Pathogenesis of Gestational Diabetes Mellitus

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Introduction

Gestational diabetes mellitus (GDM) constitutes the most common metabolic disease of pregnancy, with a continuously increasing prevalence [1, 2]. It has been associated with several maternal and fetal/neonatal complications [3, 4]. Increased maternal age, increased pre-pregnancy body mass index (BMI), excessive weight gain during pregnancy, Aboriginal Australian, Middle Eastern and Pacific Islander ethnicity, positive family history of GDM, and parity are established risk factors for the development of GDM [5, 6]. GDM, similarly to type 2 diabetes mellitus (T2DM), is a multifactorial disease; its pathogenetic mechanisms are not yet fully understood. Genetic and acquired factors that affect insulin sensitivity and insulin secretion have been implicated to GDM development and determine the disease severity [7]. Hormonal, inflammatory, and immunologic factors contribute to GDM pathogenesis. Suboptimal lifestyle, such as hypercaloric diet, unhealthy nutritional habits, and reduced physical activity, contributes to central obesity, a triggering factor for GDM [8, 9].

Insulin Action and Sensitivity

A major pathogenetic mechanism for GDM is the reduced insulin sensitivity that occurs in normal pregnancy due to placental and maternal hormonal action. Insulin action is impaired at hepatic, muscle, and adipose tissue level [10–12]. Impaired post-receptor insulin signaling is mainly responsible for pregnancy-induced insulin resistance. Experimental studies showed impaired mRNA or protein expression of insulin signaling cascade components, such as insulin receptor substrate (IRS)-1 and (IRS)-2, as well as glucose transporter (GLUT)-1 and (GLUT)-4 in adipose tissue and muscle of women whose pregnancies were complicated by GDM. Decreased IRS-1 tyrosine phosphorylation, decreased GLUT-4 insulin-induced translocation to the cell surface, and decreased glucose transport into the cell were also found in muscle and adipose tissue of women with GDM [13–16]. Similar post-receptor insulin defects have been found in the placenta of GDM-affected pregnancies [17]. Chronic low-grade inflammation that characterizes obesity, which often accompanies GDM pregnancies, contributes to insulin signaling impairment [18], as well as oxidative stress [19].

Placental Hormones

Placental hormones, such as human placental lactogen (HPL) and placental growth hormone (GH), are opposed to insulin action [20]. HPL is produced by syncytiotrophoblast and is gradually increased during pregnancy until about 30th gestational week, when it reaches a plateau. It is correlated to fetal weight and well-being as well as placental function [21]. HPL is the main insulin resistance mediator during pregnancy. It acts as an "anti-insulin" agent in order to ensure adequate glucose supply to the embryo [22, 23]. HPL results in raised maternal blood glucose concentrations by increasing insulin resistance and raised free fatty acids concentrations by increasing lipolysis [24]. A sudden drop to HPL concentrations could indicate fetal distress [25–27]. Growth hormone (GH) is an anabolic hormone, involved in carbohydrate and lipid metabolism, and, when in excess, has diabetogenic properties, opposing insulin action [28]. Human placental GH is the main GH molecule produced during pregnancy, having an effect on maternal insulin sensitivity [29]. It is produced mainly by placental syncytiotrophoblastic cells, and it is gradually increased by midpregnancy to term. Studies in transgenic mice showed severe insulin resistance induction by placental GH [30].

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Maternal Hormones

Maternal serum GH, other growth factors, such as insulin like growth factor-1 (IGF-1), their binding proteins, prolactin (PRL), progesterone, and cortisol are altered in women whose pregnancies are complicated by as compared with unaffected pregnant women [31, 32]. PRL is produced, mainly, by anterior pituitary lactotroph cells and, secondary, by the central nervous system, immune cells, nonpregnant uterus, placenta, amnion, decidua, and the mammary gland. The most well-known action of PRL is lactation. Other PRL effects are mammary epithelial proliferation, corpus luteum function, and immune response [33, 34]. Evidence about PRL's effect on insulin sensitivity is contradictory. Hyperprolactinemia, as in patients with a prolactinoma, exacerbates insulin resistance to the nonpregnant state [35, 36]. The latter effect regresses after treatment with dopaminergic receptor agonist [37]. In contrary, studies in nonpregnant healthy women (with normal prolactin concentrations) showed that lower prolactin concentrations were correlated to decreased insulin sensitivity and increased risk for diabetes [38, 39]. During pregnancy, PRL is also produced by decidual cells and fetal pituitary. Maternal PRL is increased gradually by conception to term [40]. In pregnant rats, increased prolactin concentrations have been correlated to a post-receptor insulin defect [20]. In humans, higher concentrations of PRL during the third trimester of pregnancy have been associated with decreased glucose tolerance, implying a causative relationship between hyperprolactinemia and GDM [41]. In contrary, in another study, no difference in PRL concentrations has been found between GDM and controls [42]. Maternal, placental, and fetal adrenal steroids, progesterone, cortisol, estrogen, and androgens, also contribute to pregnancy-induced insulin resistance [43]. Progesterone, produced initially by the corpus luteum and later by the placenta, inhibits insulin action in vivo and in vitro, mainly by inhibiting the PI3-kinase pathway of the insulin signaling cascade in the adipocytes [44]. Cortisol can also induce insulin resistance through post-receptor insulin defect [20]. Androgen receptors are overexpressed in placentas of GDM-affected pregnancies as compared to controls [45]. Although it is known that estrogens regulate carbohydrate metabolism, the underlying mechanisms are not fully understood. In the nonpregnant state, estradiol (E_2) partially affects insulin signaling through modification of mitochondrial function [46]. In GDM-affected pregnancies, estrogen concentrations are lower as compared to unaffected pregnant women [47].

Maternal Adipokines

Maternal adipokines have a significant effect on insulin action. Adiponectin, an adipose tissue-derived plasma protein, has a beneficial effect on carbohydrate metabolism by increasing insulin sensitivity [48, 49]. It is produced mainly by white adipose tissue (WAT). Adiponectin seems to express protective properties for the vascular endothelium and the heart through anti-inflammatory action and suppression of the atherosclerotic processes [50–52]. Higher concentrations of adiponectin have been associated with lower risk of T2DM development in nonpregnant women [53]. In pregnancy, evidence about adiponectin concentrations is not consistent; placental production of adiponectin has not been confirmed by all investigators [54, 55]. Some studies have demonstrated an increase in adiponectin concentrations in early pregnancy and a gradual decrease thereafter compared with the prepregnancy state [56, 57]. Although evidence regarding gestational concentrations of adiponectin and carbohydrate metabolism is less clear, a link between hypoadiponectinemia and insulin resistance exists [57, 58], as pregnant women with GDM have lower adiponectin levels than healthy controls [59].

Another adipokine, leptin, is strongly involved to metabolic issues affecting insulin secretion and action as well as tissue insulin sensitivity [60, 61]. Leptin is produced mainly by WAT adipocytes, proportionally to adipose tissue mass [62]. In a lesser degree, it is produced by brown adipose tissue (BAT), placenta, skeletal muscle cells, ovaries, and gastric cells. Leptin's primary action is the regulation of energy homeostasis [63]. Leptin reduces insulin synthesis and secretion, whereas it increases insulin sensitivity [61, 64]. Obesity is associated with resistance to leptin action [65]. During pregnancy, placenta-derived leptin results in nearly a 100% increase in maternal serum concentrations [66, 67]. Further increased leptin concentrations have been found in GDM-affected women as compared to non-affected pregnant women [68, 69]. Both adiponectin and leptin gene polymorphisms have been correlated to GDM occurrence [70]. Low adiponectin and high leptin concentrations during the first trimester may predict GDM occurrence during later pregnancy [71, 72].

Fetuin B, a recently identified adipokine, impairs insulin action. Women with GDM-affected pregnancies have higher fetuin B concentrations as compared with controls [73]. Data on resistin, visfatin and apelin concentrations, and their association with GDM are not consistent. Other novel adipokines, such as omentin and chemerin, have been associated to GDM development, and a causal effect is implied by some investigators [74].

Immunological Changes and Low-Grade Inflammation

Normal pregnancy is accompanied by immunological changes and a low-grade inflammation that is occurred to the benefit of the fetus [75, 76]. Inflammation is exacerbated by obesity, a common risk factor of GDM, and

affects insulin sensitivity through post-receptor signaling defect. Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), have a direct adverse effect on insulin action in healthy nonpregnant women, inducing insulin resistance [77]. TNF-α is a transmembrane protein produced mainly by activated macrophages in response to immunological stimulus [78]. In a lesser degree, it is expressed by other cells, such as lymphoid cells, cardiac myocytes, endothelial cells, and adipocytes. It expresses a cytotoxic effect on many cells; simultaneously, it has a regenerative effect on tissues [79, 80]. TNF-α induces phosphorylation of the IRS-1, thus preventing the interaction of insulin with the insulin receptor and impairing insulin action. Interleukin-6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine expressed by immune cells, such as T-cells and macrophages, visceral adipocytes, osteoblasts, and vascular smooth muscle cells. It is the main stimulator of the production of many acute-phase proteins. It impairs insulin-induced insulin receptor and IRS-1 phosphorylation, resulting to inhibition of the insulin signaling cascade [81]. C-reactive protein (CRP) is an acute-phase protein of hepatic origin that is increased in response to inflammation and IL-6 secretion. It acts through activation of the complement system, triggering phagocytosis by immune cells. CRP is associated to insulin resistance in healthy individuals; high concentrations of high-sensitivity (hs)-CRP are indicative of higher risk for metabolic, cardiovascular, and cerebrovascular disease [82]. The Generation R Study showed that increased CRP concentrations during early gestation are associated to high risk of neonatal complications [83]. During normal pregnancy, low-grade inflammatory markers, such as CRP, IL-6, TNF-α, and GlycA, have found to be increased, suggesting an upregulation of systemic maternal inflammation [75, 84]. In contrast to this normal maternal adaptation, a further increase of some inflammatory markers is considered a risk factor for adverse pregnancy outcomes, including GDM. Specifically, it has been shown that women with GDM-affected pregnancies have increased IL-6 concentrations as compared to controls [85]. In a recent meta-analysis, TNF-α has been found to be higher in GDM pregnancies compared to controls, independently of BMI [69]. CRP has been associated with GDM; an increase in its concentrations during early pregnancy is predictive of GDM development later in pregnancy [86, 87].

Oxidative Stress

Normal pregnancy is considered a condition of increased oxidative stress. Several pathologic conditions during pregnancy, including GDM, are associated with a further aggravation of oxidative stress. It is believed that oxidative stress is caused either by increased reactive oxygen species (ROS) production or by a reduction of the antioxidant capacity [19]. Both an increase in oxidative stress markers and a decrease in antioxidative factors have been found in GDM-affected pregnancies. ROS induce inflammatory response and inflammatory protein expression, aggravating the normal low-grade inflammation and insulin resistance during pregnancy. Furthermore, increased protein oxidation due to enhanced oxidative stress could be implicated to GDM pathogenesis [87, 88].

β-Cell Dysfunction and Insulin Secretion

β-Cell Dysfunction

During normal pregnancy, pancreatic cell adaptation occurs to compensate for the increased need for insulin. β-cell expansion and hyperfunctioning occur early in pregnancy in order to cope with the decreased insulin sensitivity that occurs after the second half of pregnancy [89]. GDM is characterized by decreased insulin response to oral glucose and protein, sluggish first-phase insulin secretion, and delayed peak insulin secretion [90]. Subclinical pre-existing β-cell dysfunction, rather than a gradual decline of β-cell function during pregnancy, and the effect of maternal hormones and inflammatory mediators (see Sect. 2) on β-cell function constitute main mechanisms for the occurrence of GDM [91, 92]. Pre-existing β-cell dysfunction, due to genetic predisposition, does not allow for compensatory pancreatic β-cell hyperfunction to counter-regulate for the increased insulin resistance of pregnancy (Fig. 14.1) [93]. β-cell dysfunction in pregnancies complicated by GDM persists postpartum as compared to controls. Given the normalization of insulin sensitivity after delivery, only a small percentage of women with GDM remain within diabetic ranges; nevertheless, the risk for developing T2DM in later life remains increased (Fig. 14.2) [94].

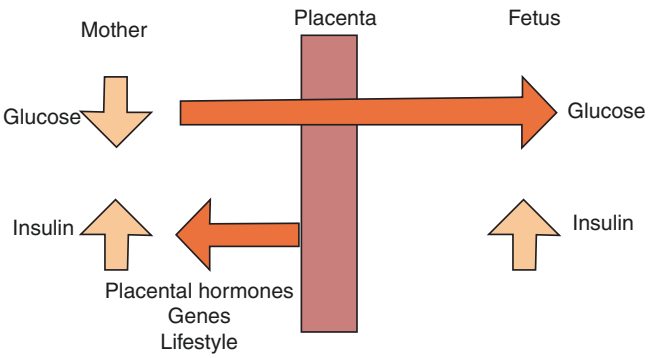

Fig. 14.1 Pathogenesis of GDM: combination of maternal and placental hormonal alteration, genetic predisposition, and suboptimal lifestyle. (Adapted from: Poulakos et al. [93])

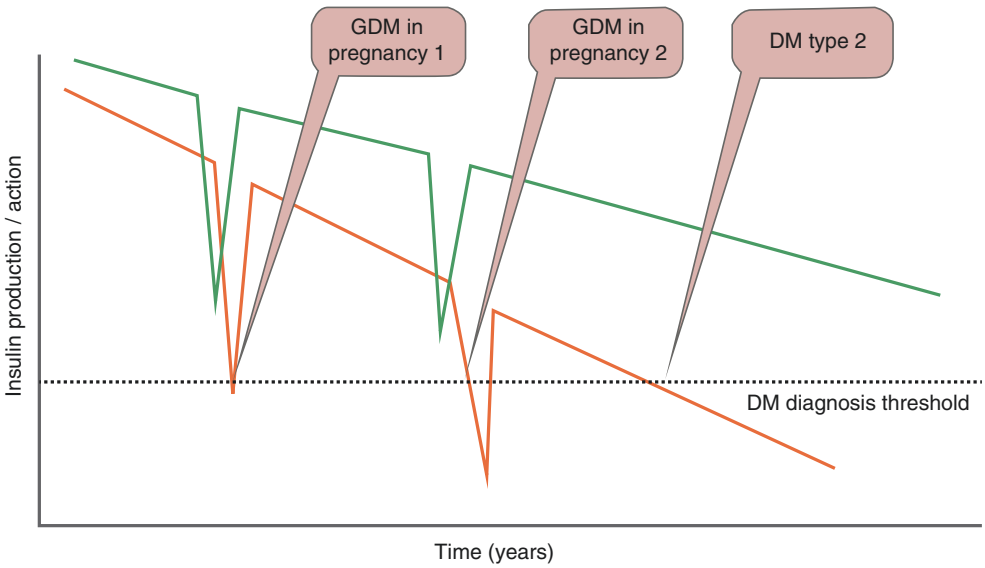

Fig. 14.2 T2DM development in women with prior GDM. Women with a history of GDM have increased probability of developing GDM in later life due to genetic predisposition and suboptimal lifestyle. (Adapted from: Poulakos et al. [93])

Vitamin D Deficiency

Hypovitaminosis D, defined as low serum concentrations of 25-hydroxy- vitamin D_3 [25(OH)D_3], has been correlated to β-cell dysfunction in the nonpregnant state; vitamin D supplementation has been shown to improve insulin secretion in rats [95, 96]. During pregnancy, lower 25(OH)D_3 concentrations have been associated with GDM [97]. Moreover, lower 25(OH)D_3 concentrations postpartum have been associated with impaired β-cell function in women with a history of GDM [98]. Increased parathyroid hormone (PTH) concentrations have been implicated to GDM pathogenesis, partially through insulin secretion impairment [99].

Maternal Hormones

The effect of maternal hormones on β-cell function and proliferation during pregnancy is still not completely understood, and some results are contradictory. Despite that PRL is considered as a major regulator of β-cell expansion and hyperfunction during pregnancy, higher prolactin concentration has been correlated to decreased glucose tolerance during late pregnancy [41, 100]. PRL receptor-null mice have shown β-cell maladaptation during pregnancy [101]. Moreover, PRL has been found to reduce menin concentrations, a known tumor suppression factor that also suppresses β-cell proliferation and may be implicated to GDM development in pregnant mice [102]. 17β-estradiol is seemed to be involved to β-cell adaptation and insulin secretion during pregnancy, specifically β-cell survival [103, 104]. Progesterone receptor-knockout mice have increased insulin secretion probably due to increased β-cell mass [105]. The latter is in accordance with another experimental study that showed an apoptotic action of progesterone to pancreatic β-cells through an oxidative stress-dependent mechanism [106]. HPL stimulates insulin secretion and may have a central role to regulation of islet function during pregnancy [107]. Recent data suggest a leptin-induced decrease of insulin secretion by direct action on β-cells. Moreover, leptin affects β-cell proliferation and apoptosis and inhibits insulin gene expression [108].

Low-Grade Inflammation

As mentioned above, the low-grade inflammation that characterizes GDM affects glucose metabolism through an increase to insulin resistance. Additionally, an impairment on adipokines production, possibly due to this inflammation, has also been correlated to β-cell dysfunction and decreased insulin secretion [69, 109]. Specifically, GDM-affected women have lower adiponectin concentrations as compared with controls [69, 110]. This hypoadiponectinemia of GDM pregnancy has been associated to β-cell dysfunction [111]. As part of the low-grade inflammation, GDM-affected women have increased TNF-α concentrations [69]. Beyond insulin resistance, TNF-α has a pro-apoptotic effect on β-cells [112]. The latter could contribute to the reduced insulin secretion of GDM. As mentioned above, GDM-affected women have lower concentrations of 25(OH)D_3. Vitamin D deficiency has also been associated to increased concentrations of inflammatory markers that could further deteriorate β-cell function [113].

Oxidative Stress

Beyond insulin resistance, oxidative stress per se or as a consequence of inflammation and hyperglycemia has been linked to decreased insulin secretion during the nonpregnant state [114]. GDM is characterized by increased oxidative stress as it is determined by increased concentrations of advanced glycosylated end-products (AGEs) and other markers of oxidative lipid and protein damage [88, 115]. Recently, a furan fatty acid metabolite, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), has been recognized as a possible negative regulator of β-cell function, inhibiting insulin synthesis and secretion through oxidative stress and mitochondrial dysfunction in human and mouse islets. Women with GDM have increased concentrations of CMPF as compared with controls [116]. Moreover, in GDM-affected women, CMPF predicted lower β-cell function indices [92].

Autoimmunity

A rare cause of GDM is an autoimmune destruction of pancreatic β-cells, similar to that of type 1 diabetes mellitus (T1DM). Autoimmune GDM consists in less than 10% of cases. GDM-affected women with autoimmune form of diabetes often develop T1DM soon after pregnancy or latent autoimmune diabetes of adulthood (LADA) some years after delivery [117]. In a Swedish population, antibodies implicated in T1DM pathogenesis [glutamic acid decarboxylase antibodies (GADA), islet cell antigen-2 antibodies (ICA)/tyrosine phosphatase antibodies (IA2)] have been detected in 6% of women with GDM [118]. Specifically, the prevalence of GADA in GDM-affected women has been shown to extend between 0% and 11%, of ICAs between 1% and 35%, of insulin autoantibodies (IAA) between 0% and 6%, and that of anti-IA2 between 0% and 6% [119]. Moreover, pancreatic autoantibodies may be developed in some GDM women postpartum [117]. GADA were positively associated with postpartum development of diabetes in women diagnosed with GDM [120]. As a consequence, positive GADA and other pancreatic autoantibodies in GDM-affected women can be predictive of postpartum T1DM development [121]. A recent meta-analysis has shown an association between HLA class II variants, which consists of up to 30–50% of the pathogenesis of T1DM, and GDM. Specifically, DQB1*02 and DRB1*1302 alleles have been significantly associated with increased risk of developing GDM. In contrary, DQB1*0602 seems to be a protective allele against GDM development [122]. HLA-DR6 alleles were also positive correlated to GDM development, whereas other haplotypes, such as HLA-DR2 and HLA-DR51, seem to be protective. Besides HLA-DR3 gene and HLA-DR6/DR9 heterozygote were associated to GDM severity and prognosis [123]. Other studies found no significant differences to the distribution of HLA class II polymorphism between GDM, impaired glucose tolerance (IGT), and unaffected pregnant women [124]. It is obvious that the evidence about the relationship between GDM and autoimmunity is still controversial and more studies are needed to establish it.

Genetic Causes

A rare cause of GDM is maturity-onset diabetes of the young (MODY) gene mutations. Several MODY gene mutations are present in GDM-affected women. MODY is an inherited form of diabetes resulting by a mutation of a single, autosomic, dominant gene that disrupts insulin secretion. It may be inherited to the offspring by both maternal and paternal origin; less frequently, it can be caused by de novo gene mutation. Nowadays, several types of MODY have been recognized. Genes that are implicated to MODY development are hepatocyte nuclear factor-1 homeobox a (HNF1a) gene that is responsible for MODY 3 development, glucokinase (GCK) gene for MODY 2, hepatocyte nuclear factor-4 homeobox a (HNF4a) gene for MODY 1, hepatocyte nuclear factor-1 homeobox b (HNF1b) gene that cause diabetes and renal cysts (MODY 5), insulin promoter factor (HPF1) gene for MODY 4, insulin gene for MODY 10, ABCC8 gene [sulfonylurea receptor-1 (SUR1) subunit] for MODY 12, potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) gene for MODY 13, neurogenic differentiation-1 gene (NEUROD1) for MODY 6, kruppel-like factor 11 (KLF 11) gene for MODY 7, carboxyl ester lipase (CEL) gene for MODY 8, paired box-4 (PAX4) gene for MODY 9, and BLK gene for MODY 11 [125–133]. These monogenic forms of diabetes constitute less than 10% of GDM; MODY 2 has been recognized as the most frequent type associated with GDM [134]. Several other mutations of MODY genes have been detected in GDM women such as HNF1a, IPF1, insulin gene, and KCNJ11 gene [135–139]. However, a causal relationship between MODY and GDM has not been established yet. Further investigation is needed regarding the possible clinical implications of MODY gene mutations on maternal and fetal health [134].

Conclusions

GDM is the most common metabolic complication of pregnancy. Its prevalence has been increasing over the years and parallels the increasing obesity trend. The main pathogenetic mechanism is insulin resistance as a result of maternal and

placental hormone alteration, maternal adipokine alteration, low-grade inflammation, and oxidative stress that accompany both pregnancy and obesity. An additional pathogenetic mechanism is β-cell dysfunction either pre-existing, as a result of occult genetic predisposition, or due to hormonal and inflammatory effect of pregnancy and obesity. Less frequent causes of GDM are autoimmune destruction of pancreatic β-cells (similarly to T1DM) and impaired insulin secretion caused by gene mutations, such as MODY.

Multiple-Choice Questions

1. Gestational diabetes mellitus constitutes:
   (a) A rare disease
   (b) The most common metabolic disease of pregnancy
   (c) A disease that begins when healthy blood cells change and grow uncontrollably
   (d) The onset of Type 2 diabetes in pregnancy
   (e) A monogenic form of diabetes occurring in pregnancy
2. In gestational diabetes mellitus-affected pregnancies, estrogen concentrations are:
   (a) Equal as compared to unaffected pregnant women
   (b) Higher as compared to unaffected pregnant women
   (c) Lower as compared to unaffected pregnant women
   (d) Abolished during pregnancy
   (e) Are highly dependent of insulin concentrations
3. The Generation R Study showed that increased CRP concentrations during early gestation are associated to high risk of:
   (a) Asthma
   (b) Neonatal complications
   (c) Weight loss
   (d) Hypoglycemia
   (e) Maternal cardiovascular disease
4. Which is the main pathogenetic mechanism of gestational diabetes mellitus?
   (a) Insulin resistance as a result of maternal and placental hormone alteration, maternal adipokine alteration, low-grade inflammation, and oxidative stress that accompany both pregnancy and obesity
   (b) Insulin as a result of maternal and placental hormone alteration, maternal adipokine, low-grade inflammation and oxidative stress that accompany the obesity
   (c) Autoimmune destruction of pancreatic β-cells (similarly to T1DM) and impaired insulin secretion caused by gene mutations, such as MODY
   (d) Insulin resistance in skeletal muscle resulting from physical inactivity during pregnancy
   (e) High levels of counter-regulatory hormones
   (f) Maternal overweight and obesity
5. Placental hormones, such as human placental lactogen (HPL) and placental growth hormone (GH) are:
   (a) Opposed to insulin action
   (b) Excellent drugs to treat gestational diabetes mellitus
   (c) Acts as a "pro-insulin" agent
   (d) Opposed to glucagon action
   (e) Supportive to insulin action
6. Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), have a direct adverse effect on insulin action in healthy nonpregnant women, inducing:
   (a) Insulin resistance
   (b) Gestational diabetes mellitus
   (c) C-reactive protein decrease
   (d) Lower risk for metabolic, cardiovascular, and cerebrovascular disease
   (e) Beta-cell failure
7. Maternal, placental, and fetal adrenal steroids, progesterone, cortisol, estrogen, and androgens, also contribute to pregnancy-induced insulin resistance.
   (a) False
   (b) True
8. An anabolic hormone, involved in carbohydrate and lipid metabolism, when in excess, has diabetogenic properties, opposing insulin action.
   (a) Growth hormone
   (b) Epinephrine
   (c) Estrogens
   (d) Progesterone
   (e) Leptin
9. Inflammation resulting from impaired adipokine synthesis has been correlated to β-cell dysfunction and decreased insulin secretion.
   (a) False
   (b) True
10. In nonpregnant healthy women (with normal prolactin concentrations), lower prolactin concentrations are associated with:
   (a) Decreased insulin sensitivity and lower risk for diabetes.
   (b) Decreased insulin sensitivity and high risk for diabetes.
   (c) Increased insulin sensitivity and low risk for diabetes.
   (d) Increased insulin sensitivity and high risk for diabetes.
   (e) No associations have been documented.

Correct Answers

1. (b) The most common metabolic disease of pregnancy
2. (c) Lower as compared to unaffected pregnant women
3. (b) Neonatal complications

4. (a) Insulin resistance as a result of maternal and placental hormone alteration, maternal adipokine alteration, low-grade inflammation, and oxidative stress that accompany both pregnancy and obesity
5. (a) Opposed to insulin action
6. (a) Insulin resistance
7. (b) True
8. (a) Growth hormone
9. (b) True
10. (b) Decreased insulin sensitivity and high risk for diabetes

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