015;16(6):13442-13473. DOI: 10.3390/ijms160613442

[23] Mahadevan S, Iftikhar A. Is body mass index a good indicator of obesity? International Journal of Diabetes in Developing Countries. 2016;36(2):140-142. DOI: DOI 10.1007/s13410-016-0506-5

[24] American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013;36(4):1033-1046. DOI: 10.2337/dc12-2625

[25] Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenatal Diagnosis. 2011;31(1):66-74. DOI: 10.1002/pd.2660

[26] Cuschieri S, Mamo J. Getting to grips with the obesity epidemic in Europe. SAGE Open Medicine. 2016;4:2050312116670406. DOI: 10.1177/2050312116670406

[27] Teh WT, Teede HJ, Paul E, Harrison CL, Wallace EM, Allan C. Risk factors for gestational diabetes mellitus: Implications for the application of screening guidelines. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011;51(1):26-30. DOI: 10.1111/j.1479-828X.2011.01292.x

[28] Surkan PJ, Hsieh CC, Johansson AL, Dickman PW, Cnattingius S. Reasons for increasing trends in large for gestational age births. Obstetrics and Gynecology. 2004;104(4):720-726. DOI: 10.1097/01.AOG.0000141442.59573.cd

[29] Lapolla A, Bonomo M, Dalfrà MG. Pre-pregnancy BMI influences maternal and fetal outcomes in women with isolated gestational hyperglycaemia: A multicentre study. Diabetes and Metabolism. 2010;36(4):265-270. DOI: 10.1016/j.diabet.2010.01.008

[30] Pham MT, Brubaker K, Pruett K, Caughey AB. Risk of childhood obesity in the toddler offspring of mothers with gestational diabetes. Obstetrics and Gynecology. 2013;121(5):976-982. DOI: 10.1097/AOG.0b013e31828bf70d
[31] Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small-and large-for-gestational-age infants. The Journal of Maternal-Fetal and Neonatal Medicine. 2015; 28(14):1679-1686. DOI: 10.3109/14767058.2014.964675

[32] Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: A systematic review and meta-analysis. Journal of the American Medical Association. 2014; 311(15):1536-1546. DOI: 10.1001/jama.2014.2269

[33] Wei B, Yeung E, Tobias DK, Hu FB, Vaag AA, Chavarro JE, et al. Long-term risk of type 2 diabetes mellitus in relation to BMI and weight change among women with a history of gestational diabetes mellitus: A prospective cohort study. Diabetologia. 2015; 58(6):1212-1219. DOI: 10.1007/s00125-015-3537-4

[34] Will JC, Williamson DF, Ford ES, Calle EE, Thun MJ. Intentional weight loss and 13-year diabetes incidence in overweight adults. American Journal of Public Health. 2002; 92(8):1245-1248

[35] Inter Act Consortium, Langenberg C, Sharp SJ, Schulze MB, Rolandsson O, Overvad K, et al. Long-term risk of incident type 2 diabetes and measures of overall and regional obesity: The EPIC-InterAct case-cohort study. PLoSMed. 2012; 9(6):e1001230. DOI: 10.1371/journal.pmed.1001230

[36] Ratner RE. Prevention of type 2 diabetes in women with previous gestational diabetes. Diabetes Care. 2007; 30(Suppl 2):S242-S245. DOI: 10.2337/dc07-s223

[37] Haslam DW, James WP. Obesity. Lancet. 2005; 366:1197-1209. DOI: 10.1016/S0140-6736(05)67483-1

[38] Eknoyan G. Adolphe Quetelet (1796-1874)-the average man and indices of obesity. Nephrology, Dialysis, Transplantation. 2008; 23(1):47-51. DOI: 10.1093/ndt/gfm517

[39] Garrow JS. Treat Obesity Seriously—A Clinical Manual. Chichester: Churchill Livingstone; 1981. p. 260. ISBN-13: 978-0443023064

[40] McIntyre HD, Chang AM, Callaway LK, Cowley DM, Dyer AR, Radaelli T, et al. Hormonal and metabolic factors associated with variations in insulin sensitivity in human pregnancy. Diabetes Care. 2010; 33(2):356-360. DOI: 10.2337/dc09-1196

[41] Retnakaran R, Qi Y, Sermer M, Connelly PW, Zinman B, Hanley AJ. Pre-gravid physical activity and reduced risk of glucose intolerance in pregnancy: The role of insulin sensitivity. Clinical Endocrinology. 2009; 70(4):615-622. DOI: 10.1111/j.1365-2265.2008.03393.x

[42] Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, et al. Prepregnancy BMI and the risk of gestational diabetes: A systematic review of the literature with meta-analysis. Obesity Reviews. 2009; 10(2):194-203. DOI: 10.1111/j.1467-789X.2008.00541.x
[43] Leddy MA, Power ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. Reviews in Obstetrics and Gynecology. 2008;1(4):170-178

[44] Gunderson EP. Childbearing and obesity in women: Weight before, during, and after pregnancy. Obstetrics and Gynecology Clinics of North America. 2009;36(2):317-332. DOI: 10.1016/j.ogc.2009.04.001

[45] Chu SY, Callaghan WM, Bish CL, D'Angelo D. Gestational weight gain by body mass index among US women delivering live births, 2004-2005: Fueling future obesity. American Journal of Obstetrics and Gynecology. 2009;200(3):271.e1-271.e7. DOI: 10.1016/j.ajog.2008.09.879

[46] Mamun AA, O’Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: Evidence from a birth cohort study. Circulation. 2009;119(13):1720-1727. DOI: 10.1161/CIRCULATIONAHA.108.813436

[47] Nohr EA, Vaeth M, Baker JL, Sørensen TA, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. The American Journal of Clinical Nutrition. 2008;87(6):1750-1759. DOI: 10.1093/ajcn/87.6.1750

[48] Abenhaim HA, Kinch RA, Morin L, Benjamin A, Usher R. Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes. Archives of Gynecology and Obstetrics. 2007;275(1):39-43. DOI: 10.1007/s00404-006-0219-y

[49] Jensen DM, Damm P, Sorensen B, Mølsted-Pedersen L, Westergaard JG, Ovesen P, et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. American Journal of Obstetrics and Gynecology. 2003;189(1):239-244. DOI: 10.1067/mob.2003.441

[50] Frederick IO, Williams MA, Sales AE, Martin DP, Killien M. Pre-pregnancy body mass index, gestational weight gain and other maternal characteristics in relation to infant birth weight. Maternal and Child Health Journal. 2008;12(5):557-567. DOI: 10.1007/s10995-007-0276-2

[51] Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. ATLANTIC-DIP: Excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism. 2014;99(1):212-219. DOI: 10.1210/jc.2013-2684

[52] Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain and gestational diabetes mellitus with large-for-gestational-age births. Obstetrics and Gynecology. 2014;123(4):737-744. DOI: 10.1097/AOG.0000000000000177

[53] Alberico S, Montico M, Barresi V, Monasta L, Businelli C, Soini V, et al. The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: Results from a prospective multicentre study. BMC Pregnancy and Childbirth. 2014;14:23. DOI: 10.1186/1471-2393-14-23
[54] Han YS, Ha EH, Park HS, Kim YJ, Lee SS. Relationships between pregnancy outcomes, biochemical markers and pre-pregnancy body mass index. International Journal of Obesity. 2011;35(4):570-577. DOI: 10.1038/ijo.2010.162

[55] Cogswell ME, Serdula MK, Hungerford DW, Yip R. Gestational weight-gain among average-weight and overweight women—What is excessive? The American Journal of Obstetrics and Gynecology. 1995;172(2 Pt1):705-712. DOI: 10.1016/0002-9378(95)90598-7

[56] Larsen CE, Serdula MK, Sullivan KM. Macrosomia: Influence of maternal overweight among a low-income population. The American Journal of Obstetrics and Gynecology. 1990;162(2):490-494. DOI: 10.1016/0002-9378(90)90418-7

[57] Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: A study of 287 213 pregnancies in London. International Journal of Obesity and Related Metabolic Disorders. 2001;25:1175-1182. DOI: 10.1016/S0002-9378(90)90418-7

[58] Johnson JW, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. The American Journal of Obstetrics and Gynecology. 1992;167(2):353-370. DOI: 10.1016/S0002-9378(11)91414-8

[59] Kabali C, Werler MM. Pre-pregnant body mass index, weight gain and the risk of delivering large babies among non-diabetic mothers. International Journal of Gynaecology and Obstetrics. 2007;97(2):100-104. DOI: 10.1016/j.ijgo.2007.02.001

[60] Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: A systematic review. Diabetes Care. 2002;25(10):1862-1868. DOI: 10.2337/diacare.25.10.1862

[61] Liu H, Zhang C, Zhang S, Wang L, Leng J, Liu D, et al. Prepregnancy body mass index and weight change on postpartum diabetes risk among gestational diabetes women. Obesity. 2014;22(6):1560-1567. DOI: 10.1002/oby.20722

[62] Nehring I, Schmoll S, Beyerlein A, Hauner H, von Kries R. Gestational weight gain and long-term postpartum weight retention: A meta-analysis. The American Journal of Clinical Nutrition. 2011;94(5):1225-1231. DOI: 10.3945/ajcn.111.015289

[63] Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC. Combining risk estimates from observational studies with different exposure cutpoints: A meta-analysis on body mass index and diabetes type 2. American Journal of Epidemiology. 2006;163(11):1042-1052. DOI: 10.1093/aje/kwj141

[64] Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB. Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. American Journal of Epidemiology. 2004;159(12):1150-1159. DOI: 10.1093/aje/kwh167

[65] Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes. 1985;34(10):1055-1058. DOI: 10.2337/diab.34.10.1055
[66] Hartz AJ, Rupley DC Jr, Kalkhoff RD, Rimm AA. Relationship of obesity to diabetes: Influence of obesity level and body fat distribution. American Journal of Preventive Medicine. 1983;12(2):351-357. DOI: 10.1016/0091-7435(83)90244-X

[67] Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: A meta analysis among different ethnic groups. International Journal of Obesity and Related Metabolic Disorders. 1998;22(12):1164-1171. DOI: 10.1038/sj.ijo.0800741

[68] Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: Results of the multicultural community health assessment trial (M-CHAT). The American Journal of Clinical Nutrition. 2007;86(2):353-359. DOI: 10.1093/ajcn/86.2.353

[69] Stevens J, Couper D, Pankow J, Folsom AR, Duncan BB, Nieto FJ, et al. Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. Obesity Research. 2001;9(11):696-705. DOI: 10.1038/oby.2001.94

[70] Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? European Journal of Clinical Nutrition. 2010;64(1):30-34. DOI: 10.1038/ejcn.2009.93

[71] Bolognani CV, de Sousa Moreira Reis LB, de Souza SS, Dias A, Rudge MV, de Mattos Paranhos Calderon I. Waist circumference in predicting gestational diabetes mellitus. The Journal of Maternal-Fetal and Neonatal Medicine. 2014;27(9):943-948. DOI: 10.3109/14767058.2013.847081

[72] Catalano PM. Editorial: Obesity and pregnancy-the propagation of a viscous cycle? The Journal of Clinical Endocrinology and Metabolism. 2003;88(8):3505-3506. DOI: 10.1210/jc.2003-031046

[73] Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. The Journal of Clinical Endocrinology and Metabolism. 2008;93(11):S64-S73. DOI: 10.1210/jc.2008-1613

[74] Coppack SW. Adipose tissue changes in obesity. Biochemical Society Transactions. 2005;33(Pt5):1049-1052. DOI: 10.1042/BST20051049

[75] Elliott JA. The effect of pregnancy on the control of lipolysis in fat cells isolated from human adipose tissue. European Journal of Clinical Investigation. 1975;5(2):159-163. DOI: 10.1111/j.1365-2362.1975.tb02282.x

[76] Fain JN, Tagele BM, Cheema P, Madan AK, Tichansky DS. Release of 12 adipokines by adipose tissue, nonfat cells, and fat cells from obese women. Obesity. (Silver Spring). 2010;18(5):890-896. DOI: 10.1038/oby.2009.335

[77] Pantham P, Irving LM, Aye H, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015;36(7):709-715. DOI: 10.1016/j.placenta.2015.04.006
[78] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annual Review of Immunology. 2011;29:415-445. DOI: 10.1146/annurev-immunol-031210-101322

[79] Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: Cells, cytokines, and chemokines. ISRN Inflammation. 2013;22:139239. DOI: 10.1155/2013/139239

[80] Jayabalan N, Nair S, Nuzhat Z, Rice GE, Zuñiga FA, Sobrevia L, et al. Talk between adipose tissue and placenta in obese and gestational diabetes mellitus pregnancies via exosomes. Front Endocrinol (Lausanne). 2017;8:239. DOI: 10.3389/fendo.2017.00239

[81] Ryan EA, Enns L. Role of gestational hormones in the induction of insulin resistance. The Journal of Clinical Endocrinology and Metabolism. 1988;67:341-347. DOI: 10.1210/jcem-67-2-341

[82] Ahmed SA, Shalayel MH. Role of cortisol in the deterioration of glucose tolerance in Sudanese pregnant women. East African Medical Journal. 1999;76(8):465-467

[83] Lappas M, Rice GE. Transcriptional regulation of the processes of human labour and delivery. Placenta. 2009;30(Suppl A):S90-S95. DOI: 10.1016/j.placenta.2008.10.005

[84] Ingvorsen C, Brix S, Ozanne SE, Hellgren LI. The effect of maternal inflammation on foetal programming of metabolic disease. Acta Physiologica (Oxford, England). 2015;214(4):440-449. DOI: 10.1111/apha.12533

[85] Martin AM, Berger H, Nisenbaum R, Lausman AY, Macgarvie S, Crerar C, et al. Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. Diabetes Care. 2009;32(7):1308-1310. DOI: 10.2337/dc09-0290

[86] Cseh K, Baranyi E, Melczer Z, Kaszas E, Palik E, Winkler G. Plasma adiponectin and pregnancy-induced insulin resistance. Diabetes Care. 2004;27(1):274-275. DOI: 10.2337/diabetic.27.1.274

[87] Ogawa R, Tanaka C, Sato M, Nagasaki H, Sugimura K, Okumura K, et al. Adipocyte-derived microvesicles contain RNA that is transported into macrophages and might be secreted into blood circulation. Biochemical and Biophysical Research Communications. 2010;398(4):723-729. DOI: 10.1016/j.bbrc.2010.07.008

[88] Brink HS, van der Lely AJ, van der Linden J. The potential role of biomarkers in predicting gestational diabetes. Endocrine Connections. 2016;5(5):R26-R34. DOI: 10.1530/EC-16-0033

[89] Xu J, Zhao YH, Chen YP, Yuan XL, Wang J, Zhu H, et al. Maternal circulating concentrations of tumor necrosis factor-alpha, leptin, and adiponectin in gestational diabetes mellitus: A systematic review and meta-analysis. Scientific World Journal. 2014;2014:926932. DOI: 10.1155/2014/926932

[90] Trayhurn P, Wood IS. Adipokines: Inflammation and the pleiotropic role of white adipose tissue. The British Journal of Nutrition. 2004;92(3):347-355. DOI: 10.1079/BJN20041213
[91] Guzik TJ, Mangalat D, Korbut R. Adipocytokines - novel link between inflammation and vascular function? Journal of Physiology and Pharmacology. 2006;57(4):505-528

[92] Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. The Journal of Clinical Investigation. 2011;121(6):2094-2101. DOI: 10.1172/JCI45887

[93] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature Reviews. Immunology. 2011;11(2):85-97. DOI: 10.1038/nri2921

[94] Xu A, Wang Y, Lam KS, Vanhoutte PM. Vascular actions of adipokines molecular mechanisms and therapeutic implications. Advances in Pharmacology. 2010;60:229-255. DOI: 10.1016/B978-0-12-385061-4.00008-8

[95] Catalano PM. Obesity, insulin resistance, and pregnancy outcome. Reproduction. 2010;140(3):365-371. DOI: 10.1530/REP-10-0088

[96] Briana DD, Malamitsi-Puchner A. Reviews: Adipocytokines in normal and complicated pregnancies. Reproductive Sciences. 2009;16(10):921-937. DOI: 10.1177/1933719109336614

[97] Christian LM, Porter K. Longitudinal changes in serum proinflammatory markers across pregnancy and postpartum: Effects of maternal body mass index. Cytokine. 2014;70(2):134-140. DOI: 10.1016/j.cyto.2014.06.018

[98] Honnorat D, Disse E, Millot E, Mathiote E, Claret M, Charrie A, et al. Are third-trimester adipokines associated with higher metabolic risk among women with gestational diabetes? Diabetes & Metabolism. 2015;41(5):393-400. DOI: 10.1016/j.diabet.2015.03.003

[99] Moreli JB, Corrêa-Silva S, Damasceno DC, Sinzato YK, Lorenzon-Ojea AR, Borbely AU, et al. Changes in the TNF-alpha/IL-10 ratio in hyperglycemia-associated pregnancies. Diabetes Research and Clinical Practice. 2015;107(3):362-369. DOI: 10.1016/j.diabres.2015.01.005

[100] Friis CM, Paasche Roland MC, Godang K, Ueland T, Tanbo T, Bollerslev J, et al. Adiposity-related inflammation: Effects of pregnancy. Obesity (Silver Spring). 2013;21(1):E124-E130. DOI: 10.1002/oby.20120

[101] Kuzmicki M, Telejko B, Szamatowicz J, Zonenberg A, Nikolajuk A, Kretowski A, et al. High resistin and interleukin-6 levels are associated with gestational diabetes mellitus. Gynecological Endocrinology. 2009;25(4):258-263. DOI: 10.1080/09513590802653825

[102] Morisset AS, Dubéé MC, Côté JA, Robitaille J, Weisnagel SJ, Tchernof A. Circulating interleukin-6 concentrations during and after gestational diabetes mellitus. Acta Obstetricia et Gynecologica Scandinavica. 2011;90(5):524-530. DOI: 10.1111/j.1600-0412.2011.01094.x

[103] Kuzmicki M, Telejko B, Lipinska D, Piszka J, Wilk J, Wawrusiewicz-Kuryłonek N, et al. The IL-6/IL-6R/ sgp130 system and Th17 associated cytokines in patients with gestational diabetes. Endokrynologia Polska. 2014;65(3):169-175. DOI: 10.5603/EP.2014.0023

[104] Kirwan JP, Hauguel-De Mouzon S, Lepercq J, Challier JC, Huston-Presley L, Friedman JE, et al. TNF-α is a predictor of insulin resistance in human pregnancy. Diabetes. 2002;51(7):2207-2213. DOI: 10.2337/diabetes.51.7.2207
[105] Lepercq J, Cauzac M, Lahlou N, Timsit J, Girard J, Auwerx J, et al. Overexpression of placental leptin in diabetic pregnancy: A critical role for insulin. Diabetes. 1998;47(5):847-850. DOI: 10.2337/diabetes.47.5.847

[106] Lappas M, Permezel M, Rice GE. Release of proinflammatory cytokines and 8-isoprostane from placenta, adipose tissue, and skeletal muscle from normal pregnant women and women with gestational diabetes mellitus. Journal of Clinical Endocrinology and Metabolism. 2004;89(11):5627-5633. DOI: 10.1210/jc.2003-032097

[107] Bi S, Gavrilova O, Gong DW, Mason MM, Reitman M. Identification of a placental enhancer for the human leptin gene. Journal of Biological Chemistry. 1997;272(48):30583-30588. DOI: 10.1074/jbc.272.48.30583

[108] Gao XL, Yang HX, Zhao Y. Variations of tumor necrosis factor-alpha, leptin and adiponectin in mid-trimester of gestational diabetes mellitus. The Chinese Medical Journal. 2008;121:701-705

[109] Soheilykhhah S, Mojibian M, Rahimi-Saghand S, Rashidi M, Hadinedoushan H. Maternal serum leptin concentration in gestational diabetes. Taiwanese Journal of Obstetrics and Gynecology. 2011;50(2):149-153. DOI: 10.1016/j.tjog.2011.01.034

[110] Mokhtari M, Hashemi M, Yaghmaei M, Naderi M, Shikhzadeh A, Ghavami S. Evaluation of the serum leptin in normal pregnancy and gestational diabetes mellitus in Zahedan, Southeast Iran. Archives of Gynecology and Obstetrics. 2011;284(3):539-542. DOI: 10.1007/s00404-010-1681-0

[111] Chen HL, Yang YP, Hu XL, Yelavarthi KK, Fishback JL, Hunt JS. Tumor necrosis factor alpha mRNA and protein are present in human placental and uterine cells at early and late stages of gestation. The American Journal of Pathology. 1991;139(2):327-335

[112] Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, et al. Nonadipose tissue production of leptin: Leptin as a novel placenta- derived hormone in humans. Nature Medicine. 1997;3(9):1029-1033

[113] Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cellular Immunology. 1999;194(1):6-11. DOI: 10.1006/cimm.1999.1490

[114] Kiguchi N, Maeda T, Kobayashi Y, Fukazawa Y, Kishioka S. Leptin enhances CC-chemokine ligand expression in cultured murine macrophage. Biochemical and Biophysical Research Communications. 2009;384(3):311-315. DOI: 10.1016/j.bbrc.2009.04.121

[115] Fasshauer M, Klein J, Neumann S, Eszlinger M, Paschke R. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochemical and Biophysical Research Communications. 2002;290(3):1084-1089. DOI: 10.1006.bbrc.2001.6307

[116] Cseh K, Baranyi E, Melczer Z, Csákány GM, Speer G, Kovács M, et al. The pathophysiological influence of leptin and the tumor necrosis factor system on maternal insulin resistance: Negative correlation with anthropometric parameters of neonates in
gestational diabetes. Gynecological Endocrinology. 2002;16(6):453-460. DOI: 10.1080/gye.16.6.453.460

[117] Kinalski M, Telejko B, Kuźmicki M, Kretowski A, Kinalska I. Tumor necrosis factor alpha system and plasma adiponectin concentration in women with gestational diabetes. Hormone and Metabolic Research. 2005;37(7):450-454. DOI: 10.1055/s-2005-870238

[118] Soheilykhah S, Mohammadi M, Mojibian M, Rahimi-Saghand S, Rashidi M, Hadinedoushan H, et al. Maternal serum adiponectin concentration in gestational diabetes. Gynecological Endocrinology. 2009;25(9):593-596. DOI: 10.1080/09513590902972109

[119] Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. The Journal of Clinical Investigation. 2007;117(1):175-184. DOI: 10.1172/JCI29881

[120] Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. The Journal of Clinical Investigation. 2003;112(12):1821-1830. DOI: 10.1172/JCI200319451

[121] Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nature Reviews. Immunology. 2011;11(2):98-107. DOI: 10.1038/nri2925

[122] Hotamisligil GS. Inflammatory pathways and insulin action. International Journal of Obesity and Related Metabolic Disorders. 2003;27(Suppl. 3):S53-S55. DOI: 10.1038/sj.ijo.0802502

[123] Bozzini C, Girelli D, Olivieri O, Martinelli N, Bassi A, De Matteis G, et al. Prevalence of body iron excess in the metabolic syndrome. Diabetes Care. 2005;28:2061-2063. DOI: 10.2337/diacare.28.8.2061

[124] Chang JS, Lin SM, Huang TC, Chao JC, Chen YC, Pan WH, et al. Serum ferritin and risk of the metabolic syndrome: A population-based study. Asia Pacific Journal of Clinical Nutrition. 2013;22(3):400-407. DOI: 10.6133/apjcn.2013.22.3.07

[125] Hubler MJ, Peterson KR, Hasty AH. Iron homeostasis: A new job for macrophages in adipose tissue? Trends in Endocrinology and Metabolism. 2015;26(2):101-109. DOI: 10.1016/j.tem.2014.12.005

[126] Chen YC, Wu YT, Wei YH. Depletion of mitoferrins leads to mitochondrial dysfunction and impairment of adipogenic differentiation in 3T3-L1 preadipocytes. Free Radical Research. 2015;49(11):1285-1295. DOI: 10.3109/10715762.2015.1067695

[127] Moreno-Navarrete JM, Ortega F, Moreno M, Ricart W, Fernandez-Real JM. Fine-tuned iron availability is essential to achieve optimal adipocyte differentiation and mitochondrial biogenesis. Diabetologia. 2014;57(9):1957-1967. DOI: 10.1007/s00125-014-3298-5

[128] Wlazlo N, van Greevenbroek MM, Ferreira I, Jansen EH, Feskens EJ, van der Kallen CJ, et al. Iron metabolism is associated with Adipocyte insulin resistance and plasma Adiponectin. Diabetes Care. 2013;36(2):309-315. DOI: 10.2337/dc12-0505
[129] Gabrielsen JS, Gao Y, Simcox JA, Huang J, Thorup D, Jones D, et al. Adipocyte iron regulates adiponectin and insulin sensitivity. The Journal of Clinical Investigation. 2012; 122(10):3529-3540. DOI: 10.1172/JCI44421

[130] Retnakaran R, Hanley AJ, Raif N, Hirning CR, Connelly PW, Sermer M, et al. Adiponectin and beta cell dysfunction in gestational diabetes: Pathophysiological implications. Diabetologia. 2005;48(5):993-1001

[131] Shukla P, Xiao X, Mishra R. Iron biomarker in gestational diabetes pathogenesis. Journal of Molecular Biomarkers and Diagnosis. 2014;5:205. DOI: 10.4172/2155-9929.1000205

[132] Kambalia AZ, Collins CE, Roberts CL, Morris JM, Powell KL, Tasevski V, et al. Iron deficiency in early pregnancy using serum ferritin and soluble transferrin receptor concentrations are associated with pregnancy and birth outcomes. European Journal of Clinical Nutrition. 2016;70(3):358-363. DOI: 10.1038/ejcn.2015.157

[133] Chiabrando D, Vinchi F, Fiorito V, Mercurio S, Tolosano E. Heme in pathophysiology: A matter of scavenging, metabolism and trafficking across cell membranes. Frontiers in Pharmacology. 2014;5:61. DOI: 10.3389/fphar.2014.00061

[134] Balla G, Vercellotti GM, Muller-Eberhard U, Eaton J, Jacob HS. Exposure of endothelial cells to free heme potentiates damage mediated by granulocytes and toxic oxygen species. Laboratory Investigation. 1991;64(5):648-655

[135] Zhao Z, Li S, Liu G, Yan F, Ma X, Huang Z, et al. Body iron stores and heme-iron intake in relation to risk of type 2 diabetes: A systematic review and meta-analysis. PLoS One. 2012;7(7):e41641. DOI: 10.1371/journal.pone.0041641

[136] Gao Y, Li Z, Gabrielsen JS, Simcox JA, Lee S-h, Jones D, et al. Adipocyte iron regulates leptin and food intake. The Journal of Clinical Investigation. 2015;125(9):3681-3691. DOI: 10.1172/JCI81860

[137] Choobineh H, Dehghani SJ, Alizadeh S, Ghabadi DV, Saiepour N, Meshkani R, et al. Evaluation of Leptin levels in major beta-Thalassemic patients. International Journal of Hematology-Oncology and Stem Cell Research. 2009;3(4):1-4

[138] Galanello R, Origa R. Beta-thalassemia. Orphanet Journal of Rare Diseases. 2010;5:11. DOI: 10.1186/1750-1172-5-11

[139] Chung B, Matak P, McKie AT, Sharp P. Leptin increases the expression of the iron regulatory hormone Hepcidin in HuH7 human Hepatoma cells. The Journal of Nutrition. 2007;137:2366-2370. DOI: 10.1093/jn/137.11.2366

[140] Andrews N. Hungry irony. The Journal of Clinical Investigation. 2015;125(9):3422-3423. DOI: 10.1172/JCI83193

[141] Shibata M, Suzuki A, Sekiya T, Sekiguchi S, Asano S, Udagawa Y, et al. High prevalence of hypovitaminosis D in pregnant Japanese women with threatened premature delivery. Journal of Bone and Mineral Metabolism. 2011;29(5):615-620. DOI: 10.1007/s00774-011-0264-x
[142] Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. The American Journal of Clinical Nutrition. 2004;79(5):820-825. DOI: 10.1093/ajcn/79.5.820

[143] Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science. 1980;209(4458):823-825. DOI: 10.1126/science.6250216

[144] Vaidya A, Williams JS. Vitamin D and insulin sensitivity: Can gene association and pharmacogenetic studies of the vitamin D receptor provide clarity? Metabolism, Clinical and Experimental. 2012;61(6):759-761. DOI: 10.1016/j.metabol.2011.12.009

[145] Draznin B, Sussman KE, Eckel RH, Kao M, Yost T, Sherman NA. Possible role of cytosolic free calcium concentrations in mediating insulin resistance of obesity and hyperinsulinemia. Journal of Clinical Investigation. 1988;82(6):1848-1852. DOI: 10.1172/JCI113801

[146] Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. The Journal of Clinical Endocrinology and Metabolism. 2007;92(6):2017-2029. DOI: 10.1210/jc.2007-0298

[147] Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes/Metabolism Research and Reviews. 2008;24(1):27-32. DOI: 10.1002/dmrr.737 16

[148] Kramer CK, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, Zinman B, et al. Vitamin D and parathyroid hormone status in pregnancy: Effect on insulin sensitivity, beta cell function, and gestational diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism. 2014;99(12):4506-4513. DOI: 10.1210/jc.2014-2341

[149] Salekzamani S, Neyestani TR, Alavi-Majd H, Houshiarrad A, Kalayi A, Shariatzadeh N, et al. Is vitamin D status a determining factor for metabolic syndrome? A case-control study. Diabetes, Metabolic Syndrome and Obesity. 2011;4:205-212. DOI: 10.2147/DMSO.S21061

[150] Park J, Gong J, Hong H, Ha C, Kang H. Serum vitamin D status and its relations to body fatness and fitness and risk factors in young adults. Journal of Exercise Nutrition & Biochemistry. 2013;17(4):143-150. DOI: 10.5717/jenb.2013.17.4.143

[151] Daniel D, Hardigan P, Bray N, Penzell D, Mint SC. The incidence of vitamin D deficiency in the obese: A retrospective chart review. Journal of Community Hospital Internal Medicine Perspectives. 2015;5(1):26069. DOI: 10.3402/jchimp.v5.26069

[152] Haidari F, Jalali MT, Shahbazian N, Haghighizadeh MH, Azadegan E. Comparison of serum levels of vitamin D and inflammatory markers between women with gestational diabetes mellitus and healthy pregnant control. Journal of Family and Reproductive Health. 2016;10(1):1-8

[153] Kim SY, Dietz P, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993-2003. Obesity. 2007;15(4):986-993. DOI: 10.1038/oby.2007.621

[154] Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070-2076. DOI: 10.2337/dc06-2559a
[155] Ramachenderan J, Bradford J, McLean M. Maternal obesity and pregnancy complications: A review. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2008;48(3):228-235. DOI: 10.1111/j.1479-828X.2008.00860.x

[156] Dennedy MC, Dunne F. The maternal and fetal impacts of obesity and gestational diabetes on pregnancy outcome. Best Practice and Research. 2010;24(4):573-589. DOI: 10.1016/j.beem.2010.06.001

[157] McTigue KM, Hess R, Ziouras J. Obesity in older adults: A systematic review of the evidence for diagnosis and treatment. Obesity (Silver Spring). 2006;14(9):1485-1497. DOI: 10.1038/oby.2006.171

[158] Rasmussen KM, Yaktine AL, editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Chichester: The National Academies Press; 2009. 868 p. DOI: 10.17226/12584

[159] Liu A, Byrne NM, Kagawa M, Ma G, Poh BK, Ismail MN, et al. Ethnic differences in the relationship between body mass index and percentage body fat among Asian children from different backgrounds. British Journal of Nutrition. 2011;106(9):1390-1397. DOI: 10.1017/S0007114511001681

[160] Hruschka DJ, Hadley C. How much do universal anthropometric standards bias the global monitoring of obesity and undernutrition? Obesity Reviews. 2016;17(11):1030-1039. DOI: 10.1111/obr.12449

[161] Balani J, Hyer SL, Shehata H, Mohareb F. Visceral fat mass as a novel risk factor for predicting gestational diabetes in obese pregnant women. Obstetric Medicine. 2018;0(0):1-5. DOI: 10.1177/1753495X17754149

[162] Balani J, Hyer S, Johnson A. The importance of visceral fat mass in obese pregnant women and relation with pregnancy outcomes. Obstetric Medicine. 2014;7(1):22. DOI: 10.1177/1753495X13495192

[163] De Souza LR, Berger H, Retnakaran R, Maguire JL, Nathens AB, Connelly PW, et al. Firsttrimester maternal abdominal adiposity predicts dysglycemia and gestational diabetes mellitus in midpregnancy. Diabetes Care. 2016;39(1):61-64. DOI: 10.2337/dc15-2027

[164] Han TS, van Leer EM, Seidell JC, Lean ME. Waist circumference action levels in the identification of cardiovascular risk factors: Prevalence study in a random sample. British Medical Journal. 1995;311:1401-1405. DOI: 10.1136/bmj.311.7017.1401

[165] Basrao SK, Mele L, Myatt L, Roberts JM, Hauth JC, Leveno KJ, et al. Relationship of early pregnancy waist to hip ratio versus body mass index with gestational diabetes and insulin resistance. American Journal of Perinatology. 2016;33(1):114-121. DOI: 10.1055/s-0035-1562928

[166] Heude B, Thiebaugeorges O, Goua V, Forhan A, Kaminski M, Foliguet B, et al. Pre-pregnancy body mass index and weight gain during pregnancy: Relations with gestational diabetes and hypertension, and birth outcomes. Maternal and Child Health Journal. 2012;16(2):355-363. DOI: 10.1007/s10995-011-0741-9
[167] Genova MP, Todorova–Ananieva K, Tzatchev K. Impact of body mass index on insulin sensitive/resistance in pregnant women with and without gestational diabetes mellitus. Acta Medica Bulgarica. 2013;XL(2):60-67

[168] Rooney B, Schauberger C. Excess pregnancy weight gain and long-term obesity: One decade later. Obstetrics and Gynecology. 2002;100(2):245-252. DOI: 10.1016/S0029-7844(02)02125-7

[169] Ornoy A. Prenatal origin of obesity and their complications: Gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia. Reproductive Toxicology. 2011;32(2):205-212. DOI: 10.1016/j.reprotox.2011.05.002

[170] Hinkle SN, Sharma AJ, Swan DW, Schieve LA, Ramakrishnan U, Stein AD. Mint: Excess gestational weight gain is associated with child adiposity among mothers with normal and overweight prepregnancy weight status. The Journal of Nutrition. 2012;142(10):1851-1858. DOI: 10.3945/jn.112.161158

[171] Raatikainen K, Heiskanen N, Heinonen S. Transition from overweight to obesity worsens pregnancy outcome in a BMI-dependent manner. Obesity (Silver Spring). 2006;14(1):165-171. DOI: 10.1038/oby.2006.20

[172] Kautzky-Willer A, Djelmis J, Desoye G, Ivanisevic M. Endocrine changes in diabetic pregnancy. Diabetology of pregnancy. In: Djelmis J, Desoye G, Ivanisevic M, editors. Diabetology of Pregnancy. Chichester: Karger; 2005. pp. 18-33. DOI: 10.1159/isbn.978-3-318-01214-9

[173] Xiang AH, Peters RK, Trigo E, Kjos SL, Lee WP, Buchanan TA. Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes. Diabetes. 1999;48(4):848-854. DOI: 10.2337/diabetes.48.4.848

[174] Davis JR. Prolactin and related peptides in pregnancy. Bailliere’s Clinical Endocrinology and Metabolism. 1990;4:273-285

[175] Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368(9548):1681-1688. DOI: 10.1016/S0140-6736(06)69703-1

[176] Mørkrid K, Jenum AK, Sletner L, Vårdal MH, Waage CW, Nakstad B, et al. Failure to increase insulin secretory capacity during pregnancy-induced insulin resistance is associated with ethnicity and gestational diabetes. European Journal of Endocrinology. 2012;167(4):579-588. DOI: 10.1530/EJE-12-0452

[177] Sokup A, Ruszkowska-Ciastek A, Góralczyk K, Walentowicz M, Szymański M, Roś M. Insulin resistance as estimated by the homeostatic method at diagnosis of gestational diabetes: Estimation of disease severity and therapeutic needs in a population-based study. BMC Endocrine Disorders. 2013;13:21. DOI: 10.1186/1472-6823-13-21

[178] Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: An approach for developing guidelines based on body mass index. The American Journal of Clinical Nutrition. 2000;72(3):694-701. DOI: 10.1093/ajcn/72.3.694
[179] Retnakaran R, Shen S, Hanley AJ, Vuksan V, Hamilton JK, Zinman B. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. Obesity (Silver Spring). 2008;16(8):1901-1907. DOI: 10.1038/oby.2008.307

[180] Al-Badri MR, Zantou MS, Azar ST. The role of adipokines in gestational diabetes mellitus. Therapeutic advances in endocrinology and metabolism. 2015;6(3):103-108. DOI: 10.1177/2042018815577039

[181] Meier JJ, Gallwitz B, Askenas M, Vollmer K, Deacon CF, Holst JJ, et al. Secretion of incretin hormones and the insulinotropic effect of gastric inhibitory polypeptide in women with a history of gestational diabetes. Diabetologia. 2005;48(9):1872-1881. DOI: 10.1007/s00125-005-1863-7

[182] Cypryk K, Vilsboll T, Nadel I, Smyczynska J, Holst JJ, Lewinski A. Normal secretion of the incretin hormones glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 during gestational diabetes mellitus. Gynecological Endocrinology. 2007;23(1):58-62. DOI: 10.1080/09513590601137004

[183] Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: The diabetes in early pregnancy study. Metabolism. 1998;47(9):1140-1144. DOI: 10.1016/S0026-0495(98)90290-6

[184] Sivan E, Chen X, Homko CJ, Reece EA, Boden G. Longitudinal study of carbohydrate metabolism in healthy obese pregnant women. Diabetes Care. 1997;20(9):1470-1475. DOI: 10.2337/diacare.20.9.1470

[185] Nelson SM, Matthews P, Poston L. Maternal metabolism and obesity: Modifiable determinants of pregnancy outcome. Human Reproduction Update. 2010;16(3):255-275. DOI: 10.1093/humupd/dmp050

[186] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-419. DOI: 10.1007/BF00280883

[187] Cobelli C, Toffolo GM, Dalla Man C, Campioni M, Denti P, Caumo A, et al. Assessment of β-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. American Journal of Physiology. Endocrinology and Metabolism. 2007;293(1):E1-E15. DOI: 10.1152/ajpendo.00421.2006

[188] Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-1495. DOI: 10.2337/diacare.27.6.1487

[189] Radziuk J. Insulin sensitivity and its measurement: Structural commonalities among the methods. The Journal of Clinical Endocrinology and Metabolism. 2000;85(12):4426-4433. DOI: 10.1210/jcem.85.12.7025

[190] Cacho J, Sevillano J, de Castro J, Herrera E, Ramos MP. Validation of simple indexes to assess insulin sensitivity during pregnancy in Wistar and Sprague-Dawley rats. American Journal of Physiology. Endocrinology and Metabolism. 2008;295(5):1269-1276. DOI: 10.1152/ajpendo.90207
[191] Kauffman RP, Castracane VD, Peghee D, Baker TE, Van Hook JV. Detection of gestational diabetes mellitus by homeostatic indices of insulin sensitivity: A preliminary study. American Journal of Obstetrics and Gynecology. 2006;194(6):1576-1584. DOI: 10.1016/j.ajog.2006.01.010

[192] Song Y, Manson JE, Tinker L, Howard BV, Kuller LH, Nathan L, et al. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women. Diabetes Care. 2007;30(7):1747-1752. DOI: 10.2337/dc07-0358

[193] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. The American Journal of Physiology. 1979;237(3):E214-E223. DOI: 10.1152/ajpendo.1979.237.3.E214

[194] Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes. 2005;54(7):1914-1925. DOI: 10.2337/diabetes.54.7.1914

[195] Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: Advantages, limitations, and appropriate usage. American Journal of Physiology Endocrinology and Metabolism. 2008;294(1):E15-E26. DOI: 10.1152/ajpendo.00645.2007

[196] Chen H, Sullivan G, Yue LQ, Katz A, Quon MJ. QUICKI is a useful index of insulin sensitivity in subjects with hypertension. American Journal of Physiology. Endocrinology and Metabolism. 2003;284(4):E804-E812. DOI: 10.1152/ajpendo.00330.2002

[197] Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World Journal of Diabetes. 2010;1(2):36-47. DOI: 10.4239/wjd.v1.i2.36

[198] Radaelli T, Farrell KA, Huston-Presley L, Amini SB, Kirwan JP, McIntyre HD, Catalano PM. Estimates of insulin sensitivity using glucose and C-peptide from the hyperglycemia and adverse pregnancy outcome glucose tolerance test. Diabetes Care. 2010;33(3):490-494. DOI: 10.2337/dc09-1463

[199] Vähämiko S, Isolauri E, Pesonen U, Koskinen P, Ekblad U, Laitinen K. Dietary sucrose intake is related to serum leptin concentration in overweight pregnant women. European Journal of Nutrition. 2010;49(2):83-90. DOI: 10.1007/s00394-009-0052-8

[200] Turner RC, Holman RR, Matthews D, Hockaday TD, Peto J. Insulin deficiency and insulin resistance interaction in diabetes: Estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism. 1979;28(11):1086-1096. DOI: 10.1016/0026-0495(79)90146-X

[201] HAPO Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study: Associations with maternal body mass index. BJOG;117(5):575-584. DOI: 10.1111/j.1471-0528.2009.02486

[202] Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: Associations of GDM
and obesity with pregnancy outcomes. Diabetes Care. 2010;35:780-786. DOI: 10.2337/dc11-1790

[203] Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care. 2013;36(1):56-62. DOI: 10.2337/dc12-0741

[204] Stuebe AM, Landon MB, Lai Y, Spong CY, Carpenter MW, Ramin SM, et al. Maternal BMI, glucose tolerance, and adverse pregnancy outcomes. American Journal of Obstetrics and Gynecology. 2012;207(1):62.e1-62.e7. DOI: 10.1016/j.ajog.2012.04.035

[205] Houldsworth A, Williams R, Fisher A, Demaine AG, Millward BA. Proposed relationships between the degree of insulin resistance, serum chromium level/BMI and renal function during pregnancy and the pathogenesis of gestational diabetes mellitus. International Journal of Endocrinology and Metabolism. 2017;3(1):1-8. DOI: 10.16966/2380-548X.132

[206] Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. American Journal of Obstetrics and Gynecology. 1991;165(6 Pt 1):1667-1672. DOI: 10.1016/0002-9378(91)90012-G

[207] Endo S, Maeda K Suto M, Kaji T, Morine M, Kinoshita T, et al. Differences in insulin sensitivity in pregnant women with overweight and gestational diabetes mellitus. Gynecological Endocrinology. 2006;22(6):343-349. DOI: 10.1080/09513590600724836

[208] Kirwan J, Huston-Presley L, Kalhan S, Catalano P. Clinically useful estimates of insulin sensitivity during pregnancy: Validation studies in women with normal glucose tolerance and gestational diabetes mellitus. Diabetes Care. 2001;24(9):1602-1607. DOI: 10.2337/diacare.24.9.1602

[209] Catalano PM, Drago NM, Amini SB. Longitudinal changes in pancreatic beta-cell function and metabolic clearance rate of insulin in pregnant women with normal and abnormal glucose tolerance. Diabetes Care. 1998;21(3):403-408. DOI: 10.2337/diacare.21.3.403

[210] Okereke NC, Huston-Presley L, Amini SB, Kalhan S, Catalano PM. Longitudinal changes in energy expenditure and body composition in obese women with normal and impaired glucose tolerance. American Journal of Physiology. Endocrinology and Metabolism. 2004;287(3):E472-E479. DOI: 10.1152/ajpendo.00589.2003

[211] Yilmaz O, Kucuk M, Ilgin A, Dagdelen M. Assessment of insulin sensitivity/resistance and their relations with leptin concentrations and anthropometric measures in a pregnant population with and without gestational diabetes mellitus. Journal of Diabetes and its Complications. 2010;24(2):109-114. DOI: 10.1016/j.jdiacomp.2009.01.006

[212] Hauth J, Clifton GG, Roberts GM, Myatt L, Spong CY, Leveno KJ, et al. Maternal insulin resistance and preeclampsia. The American Journal of Obstetrics and Gynecology. 2011;204(4):327.e1-327.e6. DOI: 10.1016/j.ajog.2011.02.024
[213] Hadden DR, McLaughlin C. Normal and abnormal maternal metabolism during pregnancy. Seminars in Fetal and Neonatal Medicine. 2009;14(2):66-71. DOI: 10.1016/j.siny.2008.09.004

[214] Catalano PM. Trying to understand gestational diabetes. Diabetic Medicine. 2014;31(3):273-281. DOI: 10.1111/dme.12381

[215] Zhu C, Yang H, Geng Q, Ma Q, Long Y, Zhou C, et al. Association of oxidative stress biomarkers with gestational diabetes mellitus in pregnant women: A case-control study. PLoS One. 2015;10(4):e0126490. DOI: 10.1371/journal.pone.0126490

[216] Yang SJ, Kim TN, Baik SH, Kim TS, Lee KW, Nam M, et al. Insulin secretion and insulin resistance in Korean women with gestational diabetes mellitus and impaired glucose tolerance. The Korean Journal of Internal Medicine. 2013;28(3):306-313. DOI: 10.3904/kjim.2013.28.3.306

[217] Jeon EJ, Hong SY, Lee JH. Adipokines and insulin resistance according to characteristics of pregnant women with gestational diabetes mellitus. Diabetes and Metabolism Journal. 2017;41(6):457-465. DOI: 10.4093/dmj.2017.41.6.457

[218] Jacob S, Nodzenski M, Reissetter AC, Bain JR, Muehlbauer MJ, Stevens RD, et al. Targeted metabolomics demonstrates distinct and overlapping maternal metabolites associated with BMI, glucose, and insulin sensitivity during pregnancy across four ancestry groups. Diabetes Care. 2017;40(7):911-919. DOI: 10.2337/dc16-2453

[219] Hellmuth C, Lindsay KL, Uhl O, Buss C, Wadhwa PD, Koletzko B, et al. Association of maternal prepregnancy BMI with metabolomic profile across gestation. International Journal of Obesity. 2017;41(1):159-169. DOI: 10.1038/ijo.2016.153

[220] Angueira AR, Ludvik AE, Reddy TE, Wicksteed B, Lowe WL Jr, Layden BT. New insights into gestational glucose metabolism: Lessons learned from 21st century approaches. Diabetes. 2015;64(2):327-334. DOI: 10.2337/db14-0877

[221] Huynh J, Xiong G, Bentley-Lewis R. A systematic review of metabolite profiling in gestational diabetes mellitus. Diabetologia. 2014;57(12):2453-2464. DOI: 10.1007/s00125-014-3371-0

[222] Dudzik D, Zorawski M, Skotnicki M, Zarzycki W, Kozlowska G, Bibik-Malinowska K, et al. Metabolic fingerprint of gestational diabetes mellitus. Journal of Proteomics. 2014;103:57-71. DOI: 10.1016/j.jprot.2014.03.025

[223] Lowe WL Jr, Karban J. Genetics, genomics and metabolomics: New insights into maternal metabolism during pregnancy. Diabetic Medicine. 2014;31(3):254-262. DOI: 10.1111/dme.12352

[224] Hajduk J, Klupczynska A, Drezinski P, Matysiak J, Kokot P, Nowak DM, et al. A combined metabolomic and proteomic analysis of gestational diabetes mellitus. International Journal of Molecular Sciences. 2015;16(12):30034-30045. DOI: 10.3390/ijms161226133

[225] Lindsay KL, Hellmuth C, Uhl O, Buss C, Wadhwa PD, Koletzko B, et al. Longitudinal metabolomic profiling of amino acids and lipids across healthy pregnancy. PLoS One. 2015;10(12):e0145794. DOI: 10.1371/journal.pone.0145794
[226] Luan H, Meng N, Liu P, Feng Q, Lin S, Fu J, et al. Pregnancy-induced metabolic phenotype variations in maternal plasma. Journal of Proteome Research. 2014;13(3):1527-1536. DOI: 10.1021/pr401068k

[227] Pinto J, Barros AS, Domingues MR, Goodfellow BJ, Galhano E, Pita C, et al. Following healthy pregnancy by NMR metabolomics of plasma and correlation to urine. Journal of Proteome Research. 2015;14(2):1263-1274. DOI: 10.1021/pr5011982

[228] Sandler V, Reisetter AC, Bain JR, Muehlbauer MJ, Nodzenski M, Stevens RD, et al. Associations of maternal BMI and insulin resistance with the maternal metabolome and newborn outcomes. Diabetologia. 2017;60(3):518-530. DOI: 10.1007/s00125-016-4182-2

[229] Pessin JE, Saltiel AR. Signaling pathways in insulin action: Molecular targets of insulin resistance. The Journal of Clinical Investigation. 2000;106(2):165-169. DOI: 10.1172/JCI10582

[230] Di Cianni G, Miccoli R, Volpe L, Lencioni C, Del Prato S. Intermediate metabolism in normal pregnancy and in gestational diabetes. Diabetes/Metabolism Research and Reviews. 2003;19(4):259-270. DOI: 10.1002/dmrr.390

[231] Colomiere M, Permezel M, Riley C, Desoye G, Lappas M. Defective insulin signaling in placenta from pregnancies complicated by gestational diabetes mellitus. European Journal of Endocrinology. 2009;160(4):567-578. DOI: 10.1530/EJE-09-0031

[232] Alonso A, Del Rey CG, Navarro A, Tolivia J, Gonzalez CG. Effects of gestational diabetes mellitus on proteins implicated in insulin signaling in human placenta. Gynecological Endocrinology. 2006;22(9):526-535. DOI: 10.1080/09513590600921374

[233] VanWinden K, Montoro M, Korst LM, Ouzounian JG. A homeostatic model assessment of insulin resistance (HOMA-IR) relates to gestational diabetes, glycemic control [1K]. Obstetrics and Gynecology. 2017;129(Supl.1)

[234] Wei J, Gao J, Cheng J. Gestational diabetes mellitus and impaired glucose tolerance in pregnant women. Pakistan Journal of Medical Sciences. 2014;30(6):1203-1208. DOI: 10.12669/pjms.306.5755

[235] Bartha JL, Comino-Delgado R, Martinez-Del-Fresno P, Fernandez-Barrios M, Bethencourt I, Moreno-Corral L. Insulin-sensitivity index and carbohydrate and lipid metabolism in gestational diabetes. The Journal of Reproductive Medicine. 2000;45(3):185-189

[236] Das S, Behera MK, Misra S, Baliarsingh AK. Beta-cell function and insulin resistance in pregnancy and their relation to fetal development. Metabolic Syndrome and Related Disorders. 2010;8(1):25-32. DOI: 10.1089/met.2009.0017

[237] Culha C, Gorar S, Demir Y, Serter R, Aral Y. The importance of serum adiponectin concentrations during pregnancy and postpartum period in women with gestational diabetes mellitus. Acta Endocrinologica (Buc). 2011;7(2):173-187. DOI: 10.4183/aeb.2011.173

[238] Ismail NA, Kasim MM, Noor Aizuddin A, Umar NA. Homeostatic indices of insulin resistance among gestational diabetics in anticipating pregnancy complications. Gynecological Endocrinology. 2013;29(7):691-694. DOI: 10.3109/09513590.2013.797398
[239] Liang Z, Wu Y, Xu J, Fang Q, Chen D. Correlations of serum visfatin and metabolisms of glucose and lipid in women with gestational diabetes mellitus. The Journal of Diabetes Investigation. 2016;7(2):247-252. DOI: 10.1111/jdi.12385

[240] Huo Y, Liu SX, Song GY, Ren LP, Wang C, Zhang DH. Plasma levels and placental expression of vaspin in pregnant women with diabetes mellitus. Brazilian Journal of Medical and Biological Research. 2015;48(3):273-279. DOI: 10.1590/1414-431X20143432

[241] Stepan H, Kralisch S, Klostermann K, Schrey S, Reisenbüchler C, Verlohren M, et al. Preliminary report: Circulating levels of the adipokine vaspin in gestational diabetes mellitus and preeclampsia. Metabolism. 2010;59(7):1054-1056. DOI: 10.1016/j.metabol.2009.11.001

[242] Telejko B, Kuzmicki M, Zonenberg A, Szamatowicz J, Wawrusiewicz-Kuryleknow N, Nikolajuk A, et al. Visfatin in gestational diabetes: Serum level and mRNA expression in fat and placental tissue. Diabetes Research and Clinical Practice. 2009;84(1):68-75. DOI: 10.1016/j.diabres.2008.12.017

[243] Gok DE, Yazici M, Uckaya G, Bolu SE, Basaran Y, O zgurtas T, et al. The role of visfatin in the pathogenesis of gestational diabetes mellitus. Journal of Endocrinological Investigation. 2011;34(1):3-7. DOI: 10.1007/BF03346687

[244] Harreiter J, Simmons D, Desoye G, Corcoy R, Adelantado JM, Devlieger R, et al. IADPSG and WHO 2013 gestational diabetes mellitus criteria identify obese women with marked insulin resistance in early pregnancy. Diabetes Care. 2016;39(7):e90-e92. DOI: 10.2337/dc16-0200

[245] Bozkurt L, Göbl CS, Pfligl L, Leitner K, Bancher-Todesca D, Luger A, et al. Pathophysiological characteristics and effects of obesity in women with early and late manifestation of gestational diabetes diagnosed by the International Association of Diabetes and Pregnancy Study Groups criteria. The Journal of Clinical Endocrinology and Metabolism. 2015;100(3):1113-1120. DOI: 10.1210/jc.2014-4055

[246] Egan AM, Vellinga A, Harreiter J, Simmons D, Desoye G, Corcoy R, et al. Epidemiology of gestational diabetes mellitus according to IADPSG/WHO 2013 criteria among obese pregnant women in Europe. Diabetologia. 2017;60(10):1913-1921. DOI: 10.1007/s00125-017-4353-9

[247] Kumru P, Arisoy R, Erdogan O, Demirci O, Kavrut M, Ardic C, et al. Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies. Taiwanese Journal of Obstetrics and Gynecology. 2016;55(6):815-820. DOI: 10.1016/j.tjog.2016.04.032

[248] Smirnakis KV, Plati A, Wolf M, Thadhani R, Ecker JL. Redicting gestational diabetes: Choosing the optimal early serum marker. American Journal of Obstetrics and Gynecology. 2007;196(4):410, e6-417. DOI: 10.1016/j.ajog.2006.12.011

[249] Alptekin H, Çizmecioglu A, Işık H, Cengiz T, Yildiz M, Iyisoy MS. Predicting gestational diabetes mellitus during the first trimester using anthropometric measurements and HOMA-IR. Journal of Endocrinological Investigation. 2016;39(5):577-583. DOI: 10.1007/s40618-015-0427-z
[250] Genova MP, Todorova K, Atanasova B. Diagnostic Approach for Assessment of Beta Cell Function during Pregnancy and after Delivery. Clinical Significance and Interpretation. Chichester: LAP LAMBERT Academic publishing; 2015. 65 p. ISBN: 978-3-659-69762-3

[251] Kafkasli A, Sertkaye AC, Selcuk EB, Dogan K, Burak F, Yologlu S. Abnormal glucose challenge test and mild gestational diabetes. Gynaecologia et Perinatologia. 2008;17(1):3-8. https://hrcak.srce.hr/23519

[252] Akdeniz N, Kuyumroglu U, Kalc A, Arikan S, Kale E, Erdemoglu M. Resistin may not associate with gestational diabetes mellitus although insulin resistance. Clinical and Experimental Obstetrics and Gynecology. 2011;38(3):236-238

[253] Ramirez V, Miller E, Meireles CL, Gelfond J, Krummel DA, Powell TL. Adiponectin and IGFBP-1 in the development of gestational diabetes in obese mothers. BMJ Open Diabetes Research and Care. 2014;2:e000010. DOI: 10.1136/bmjdr-2013-000010

[254] Kac G, Vaz JS, Schlüssel MM, Moura AS. C-reactive protein and hormones but not IL-6 are associated to body mass index in first trimester of pregnancy. Archives of Gynecology and Obstetrics. 2011;284(3):567-573. DOI: 10.1007/s00404-010-1573-3

[255] Imoh LC, Ocheke AN. Correlation between maternal weight and insulin resistance in second half of pregnancy. Nigerian Medical Journal. 2014;55(6):465-468. DOI: 10.4103/0300-1652.144697

[256] Gashlan HM. Relationship between levels of retinol binding protein, vaspin and cheimerin and insulin resistance in gestational diabetes mellitus. The International Journal of Pharmaceutical Research and Allied Sciences. 2017;6(1):236-250

[257] Huidobro MA, Prentice AM, JC Fulford A, Rozowski NJ. Anthropometry as predictor of gestational diabetes mellitus. Revista Médica de Chile. 2010;138(11):1373-1377. DOI: S0034-98872010001200005

[258] Sommer C, Jenum AK, Waage CW, Morkrid K, Sletner L, Birkeland KI. Ethnic differences in BMI, subcutaneous fat, and serum leptin levels during and after pregnancy and risk of gestational diabetes. European Journal of Endocrinology. 2015;172:649-656. DOI: 10.1530/EJE-15-0060

[259] Tomedi LE, Simhan HN, Chang CC, McTigue KM, Bodnar LM. Gestational weight gain, early pregnancy maternal adiposity distribution, and maternal hyperglycemia. Maternal and Child Health Journal. 2014;18(5):1265-1270. DOI: 10.1007/s10995-013-1361-3

[260] Catalano PM, Nizielski SE, Shao J, Preston L, Qiao L, Friedman JE. Downregulated IRS-1 and PPARgamma in obese women with gestational diabetes: Relationship to FFA during pregnancy. American Journal of Physiology-Endocrinology and Metabolism. 2002;282(3):E522-E533. DOI: 10.1152/ajpendo.00124.2001
