6

Pathophysiology of Gestational Diabetes Mellitus: The Past, the Present and the Future

Mohammed Chyad Al-Noaemi[1] and
Mohammed Helmy Faris Shalayel[2]
[1]*Al-Yarmouk College, Khartoum,*
[2]*National College for Medical and Technical Studies, Khartoum,*
Sudan

1. Introduction

It is just to remember that "Pathophysiology" refers to the study of alterations in normal body function (physiology and biochemistry) which result in disease. E.g. changes in the normal thyroid hormone level causes either hyper or hypothyroidism. Changes in insulin level as a decrease in its blood level or a decrease in its action will cause hyperglycemia and finally diabetes mellitus.

Scientists agreed that gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy.

From our experience most women with GDM in the developing countries are not aware of the symptoms (i.e., the disease will be symptomless). While some of the women will have few symptoms and their GDM is most commonly diagnosed by routine blood examinations during pregnancy which detect inappropriate high level of glucose in their blood samples. GDM should be confirmed by doing fasting blood glucose and oral glucose tolerance test (OGTT), according to the WHO diagnostic criteria for diabetes.

A decrease in insulin sensitivity (i.e. an increase in insulin resistance) is normally seen during pregnancy to spare the glucose for the fetus. This is attributed to the effects of placental hormones. In a few women the physiological changes during pregnancy result in impaired glucose tolerance which might develop diabetes mellitus (GDM). The prevalence of GDM ranges from 1% to 14% of all pregnancies depending on the population studied and the diagnostic tests used. Although the majority of women with GDM return to normal glucose tolerance immediately after delivery, a significant number will remain diabetic or continue to have impaired glucose tolerance (IGT).

To understand how gestational diabetes occurs, it is necessary to understand the normal physiological metabolism of glucose during pregnancy and the physiological changes - mainly the endocrine changes during pregnancy in the feto-placental unit, which might explain the development of insulin resistance and GDM.

1.1 Insulin

Only about 1-2% of the pancreatic structure is endocrine tissues which are represented by the presence of 1-2 million islets of langerhans. These islets contain four main types of cells (A, B, D, and F cells). Insulin is secreted by B (beta) cells which constitute about 60-70% of the islets

cells. Insulin is a 51-amino acid polypeptide (small protein) hormone consist of A and B-chains connected together by disulphide bridges (Ganong, 2003; Guyton & Hall, 2006).

1.2 Insulin Receptor (IR)

The IR is a large heterotetrameric, transmembrane glycoprotein, having a molecular weight of about 300,000. Each receptor consists of two alpha (α) subunit that lie outside the cell membrane and two beta (β) subunits that penetrate the cell membrane protruding into the cytoplasm connected together by disulphide bridges in a β-α- α-β configuration. IR is assembled from a single polypeptide pro-receptor, by dimerization, proteolytic cleavage, and glycosylation within the cytoplasm and Golgi apparatus, before trafficking of the mature receptor to the plasma membrane. These insulin receptors have also been designated recently as CD220 (cluster of differentiation 220) (Ganong, 2003; Guyton & Hall, 2006; Ward & Lawrence, 2009).

1.3 Insulin action

Insulin has many metabolic functions such as enhancing cellular uptake of glucose, fatty acids, amino acids, and potassium ions. It also has an anabolic action by increasing cellular formation of glycogen, lipids, and protein. These physiological functions will be reversed if insulin action is decreased as seen with the increase in insulin resistance during pregnancy.
The main function of insulin concerning gestational diabetes mellitus (GDM) is its action on glucose and lipid metabolism.

1.3.1 Insulin effect on lipid metabolism

Normally insulin stimulates the synthesis and release of lipoprotein lipase from the endothelial cells of blood vessels causing lipolysis of triglycerides in the blood and release of free fatty acids (FFA). Insulin enhances the transport of FFA to the fatty cells (adipocytes) to be stored as lipids. Furthermore, insulin inhibits lipoprotein lipase in adipose cells preventing lipolysis.

1.3.2 Insulin effect on glucose metabolism

Insulin enhances entrance of glucose to the cells through its action on the insulin receptors. Insulin receptor complex will stimulates mobilization of glucose carrier protein (GLUT- 4 transporter) from the interior of the cell to the plasma membrane which will transport glucose inside the cell by the process of facilitated diffusion. Furthermore, insulin-receptor complex will activates the storage of some glucose as glycogen while others will be metabolized into pyruvate and then fatty acids which are stored as triglycerides (fat) (Ganong, 2003; Guyton & Hall, 2006).

1.4 Insulin-receptor interaction

To initiate insulin effects on target cells, it first binds with and activates a membrane receptor protein. [4] It is the activated receptor, not the insulin that causes the subsequent effects. The combination of insulin with the alpha subunits will induce autophosphorylation of the beta subunits which will activates a local tyrosine kinase [(phosphatidylinositol 3-kinase (PI3-K)] , which in turn begins a cascade of cell phosphorylation that increase or decrease the activity of enzymes, including insulin receptor substrates (IRSs). There are different types of IRSs (IRS-1, IRS-2, and IRS-3) which are expressed in different tissues

which explain the diversity of insulin action, activating or inactivating certain enzymes to produce the desired effect on the cellular carbohydrate, fat, and protein metabolism (Zwick et al., 2001; Pawson, 1995; Hans-Georg,1995; Perz & Torlińska, 2001).
Within seconds after insulin binds with its membrane receptors, glucose transporters are moved to the cell membrane to facilitate glucose entry into the cell especially to the muscle and adipose tissues (Guyton & Hall, 2006; Sherwood, 2010).

2. Physiology of pregnancy

The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus, known as the feto-placental unit (FPU), this interface is a major site of protein and steroid hormone production and secretion. Many of the endocrine and metabolic changes that occur during pregnancy can be directly attributed to hormonal signals originating from the FPU (Ganong, 2003; Guyton & Hall, 2006; Monga & Baker, 2006).
During early pregnancy, glucose tolerance is normal or slightly improved and peripheral (muscle) sensitivity to insulin and hepatic basal glucose production is normal (Catalano et al., 1991; Catalano et al., 1992; Catalano et al., 1993). These could be caused by the increased maternal estrogen and progesterone in early pregnancy which increase and promote pancreatic ß-cell hyperplasia (Expansion of beta-cell mass in response to pregnancy) causing an increased insulin release (Carr & Gabbe, 1998; Rieck & Kaestner, 2010). This explains the rapid increase in insulin level in early pregnancy, in response to insulin resistance. In the second and third trimester, the continuous increase in the feto-placental factors will decrease maternal insulin sensitivity, and this will stimulate mother cells to use sources of fuels (energy) other than glucose as free fatty acids, and this will increase supply of glucose to the fetus (Catalano et al., 1991; Catalano et al., 1992; Ryan & Enns, 1988). In the normal physiological conditions, the fetal blood glucose is 10-20% less than maternal blood glucose allowing the transport of glucose in the placenta to the fetal blood by the process of simple diffusion and facilitated transport. Therefore, glucose is the main fuel required by the developing fetus, whether as a source of energy for cellular metabolism or to provide energy for the synthesis of protein, lipids, and glycogen.
During pregnancy, the insulin resistance of the whole body is increased to about three times the resistance in the non-pregnant state.
In general, the resistance to insulin can be characterized as pre-receptor (insulin antibodies) as in autoimmune diseases, receptor (decreased number of receptors on the cell surface) as in obesity, or post-receptor (defects in the intracellular insulin signaling pathway). In pregnancy, the decreased insulin sensitivity is best characterized by a post-receptor defect resulting in the decreased ability of insulin to bring about SLC2A4 (GLUT4) mobilization from the interior of the cell to the cell surface (Catalano, 2010). This could be due to increase in the plasma levels of one or more of the pregnancy-associated hormones (Kühl, 1991; Hornns, 1985).
Although, pregnancy is associated with increase in the beta-cell mass and increase in insulin level throughout pregnancy but certain pregnant women are unable to up-regulate insulin production relative to the degree of insulin resistance, and consequently become hyperglycemic, developing gestational diabetes (Kühl, 1991).

3. Diagnosis of gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance resulting in hyperglycemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated but has been previously unrecognized (Metzger, 1991; Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia *World Health Organization* [WHO], 2006). Women who become pregnant and who are known to have diabetes mellitus which antedates pregnancy do not have gestational diabetes but have "diabetes mellitus and pregnancy" and should be treated accordingly before, during, and after the pregnancy (WHO, 2006).

Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples.

3.1 WHO diagnostic criteria for hyperglycemia and GDM (2006)

In the early part of pregnancy (e.g. first trimester and first half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal, non-pregnant women. Elevated fasting or postprandial plasma glucose levels at this time in pregnancy may well reflect the presence of diabetes which has antedated pregnancy. The occurrence of higher than usual plasma glucose levels at this time in pregnancy mandates careful management and may be an indication for carrying out an oral glucose tolerance test (OGTT). Nevertheless, normal glucose tolerance in the early part of pregnancy does not by itself establish that gestational diabetes will not develop later.

It may be appropriate to screen pregnant women belonging to high-risk populations during the first trimester of pregnancy in order to detect previously undiagnosed diabetes mellitus. Formal systematic testing for gestational diabetes is usually done between 24 and 28 weeks of gestation.

To determine if gestational diabetes is present in pregnant women, a standard OGTT should be performed after overnight fasting (8-14 hours) by giving 75 g anhydrous glucose in 250-300 ml water. Plasma glucose is measured fasting and after 2 hours. Pregnant women who meet WHO criteria for diabetes mellitus or impaired glucose tolerance (IGT) are classified as having GDM. After the pregnancy ends, the woman should be re-classified as having either diabetes mellitus, or IGT, or normal glucose tolerance based on the results of a 75 g OGTT six weeks or more after delivery.

The following table (table 1) summarizes the 2006 WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia (WHO, 2006).

Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl), or
2–h plasma glucose *	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2–h plasma glucose*	≥7.8 and <11.1mmol/l (140mg/dl and 00mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9 mmol/L (110mg/dl to 125 mg/dl)
2-h Plasma glucose*	< 7.8 mmol/dl (140mg/dl)

* Venous plasma 2-h after ingestion of 75gm oral glucose load (OGTT)

Table 1. Diagnostic criteria for diabetes and intermediate hyperglycemia

3.2 Glycosylated hemoglobin (HbA1c) as a diagnostic test for GDM

Since 1984, professor Alwan AAS and collaborators have adopted the measurement of HbA1c levels as another index for follow-up of pregnant diabetic patients, and reported a significant relationship between elevated levels of HbA1c late in the third trimester and feto-maternal complications (Al-Dahwi et al., 1986; Al- Dahwi et al., 1987; Al-Dahwi et al., 1988; Al-Dahwi et al., 1989). Recently, the American Diabetic Association (2009) added that HbA1c ≥ 6.5% is another criterion for the diagnosis of diabetes (Nathan, 2009). Therefore we highly recommend the measurement of HbA1c during pregnancy, as an additional diagnostic criteria and to anticipate the maternal and fetal complications if it is abnormally elevated.

4. Pathophysiology of GDM

In the pathophysiology of GDM we have to consider two main points.
4.1 Role of feto-placental unit in GDM.
4.2 Role of the adipose tissue in GDM.

4.1 The role of feto-placental unit in the development of GDM

The past; In the last century insulin resistance and the decrease in insulin sensitivity during pregnancy is mainly attributed to the increase in the levels of **pregnancy-associated hormones** as estrogen, progesterone, cortisol, and placental lactogen in the maternal circulation (Ryan, 1988; Hornns, 1985; Ahmed & Shalayel, 1999; Polderman et al., 1994; Barbour et al., 2002). Normally the insulin resistance of the whole body is increased to about three times that seen in the non-pregnant state (Kuhl, 1998; Catalano et al., 1999). The increased resistance is caused by post-insulin receptor events and is probably brought about by the cellular effects of the increased levels of one or all of the above hormones (Davis, 1990). As pregnancy progresses and the placenta grow larger, hormone production also increases and so does the level of insulin resistance. This process usually starts between 20 and 24 weeks of pregnancy. At birth, when the placenta is delivered, the hormone production stops and so does the condition, strongly suggesting that these hormones cause GDM (Ryan & Enns, 1988; Kuhl, 1975; Buchanan & Xiang, 2005).

4.1.1 Feto-placental unit

The placenta synthesizes pregnenolone and progesterone from cholesterol. Some of the progesterone enters the fetal circulation and provides the substrate for the formation of cortisol and corticosterone in the fetal adrenal glands. Some of the pregnenolone enters the fetus and, along with pregnenolone synthesized in the fetal liver, is the substrate for the formation of dehydroepiandrosterone sulfate (DHEAS) and 16-hydroxydehydroepiandrosterone sulfate (16-OHDHEAS) in the fetal adrenal. Some 16-hydroxylation also occurs in the fetal liver. DHEAS and 16-OHDHEAS are transported back to the placenta, where DHEAS forms estradiol and 16-OHDHEAS forms estriol. The principal estrogen formed is estriol, and since fetal 16-OHDHEAS is the principal substrate for the estrogens, the urinary estriol excretion of the mother can be monitored as an index of the state of the fetus (Ganong, 2003).

4.1.2 Diabetic action of steroid hormones (cortisol, estrogen, and progesterone)

These hormones are increased steadily with the advance of pregnancy. The anti-insulin action of these hormones is a well known fact since the last century (Ryan & Enns, 1988;

Barbour et al., 2002; Barbieri, 1999; Kirwan et al., 2002; Shalayel et al., 2010). The fetus and the placenta interact in the formation of these steroid hormones. It has been shown that the increase in **cortisol** level during pregnancy is considered as the main hormone which cause decrease in glucose tolerance in normal pregnancy (Hornns, 1985; Ahmed & Shalayel, 1999). While others considered that **estrogen** and **progesterone** which are elevated steadily during pregnancy are the main hormones which influence beta cell function in early pregnancy and insulin resistance especially in late pregnancy (Ryan & Enns, 1988; Polderman et al., 1994; Glass & Kase, 1984).

Although some scientists have considered that human chorionic gonadotropin (HCG) may participates in the development of insulin resistance during pregnancy as it shows higher level in women with GDM in comparison with normal pregnancies (Merviel et al., 2001). But, as we know from the normal changes during pregnancy, the main increase of HCG occurs during the first trimester, and this period is associated with an increase in insulin sensitivity and improvement of glucose tolerance. Therefore, we consider that HCG has no direct role as a cause of GDM.

4.1.3 Human placental lactogen (hPL), [human chorionic somatomammotropin (hCS)]

It is a single polypeptide chain held together by disulphide bonds. It is about 96% similar to human growth hormone (HGH), but has only 3% of HGH activity. Its half life is short (15minutes); hence its appeal as an index of placental problems (Glass & Kase, 1984). HPL, which is the product of the HPL-A and HPL-B genes, is secreted into both the maternal and fetal circulations after the sixth week of pregnancy (Handwerger & Freemark, 2000). The level of HPL in the maternal circulation is correlated with fetal and placental weight, plateauing in the last 4 weeks of pregnancy. Therefore, measurement of HPL levels is used as a screening test for fetal distress and neonatal asphyxia (Glass & Kase, 1984; Letchworth & Chard, 1972).

4.1.3.1 Physiologicalfunction of HPL

During pregnancy the maternal level of HPL can be altered by changing the circulating level of glucose. HPL is elevated with hypoglycemia and depressed with hyperglycemia (Barbour et al., 2002; Kuhl, 1998). The metabolic role of HPL is to mobilize lipids and free fatty acids. In the fed state, there is abundant glucose available, leading to increased insulin level, lipogenesis, and glucose utilization. This is associated with decreased gluconeogenesis, and a decrease in the circulating free fatty acid levels, as the free fatty acids are utilized in the process of lipogenesis to deposit storage packets of triglycerides (Glass & Kase, 1984; Kim & Feling, 1971).

4.1.3.2 Diabetogenic action of HPL

In the second half of pregnancy, HPL level rises approximately 10 folds. HPL stimulates lipolysis leading to an increase in circulating free fatty acids in order to provide a different fuel for the mother so that glucose and amino acids can be conserved for the fetus. The increase in free fatty acid levels, in turn directly interferes with insulin-directed entry of glucose into cells. Therefore, HPL is considered as a potent antagonist to insulin action during pregnancy (Glass & Kase, 1984; Mills et al., 1985). Furthermore, HPL and placental growth hormone act in concert in the mother to stimulate insulin-like growth factor (IGF) production and modulate intermediary metabolism, resulting in an increase in the availability of glucose and amino acids to the fetus (Handwerger & Freemark, 2000).

4.1.4 Placental growth hormone (PGH)

PGH is the product of the GH-V gene specifically expressed in the syncytiotrophoblast layer of the human placenta. PGH (20-kDa HGH-V) differs from pituitary growth hormone by 13 amino acids. It has high somatogenic and low lactogenic activities (Lacroix et al., 2002). PGH is produced by the placenta and found predominantly in the maternal circulation. It progressively replaces pituitary growth hormone (hGH) in the human maternal circulation from mid-gestation onwards, peaking towards term (Chellakooty et al., 2004). PGH appears to be an important potential regulator of maternal insulin resistance in human pregnancy and may influence fetal growth both by modifying substrate availability and through paracrine actions in the placental bed (McIntyre et al., 2009).

Barbour et al (2004) demonstrated a unique mechanism of insulin resistance in non-pregnant transgenic mice and suggested that human placental growth hormone (hPGH) may contribute to the insulin resistance of normal pregnancy secondary to its effect on p85α expression and its interference with PI 3-kinase activity in skeletal muscle.

Nevertheless, in a recent experimental study by Vickers and Gilmour (2009), it was demonstrated that rats treated with HGH enhanced insulin sensitivity and suggested that HGH have an antidiabetic action.

It seems that there is a controversy about the involvement of HGH with insulin resistance and GDM.

In conclusion, considering the previously discussed hormones, HPL is considered as the main diabetogenic hormone synthesized and released from the feto-placental unit. But during pregnancy, there is another maternal hormone which is involved in insulin resistance which is prolactin.

4.1.5 Prolactin

Prolactin level begins to rise at 5-8 weeks of gestation, followed by a progressively increase in its level as pregnancy advances (Shalayel et al., 2010; Glass & Kase, 1984). The increase in prolactin secretion is due the increase in the size and number of maternal pituitary lactotrophs (Kuhl et al., 1985) and its secretion from the uterine decidual cells seems to be stimulated by progesterone and insulin (Ahmed & Shalayel, 1999; Davis, 1990).

Shalayel et al (2010) revealed that prolactin increases progressively as pregnancy advances, reaching a peak in the third trimester when many pregnant ladies may develop gestational diabetes due to the state of insulin resistance which may occur although there is no evidence that prolactin may be directly incorporated with the pathogenesis of glucose intolerance in pregnancy. A decline in insulin secretion may lead to a decline in prolactin since insulin stimulates both acute secretion and de novo synthesis of decidual prolactin.

There were no significant differences in the level of plasma prolactin in normal or diabetic pregnancies; in fact its level might be lower in the pregnancies with GDM (Guyton & Hall, 2006). Therefore, prolactin might have no effect on glucose intolerance during pregnancy (Milasinovic et al., 1997).

4.2 The role of adipose tissue in the development of GDM

4.2.1 Adipocytokines

Historically, placental hormones have been considered as the primary mediators of insulin resistance during gestation. Over the past decade, adipose tissue has been shown to produce numerous factors (adipocytokines), most of them act as hormones. These adipocyte-derived hormones have been implicated in the regulation of maternal metabolism and gestational insulin resistance. Adipocytokines, including leptin, adiponectin, tumor necrosis factor

alpha, interleukin-6, as well as the newly discovered resistin, visfatin, and apelin, are also known to be produced within the intrauterine environment (Catalano, 2010; Briana & Malamitsi-Puchner, 2009; Henry & Clarke, 2008).

Although human placental lactogen has often been cited as the cause of the decreased insulin sensitivity in pregnancy, because of its production from the placenta and increasing concentrations with advancing gestation as described previously (Ryan & Enns, 1988), more recently the role of adipocytokines and elevated lipid concentrations in pregnancy have been correlated with the longitudinal changes in insulin sensitivity in non-pregnant women (Hotamisligil et al., 1994) as well as in pregnant women (Kirwan et al., 2002; Hotamisligil et al., 1996). Evidence suggests that one or more of these adipokines (as TNF-α and leptin) could impair insulin signaling and cause insulin resistance (Briana & Malamitsi-Puchner, 2009; Xiang et al., 1999). TNF-α in specific has a potential effect in decreasing insulin sensitivity (Catalano, 2010). While other adipocytokines might increase insulin sensitivity as adiponectin which has been shown to be decreased especially in late pregnancy (Al-Noaemi & Shalayel, 2009).

4.2.1.1 Adiponectin

Adiponectin is a novel adipocyte secreting protein hormone discovered in 1995/1996 (Scherer et al., 1995; Nakano et al., 1996; Maeda et al., 1996; Hu et al., 1996; Tsao et al., 2002). Adiponectin is abundant in the circulation of humans, with plasma levels in the microgram per ml range, thus accounting for approximately 0.01% of total plasma protein.

Chen *et al.* (2006) reported that the human placenta produces and secretes adiponectin and that adiponectin and its receptors are differentially regulated by cytokines and their expression altered in women with gestational diabetes mellitus, suggesting that adiponectin may play a role in adapting energy metabolism at the materno-fetal interface.

4.2.1.1.1 Functions of Adiponectin

Although the physiological role of adiponectin is not yet fully determined, but it has been shown that there are a variety of physiological functions induced by adiponectin such as:

4.2.1.1.1.A General functions

i. Anti-atherosclerotic action: By inhibiting lipid-laden foam cell formation (Ouchi et al., 2001), and inhibiting the inflammatory adipokine, tumor necrosis factor-α (TNF-α) (Ouchi et al., 2000).
ii. Anti-inflammatory action: By inhibiting the phagocytic activity of macrophages and inhibiting the production of TNF-α by these macrophages (Yokota et al., 2000).
iii. Anti-oxidant action: By stimulating the endothelial cells to produce nitric oxide (NO) (Ouchi et al., 1999).
iv. Anti-tumor action: There is a significant inverse association of adiponectin with postmenopausal endometrial and breast cancer (Mantzoros et al., 2004; Petridou et al., 2003).

4.2.1.1.1.B Specific anti-diabetic functions such as its actions on glucose and lipid metabolism

i. Effects of adiponectin on insulin and glucose metabolism: Adiponectin has insulin-sensitizing effects. Replenishment of a physiological dose of recombinant adiponectin to lipoatrophic mice significantly ameliorated insulin resistance. Moreover, insulin resistance in lipoatrophic mice was completely reversed by the combination of physiological doses of adiponectin and leptin (Hotta et al., 2000; Berg et al., 2001). In

addition to that, adiponectin has indirect insulin-sensitizing effect by decreasing tissue triglyceride (TG) content (Shulman, 2000). It is well known that tissue triglycerides interfere with insulin-stimulated phosphatidylinositol (PI) 3-kinase activation and subsequent glucose transporter 4 (GLUT-4) translocations and glucose uptake, leading to insulin resistance (Shulman, 2000; Godoy-Matos et al., 2010). Thus, decreased tissue TG content in muscle may contribute to the improved insulin signal transduction. Interestingly, in skeletal muscle, adiponectin increases expression of molecules involved in fatty acid transport such as CD36, in combustion of fatty-acid such as acyl-coenzyme-A oxidase, and in energy dissipation such as uncoupling protein 2. These changes led to decreased tissue TG content in skeletal muscle whether in experimental animals or in human (Godoy-Matos et al., 2010; Yamauchi et al., 2001; Thamer et al., 2002).

ii. Effect of adiponectin on glucose metabolism: It has been reported that an acute increase in circulating adiponectin levels triggers a transient decrease in basal glucose levels by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in both wild-type mice and a type 2 diabetic mouse model (Berg et al., 2001; Combs et al., 2001). Furthermore, Kubota et al (2002) provided the first direct evidence that adiponectin plays a protective role against insulin resistance by generating adiponectin-deficient mice. Adiponectin improves insulin resistance and glucose tolerance in both heterozygous (+/-) and homozygous (-/-) adiponectin-deficient mice.

iii. Effects of adiponectin on lipid metabolism: Adiponectin activates AMP-Kinase (AMPK) and peroxisome proliferator-actvated receptor (PPAR α) in the liver and muscle, thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver and muscle (Thamer et al., 2002; Fruebis et al., 2001; Yamauchi et al., 2003a). Furthermore, adiponectin decreases lipid synthesis and glucose production in the liver and causes a decrease in glucose and fatty acid concentration in the blood (Meier & Gressner, 2004; Yool et al., 2006).

4.2.1.1.2 Adiponectin and the pathophysiology of obesity and diabetes

Many studies have shown that plasma adiponectin concentration is negatively correlated with body mass index (BMI) and accordingly, lower in obese than in lean subjects (Ouchi et al., 1999; Hotta et al., 2000; Pena et al., 2009). Furthermore, scientists extended these finding by demonstrating that plasma adiponectin concentrations are inversely related to percentage of body fat, a direct measure of adiposity. And that is consistent across different ethnic groups. These results thus confirm that adiponectin is the main adipose-specific protein known to date that despite its excusive production in white adipose tissue, is negatively regulated in obesity (Hu et al., 1996; Weyer et al., 2001; Statnick et al., 2000). These scientific data suggest that adiponectin may have a role in the pathogenesis of obesity. As obesity is a predisposing factor for the development of diabetes mellitus in general and GDM in specific, this might explain the indirect involvement of a decreased adiponectin in the pathogenesis of diabetes mellitus. It has also been shown that in pregnant women there is a decrease in adiponectin which is associated with an increase in insulin resistance in the third trimester and a further decrease in women with IGT or GDM compared to pregnant women with normal glucose tolerance test, even after adjustment for varying degree of adiposity. Hypoadiponectinemia was also found in women with GDM independently of

their body fat mass compared to women with normal glucose tolerance during and after pregnancy (Yamauchi et al., 2003; Weyer et al., 2001; Kadowaki & Yamaushi, 2005).
On experimental animal studies, it was shown that adiponectin causes glucose-lowering effects and ameliorates insulin resistance in mice (Yamauchi et al., 2003b). Thus, decreased plasma adiponectin concentrations (hypoadiponectinemia) could be involved in the pathophysiology of pregnancy-driven insulin resistance and in the pathogenesis of GDM and Diabetes mellitus type 2 (DM2).
It is known that peroxisome proliferator-activated receptors (PPARs) are transcriptional factors involved in the regulation of insulin resistance, fat cell differentiation, and adipogenesis (*Joosen et al., 2006; Schoonjans et al., 1996; Zeghari et al., 2000)*. It has been shown that adiponectin activates AMP-kinase and PPARγ and α which improves insulin resistance and reduces fasting glucose level (Tsuchida et al., 2005; Kadowaki & Yamauchi, 2005). Low plasma adiponectin correlates highly with insulin resistance in obesity, type 2 DM and GDM (Weyer et al., 2001; *Worda* et al., 2004; *Cseh et al., 2004)*.
Low adiponectin level in normal pregnancy and GDM could be due to the suppression effect of TNF-α and other inflammatory factors on adiponectin transcription in adipocytes (*Bruun* et al., 2003; *Fasshauer* et al., 2003). These data highly support the antidiabetic effect of adiponectin.

4.2.1.2 Tumor necrosis factor-α (TNF-α)

In 1975 Carswell et al discovered the so-called tumor necrosis factor (TNF) which is released from macrophages and induces tumor necrosis. Increased circulating TNF-α levels have been associated with insulin resistance in obesity, aging, sepsis, muscle damage, and burn patients (Hotamisligil et al., 1996; del Aguila et al., 2000; Kirwan et al., 2001; Ling et al., 1994; Conrad et al., 1998). Obese animals and humans show a positive correlation between TNF-α levels and BMI and hyperinsulinemia (Ling et al., 1994; Clapp & Kiess, 2000; Laham et al., 1994).
Kirwan et al (2001) reported that TNF-α is a significant predictor of insulin resistance during pregnancy. Together with a small additive contribution from leptin and cortisol, TNF-α exerted a significant influence on insulin-mediated glucose disposal. Circulating TNF-α showed a downward trend during early pregnancy and increased during the third trimester, thus mirroring insulin sensitivity changes during those periods. This observation is consistent with studies showing an increase in plasma TNF-α in late pregnancy (Kirwan et al., 2002; Clapp & Kiess, 2000; Boyd et al., 2007). TNF-α correlates inversely with insulin secretion in normal pregnancy and was significantly higher in GDM group (McLachlan et al., 2006).
TNF-alpha mRNA and protein are present in human placenta and uterine cells at both early and late stages of gestation (Chen et al., 1991). In maternal obesity, the level of TNF-α is increased in the placenta compared with the non-obese pregnant women (Denison et al., 2010). Furthermore, it has been shown that placenta and subcutaneous adipose tissues obtained from women with GDM release greater amount of TNF-α in response to high glucose compared with normal glucose. On the other hand, there was no stimulatory effect of high glucose on TNF-α release by tissues obtained from normal pregnant women which suggests that TNF-α might be involved in the pathogenesis and /or progression of GDM (Coughlan et al., 2001). These results could highly explain the increase in the level of TNF-α throughout pregnancy. The increased TNF-α levels in pregnancy fall rapidly after delivery (Kirwan et al., 2002; Uvena et al., 1999), which is consistent with the idea that the increase in

circulating TNF-α during late pregnancy is mainly due to placental secretion. These findings may also help to explain the rapid reversal of insulin resistance after delivery, since maternal levels of TNF-α decrease substantially after delivery of the placenta (Kirwan et al., 2002; Coughlan et al., 2001).

4.2.1.2.1 The Diabetogenic action of TNF-a

In-vitro studies have described a direct role for TNF-α in the pathophysiology of insulin resistance. TNF-α downregulates insulin receptor signaling in cultured adipocytes (Catalano, 2010), hepatocytes (Feinstein et al., 1993), and skeletal muscle (del Aguila et al., 1999). TNF-α activates a pathway that increases sphingomyelinase and ceramides and appears to interfere with insulin receptor autophosphorylation (Catalano, 2010). Also it has been shown that TNF-α promotes serine phosphorylation of insulin receptor substrate (IRS)-1, thus impairing its association with the insulin receptor (Rui et al., 2001). In pregnancy, there is an evidence that insulin receptor and IRS-1 tyrosine phosphorylation are impaired, and serine phosphorylation is increased in late gestation in skeletal muscle (Friedman et al., 1999; Shao et al., 2000). Therefore, it seems that elevated levels of TNF-α in late gestation could attenuate insulin signaling, thus causing the decreased insulin sensitivity observed in pregnancy.

Barbour et al (2007) demonstrated that in skeletal muscle there is 40% decrease in glucose entrance in normal pregnant women and 65% decrease in GDM compared with obese pregnant women. Although there is no decrease in GLUT4 protein transporter in skeletal muscle (Garvey et al., 1992), the GLUT4 transporters are decreased in adipose tissue (Garvey & Birnbaum, 1993). The increase in circulating TNF-α in women with GDM is also associated with an increased TNF-α in the skeletal muscle and the impaired insulin signaling persist in obese women with gestational diabetes mellitus up to one year postpartum (Kirwan et al., 2004).

TNF- α is considered as one of the factors which suppress PPAR-γ (Kirwan et al., 2002). Furthermore, it has been shown that TNF-α downregulates PPAR-γ expression in 3T3-L1 cells and can inhibit adipose differentiation (Zhang et al., 1996).

Catalano et al (2002) observed a decrease in steady-state PPARγ mRNA and protein concentration in normal and GDM subjects during late gestation. Furthermore, it has been demonstrated that TNF-α decreases adiponectin gene expression in human adipocytes (Kappes & Loffler, 2000), and 3t3-L1 adipocytes (Fasshauer et al., 2002). Whereas thiazolidinediones (synthetic PPAR-gamma ligand) significantly increases the plasma adiponectin concentrations in insulin resistant humans and rodents without affecting their body weight, suggesting that the anti TNF-α will restore the adiponectin and improve the insulin sensitivity (Maeda et al., 2005).

Thus the increase in TNF-α whether in subjects with normal pregnancy or with GDM might explain the lower level of adiponectin (insulin-sensitizing hormone). The above data highly suggest the involvement of TNF-α in the development of GDM.

4.2.1.3 Resistin

Steppan et al. (2001) showed that adipocytes secrete a unique signalling molecule, which is considered as a hormone and named 'resistin' (for resistance to insulin). Resistin is a 114-amino acid polypeptide hormone (Doshani & Konje, 2009).

There is a great argument about the involvement of resistin in the pathogenesis of diabetes mellitus. Some scientists reported the involvement of resistin in the pathogenesis of diabetes mellitus relying on their studies that revealed strong correlations between resistin and obesity as serum resistin levels increased with increased adiposity (Steppan et al., 2001; Vendrell et al.,

2004; Lee et al., 2005). Conversely, serum resistin levels have been found to decline with decreased adiposity following medical treatment (Valsamakis et al., 2004). This discovery is further authenticated by studies which confirmed a direct correlation between resistin levels and subjects with type 2DM (Steppan et al., 2001; Fujinami et al., 2004; McTernan et al., 2003). Nevertheless, this theory lacks support from the entire scientific community at large as an increasingly greater number of studies presenting contradictory evidences continue to emerge (Lee et al., 2003; Nagaev & Smith, 2001). Some studies found significant decreased serum concentrations of resistin with increased adiposity (Heilbronn et al., 2004; Way et al., 2001) suggesting that not only resistin is downregulated in obese subjects but that it also presents itself as an unlikely candidate for linking obesity to Type 2DM. Milan et al (2002) mentioned that a decrease of resistin mRNA after weight loss does not support the hypothesis that resistin may play a causative role in insulin resistance in obese rats.

Many studies reported that in patients with type 2 diabetes or obesity, both resistin levels and resistin expression in fat cells are increased, correlating with hepatic, but not muscle, insulin resistance. In humans, the major source of resistin is the immune cells rather than the adipocytes, resistin being a potent inflammatory agent. Insulin inhibits resistin expression in adipocytes. Therefore, the elevated basal plasma resistin levels found in patients with type 2 diabetes, despite increased insulin concentrations, may be the result of adipocyte insulin resistance. Resistin inhibits the phosphorylation of hepatic AMPK, decreasing β oxidation and increasing fatty acid esterification in triglycerides, and eventually leading to lipid accumulation (Maiorana et al., 2007).

4.2.1.4 Leptin

It was discovered as an antiobesity hormone in *ob/ob* mice (Zhang et al., 1994). In human adult, the white adipose tissue is the main source of leptin, and its circulating concentration is positively correlated with body mass index and fat mass (Maffei et al., 1995; Hellstrom et al., 2000).

Leptin has been detected in the placenta (Masuzaki et al., 1997), and shown to be increased in early pregnancy, remained elevated in late pregnancy (Kirwan et al., 2002; Highman et al., 1998), and was highest in the more obese GDM group (Kirwan et al., 2002). The increased leptin during pregnancy is not proportional with the change in adipose tissue mass, and it return to the normal level after delivery suggesting that leptin production by the placenta contributes to maternal leptinemia during pregnancy (Lepercq et al., 2001).

In vitro study on muscle, Muoio et al (1997) demonstrated that leptin attenuated both the antioxidative and the lipogenic effects of insulin by 50%. Cseh K et al (2002) suggested that the increased TNF-alpha and leptin levels may contribute to insulin resistance in GDM and in the third trimester of normal pregnancy. Furthermore, Qiu et al (2004) demonstrated that Hyperleptinemia, independent of maternal adiposity, in early pregnancy appears to be predictive of an increased risk of GDM later in pregnancy. Kirwan et al (2002) reported that leptin was increased in all women in early pregnancy, remained elevated in late pregnancy, and was highest in the more obese GDM group. But to adjust for the possible confounding effect of obesity and increased fat mass on the relationship between leptin and insulin sensitivity, they covaried for body fat and found that the correlation was no longer significant, because the increased leptin per se was not predictive of insulin sensitivity. They interpreted that, in addition to insulin resistance, leptin resistance may also develop in late pregnancy.

Chen et al (2010) carried out a study in which twenty women with normal pregnancy and 20 with GDM were recruited and blood samples were taken on the day of delivery and Days 1, 3 and 5 after delivery. Serum leptin levels were significantly higher in women with GDM than in the controls before delivery and decreased significantly after delivery ($p < 0.001$). After delivery there were no significant differences in serum leptin concentrations between women with GDM and the controls. Serum soluble leptin receptor concentrations did not differ neither between the two groups, nor before or after delivery. Thus, they concluded that Leptin may play a role in GDM through a positive correlation with insulin resistance.

4.2.1.5 Visfatin

Fukuhara et al (2005) isolated a newly adipocytokine, named as 'visfatin', which is highly enriched in the visceral fat of both humans and mice and whose expression level in plasma increases during the development of obesity. Visfatin exerted insulin-mimetic effects in cultured cells and lowered plasma glucose levels in mice by binding and activating the insulin receptors. Suggesting that visfatin's physiological role may lead to new insights into glucose homeostasis and/or new therapies for metabolic disorders such as diabetes.

According to some authors, plasma concentrations of visfatin are elevated in obesity (Berndt et al., 2005), type 2 diabetes (Chen et al., 2006) and the increase is typically observed in GDM (Krzyzanowska et al., 2006; Lewandowski et al., 2007), all of which are states characterized by insulin resistance. There are also, however, data pointing to possible lower visfatin levels in obese subjects (Pagano et al., 2006), similarly, Chan et al. (2006) have reported lower visfatin levels in women of Chinese origin with GDM. The precise reason for these differences is unclear.

Shali et al (2009) reported that maternal GDM, as well as delivery of a large-for-gestational-age (LGA) neonate were independently associated with higher maternal plasma visfatin concentrations. The linkage between increased maternal circulating visfatin and the presence of GDM or delivery of an LGA neonate supports the hypothesis that perturbation of adipokines homeostasis may play a role in the pathophysiology of GDM or excess fetal growth.

The current data regarding the relationship between visfatin and insulin sensitivity in humans are conflicting. Some authors report a lack of correlation (Berndt et al., 2005; Pagano et al., 2006; Zhang et al., 2010), while others observed a significant correlation (Chen et al., 2006; Lewandowski et al., 2007).

The role of visfatin in human physiology and pathophysiology remains to be elucidated and further work is needed to establish the exact function of visfatin and its mode of action on insulin resistance during normal pregnancy and GDM.

4.2.1.6 Apelin

Tatemoto et al (1998) isolated an APJ receptor ligand, designated apelin, from bovine stomach extracts. The preproproteins consisted of 77 amino acid residues, and the apelin sequence was encoded in the C-terminal regions indicating that apelin is an endogenous ligand for the APJ receptor.

Apelin has been described as an adipocyte-secreted factor (adipokine), that is up-regulated in obesity and the expression of apelin gene in adipose tissue is reported to increase by insulin and TNF-α (Carpéné et al., 2007). Apelin synthesis in adipocytes is stimulated by insulin, and plasma apelin level markedly increases in obesity associated with insulin resistance and hyperinsulinemia (Bełtowski, 2006).

Dray et al (2010) reported that apelin is increased in adipose tissue in different mice models of obesity and in the type2 diabetic patients. They reported that apelin plasma levels were significantly increased in type 2 diabetic patients. They suggested that apelin and APJ expression in mice and humans are regulated in a tissue dependent manner and according to the severity of insulin resistance. But, Meral et al (2010) reported that no significant relation was found between apelin and BMI, glucose, lipids levels, and also insulin sensitivity. In addition, Telejko et al (2010) reported that there is no associations between circulating apelin or apelin/APJ mRNA expression and GDM and no indices of insulin resistance were noted in their study. Furthermore, Tapan et al (2010) recently reported a significant decrease in plasma apelin and adiponectin levels in pubertal obese children.
More work is needed to establish the involvement/or not of apelin and insulin resistance in normal pregnancy and GDM.

5. The future

Every now and then, there will be a new factor, hormone, adipocytokine, etc. which is involved in the development of insulin resistance and GDM. But the precise pathophysiological mechanisms which make the women unable to balance insulin needs and develop GDM, remain unknown. However, a number of future studies could explain some of these mechanisms.

5.1 Genotyping

Genetic variants might be involved in the defect in B-cell function and/or subcellular insulin signaling which contribute to the development of GDM. Therefore, we suggest a screening genotyping test for a significant number of pregnant women, to identify any genetic variants in those who develop GDM. Extending this genotyping to involve familial studies, to demonstrate any involvement of these genetic variants and whether they run in families. Any positive result will help to give a special care to those women anticipated to develop GDM, and thus reducing the associated maternal or fetal complications.

5.2 Subcellular studies

Certain studies should be done to identify the exact subcellular reactions in the normal insulin resistance that develop during normal pregnancy compared with those subcellular changes that lead to glucose intolerance and GDM. The use of radioactive substances might help to identify the change in phosphorylation of serine instead of tyrosine residues, or in any other subcellular reaction change which occurs in GDM.

5.3 Autoimmunity

To study certain aspects of the immune system, which could demonstrate any B-cell dysfunction that develops GDM and is related to autoimmunity. Furthermore, if there is any interference of the immune system with insulin-receptor interaction, this might contribute to the development of GDM.

5.4 Environmental and diet factors

30-40 years ago or more, it has been reported that the percent of GDM range from 1-2%, 2-3% then the percent increased to 1-4%, 2-7%, 5-10%. Until recently using 1-hour glucose

challenge OGTT had demonstrated that up to 17% of pregnant women develop GDM. That means there is a significant increase in the development of GDM in these days. Could there be more in future? Environmental factors, changes in life style, and change of diet, such as decrease in using fresh diet while increase in using canned food, in addition to the use of high caloric diet and food with high glycemic index. All these factors, could highly participate in the development of GDM whether directly or indirectly by increasing the incidence of obesity.

6. Conclusions

The precise mechanisms causing GDM remain unknown. All the previously described maternal and feto-placental factors interact in an integrated manner in the development of insulin resistance and GDM. The most prominent factors, which are involved in the pathogenesis of GDM, are the increase in HPL and TNF-α and the decrease in adiponectin during pregnancy.

Most of the women reverting to normal after delivery, will suggest that the placenta is the major contributing organ in the development of GDM.

The main cause of insulin resistance during GDM is post-cellular defect manifested by a decreased phosphorylation of tyrosine residues in insulin receptors and insulin receptor substrate-1, while serine phosphorylation is increased which inhibit insulin signaling from activating GLUT4 translocation.

Finally, GDM is probably produced by a complex and variable interaction of all the previously mentioned factors - pregnancy-induced factors, genetic, diet, environmental, autoimmunity, etc.

7. References

Ahmed SA, Shalayel MH. (1999). Role of cortisol in the deterioration of glucose tolerance in Sudanese pregnant women. *East Afr Med J*, 76(8):465-7.

Al- Dahwi AN, Al-Noaemi M, Alwan AAS, Al-Dahwi RN and Al-Taie ID. (1987) Glycosylated hemoglobin as an index for maternal and fetal complications. Abstract submitted in the first scientific congress of the Iraqi Society for obstetrics and gynecology. Baghdad, Iraq.

Al-Dahwi AN, Al-Noaemi M, Alwan AAS, et al. (1988). Glycosylated haemoglobin in normal and diabetic pregnancies. *Iraqi Medical Journal*, 37 (2): 68-371.

Al-Dahwi AN, Al-Noaemi M, Alwan AAS, et al. (1986). Glycosylated hemoglobin in diabetic Pergnancy. Abstract submitted in the first scientific congress of Al- Mustansiryah Medical College. Baghdad, Iraq.

Al-Dahwi RN, Alwan AAS, Al-Noaemi M and Al-Dahwi AN. (1989). Clinical experience with fifty pregnancies in diabetic patients Abstract submitted to the 4th congress of the Mediterranean Medical Association. Tunis 10-13th September 1989. Tunisia.

Al-Noaemi M and Shalayel MHF. (2009). Adiponectin (review article). *Sudan Journal of Medical Sciences*, 4 (30): 297-305.

Baker P N (2006) Physiology of pregnancy In: *Obstetrics by ten teachers* (18th Edition), pp 48-62. A Hodder Arnold Publication. ISBN: 0340816651.

Barbieri RL (1999) Endocrine disorders in pregnancy In: *Reproductive Endocrinology* (4th edition). Yen SSC, Jaffe RB, Barbieri RL, Eds. Philadelphia, W.B. Saunder.

Barbour LA, Carrie E. McCurdy, Teri L. Hernandez, John P. Kirwanet et al. (2007). Cellular Mechanisms for Insulin Resistance in Normal Pregnancy and Gestational Diabetes. *Diabetes Care,* 30 (2): S112-S119.

Barbour LA, Shao J, Qiao L, et al. (2002). Human placental growth hormone causes severe insulin resistance in transgenic mice. *Am J Obstet Gynecol,* 186: 512–517.

Barbour LA, Shao J, Qiao L, et al. (2004). Human Placental Growth Hormone Increases Expression of the P85 Regulatory Unit of Phosphatidylinositol 3-Kinase and Triggers Severe Insulin Resistance in Skeletal Muscle. *Endocrinology,* 145 (3): 1144-1150.

Bełtowski J. (2006). Apelin and visfatin: unique "beneficial" adipokines upregulated in obesity? *Med Sci Monit*, 12(6): RA112-9.

Berg AH, Combs TP, Du X et al. (2001). The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med*, 7: 947-953.

Berndt J, Kloting N, Kralisch S et al. (2005). Plasma visfatin concentrations and fat-specific mRNA expression in humans. *Diabetes*, 54:2911–2916

Boyd E. Metzger, Thomas A. Buchanan, Donald R. Coustan, et al. (2007). Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*, 30 (2) S251-S260.

Briana DD, Malamitsi-Puchner A. (2009). Reviews: adipocytokines in normal and complicated pregnancies. *Reprod Sci*., 16(10):921-37.

Bruun JM, Lihn AS, Verdich C, et al. (2003). Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol Endocrinol Metab.,* 285*:* E527–E533.

Buchanan TA, Xiang AH. (2005). Gestational diabetes mellitus. *J. Clin Invest*., 115: 485-491.

Carpéné C, Dray C, Attané C, et al. (2007). Expanding role for the apelin/APJ system in physiopathology. *J Physiol Biochem*., 63 (4): 359-73.

Carr DB, and Gabbe S. (1998). Gestational Diabetes: Detection, Management, and Implications. *Clinical diabetes*, 16: 5-19.

Carswell, E. A., Old, L. J., Kassel, R. L., et al. (1975). An endotoxin-induced serum factor that causes necrosis of tumors. *Proc. Natl. Acad. Sci. U. S. A*., 72, 3666-3670.

Catalano PM, Huston L, Amini SB, Kalhan SC. (1999). Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus*. Am J Obstet Gynecol.*, 180:903–916.

Catalano PM, Nizielski SE, Shao J, et al. (2002). Downregulated IRS-1 and PPARgamma in obese women with gestational diabetes: relationship to FFA during pregnancy. *Am J Physiol Endocrinol Metab*., 282:E522–E533.

Catalano PM, Tyzbir ED, Roman NM, et al. (1991). Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol.*, 165: 1667-1672.

Catalano PM, Tyzbir ED, Wolfe RR, et al. (1993). Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol Endocrinol Metab.,* 264*:* E60–E67.

Catalano PM, Tyzbir ED, Wolfe RR, et al. (1992). Longitudinal changes in basal hepatic glucose production and suppression during insulin infusion in normal pregnant women. *Am J Obstet Gynecol* , 167:913–9

Catalano PM. (2010). Obesity, insulin resistance, and pregnancy outcome. Focus Review on Obesity. *Reproduction*, 140: 365-371

Chan TF, Chen YL, Lee CH et al. (2006). Decreased plasma visfatin concentrations in women with gestational diabetes mellitus. *J Soc Gynecol Investig*., 13: 364–367.

Chellakooty M, Vangsgaard K, Larsen T, et al. (2004). A longitudinal study of intrauterine growth and the placental growth hormone (GH)-insulin-like growth factor I axis in maternal circulation: association between placental GH and fetal growth. *J Clin Endocrinol Metab*., 89: 384–391.

Chen D, Xia G, Xu P, Dong M. (2010). Peripartum serum leptin and soluble leptin receptor levels in women with gestational diabetes. *Acta Obstetrica et Gynecologica Scandinavica,* 89(12): 1595-1599.

Chen H, Yang Y, Hu X, et al. (1991). Tumor necrosis factor alpha mRNA and protein are present in human placental and uterine cells at early and late stages of gestation. *Am J Pathol*., 139: 327–335.

Chen J, Tan B, Karteris E, et al. (2006). Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. *Diabetologia,* 49(6): 1292-1302.

Chen MP, Chung FM, Chang DM et al. (2006). Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*., 91:295–299.

Clapp JF, Kiess W. (2000). Effects of pregnancy and exercise on concentrations of the metabolic markers tumor necrosis α and leptin. *Am J Obstet Gynecol*, 182: 300–306.

Combs TP, Berg AH, Obici S et al. (2001). Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest*, 108: 1875-1881.

Conrad KP, Miles TM, Fairchild Benyo D. (1998). Circulating levels of immunoreactive cytokines in women with preeclampsia. *AJRI*, 40:102–111.

Coughlan MT, K. Oliva, H. M. Georgiou, et al. (2001). Glucose-induced release of tumour necrosis factor-alpha from human placental and adipose tissues in gestational diabetes mellitus. *Diabetic Medicine*, 18 (11):921-927.

Cseh K, Baranyi E, Melczer Z, et al. (2002). 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. *Gynecol Endocrinol*., 16 (6): 453-460.

Cseh K, Baranyi E, Melczer Z, et al. (2004). Plasma adiponectin and pregnancy-induced insulin resistance. *Diabetes Care,* 27:274–275.

Davis JRE. (1990). Prolactin and related peptides in pregnancy. *Bailliere's Clinical Endocrinology and Metabolism*, 4: 273-285.

Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia (2006). *World Health Organization*. www.who.int. http://www.who.int/diabetes/publications/Definition and diagnosis of diabetes_new.pdf. Retrieved 2011-02-20.

del Aguila LF, Claffey KP, Kirwan JP (1999). TNF-α impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells. *Am J Physiol*, 276: E849–E855.

del Aguila LF, Krishnan RK, Ulbrecht JS, et al. (2000). Muscle damage impairs insulin stimulation of IRS-1, PI3-kinase, and Akt-kinase in human skeletal muscle. *Am J Physiol*., 279: E206–E212.

Denison FC, RobertsKA, Barr SM and Norman JE. (2010). Obesity, pregnancy, inflammation, and vascular function. *Reproduction*, 140: 373-385.

Doshani A and Konje JC. (2009). Review: Diabetes in pregnancy: insulin resistance, obesity and placental dysfunction. *British Journal of Diabetes & Vascular Disease*, 9(5): 208 - 212.

Dray C, Debard C, Jager J, et al. (2010). Apelin and APJ regulation in adipose tissue and skeletal muscle of type 2 diabetic mice and humans. *Am J Physiol Endocrinol Metab.*, 298(6): E1161-9.

Fasshauer M, Klein J, Neumann S, et al. (2002). Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. *Biochem Biophys Res Commun.*, 290: 1084-1089.

Fasshauer M, Kralisch S, Klier M, et al. (2003). Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3–L1 adipocytes. *Biochem Biophys Res Commun.*, 301:1045–1050.

Feinstein R, Kanety H, Papa MZ, Lunefeld B, Karasik A. (1993). Tumor necrosis factor-alpha suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates. *J Biol Chem.*, 268:26055–26058.

Friedman JE, Ishizuka T, Shao J, et al. (1999). Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes. *Diabetes*, 49:1807–1814.

Fruebis J, Tsao TS, Javorschi S et al. (2001). Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci U S A*, 98:2005-10.

Fujinami A, Obayashi H, Ohta K, et al. (2004). Enzyme-linked immunosorbent assay for circulating human resistin: resistin concentrations in normal subjects and patients with type 2 diabetes. *Clin. Chim. Acta.*, 339 (1-2): 57–63.

Fukuhara A, Matsuda M, Nishizawa M et al. (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science*, 307: 426–430.

Ganong WF (2003) Review of Medical Physiology (21st edition), pp 433-436. Lange Medical Books/McGraw-Hill Medical Publishing Division. ISBN: 0071402365.

Garvey WT, Birnbaum MJ. (1993). Cellular insulin action and insulin resistance. *Baillieres Clin Endocrinol Metab.*, 7:785–873.

Garvey WT, Maianu L, Hancock JA, et al. (1992). Gene expression of GLUT4 in skeletal muscle from insulin-resistant patients with obesity, IGT, GDM, and NIDDM. *Diabetes*, 41:465–475.

Glass R H, and Kase N G. (1984) Chapter 10: The endocrinology of pregnancy In: *Clinical Gynecology Endocrinology &Metabolism.* P271-305 (3rd edition), Leon Speroff. .

Godoy-Matos AF, Bahia LR, Dominhues RC et al. (2010). Adiponectin is related to intramyocellular lipid content in non-diabetic adults. *J Endocrinol Invest*, 33 (6): 382-7.

Guyton AC and Hall JE. (2006) Ch. 78: Insulin, Glucagon, and Diabetes, In: *Textbook of Medical Physiology* (11th edition), Guyton & Hall, pp.961-970, ELSEVIER SAUNDERS Publication. ISBN: 0-7216-0240-1.

Handwerger S, Freemark M. (2000). The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. *J Pediatr Endocrinol Metab.*, 13(4):343-56.

Hans-Georg Joost. (1995). Structural and functional heterogeneity of insulin receptors. *Cellular Signalling*, 7 (2): 85-91.

Heilbronn LK, Rood J, Janderova L, et al. (2004). Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *J. Clin. Endocrinol. Metab.*, 89 (4): 1844–8.

Hellstrom L, Wahrenberg H, Hruska K, et al. Mechanisms behind (2000). Gender differences in circulating leptin levels. *J Intern Med*., 247:457– 462.

Henry BA, Clarke IJ. (2008). Adipose tissue hormones and the regulation of food intake. *J. Neuroendocrinol*., 2: 842-9.

Highman TJ, Friedman JE, Huston LP, et al. (1998). Longitudinal changes in maternal serum leptin concentrations, body composition, and resting metabolic rate in pregnancy. *Am J Obstet Gynecol.*, 178:1010–1015.

Hornns PJ. (1985). On the decrease of glucose tolerance in pregnancy. A review. *Diabet Metab*., 11(5): 310-315.

Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. (1994). Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proc Natl Acad Sci U S A.*, 91: 4854–4858.

Hotamisligil GS, Peraldi P, Budavari A, et al. (1996). IRS-1 mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α and obesity-induced insulin resistance. *Science*, 271: 665–668.

Hotta K, Funahashi T, Arita Y et al. (2000). Plasma concentration of a novel, adipose-specific protein, adiponectin, in type2 diabetic patients. *Arteioscler Thromb Vasc Biol.* 20: 1595-9.

Hu E, Liang P, Spiegelman BM. (1996). Adipo1 is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem*., 271: 10697–10703

Joosen AM, Bakker AH, Zorenc AH, et al. (2006). PPARgamma activity in subcutaneous abdominal fat tissue and fat mass gain during short-term overfeeding. *Int J Obes (Lond),* 30*:* 302–*307.*

Kadowaki T and Yamaushi T. (2005). Adiponectin and Adiponectin Reseptors. *Endocrine Reviews*, 26: 439-451.

Kappes A and Loffler G. (2000). Influences of ionomycin, dibutyrylcycloAMP and tumour necrosis factor-alpha on intracellular amount and secretion of apM1 in differentiating primary human preadipocytes. *Horm Metab Res*., 32: 548-554.

Kim YJ, Feling P. (1971). Plasma chorionic somatomammotropin levels during starvation in mid-pregnancy. *J Clin Endocrinol Metab*, 32: 864-866.

Kirwan JP, Hauguel-De Mouzon S, Lepercq J, et al. (2002). TNF-α Is a Predictor of Insulin Resistance in Human Pregnancy. *Diabetes*, 51 (7): 2207-2213.

Kirwan JP, Krishnan RK, Weaver JA, et al. (2001). Human aging is associated with altered TNF-α production during hyperglycemia and hyperinsulinemia. *Am J Physiol.*, 281:E1137–E1143.

Kirwan JP, Varastehpour A, Jing M, et al. (2004). Reversal of Insulin Resistance Postpartum Is Linked to Enhanced Skeletal Muscle Insulin Signaling. *The Journal of Clinical Endocrinology & Metabolism*, 89(9): 4678-4684.

Krzyzanowska K, Krugluger W, Mittermayer F, et al. (2006). Increased visfatin concentrations in women with gestational diabetes mellitus. *Clin Sci*., 110: 605-609.

Kubota N, Terauchi Y, Yamauchi T et al. (2002). Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem*., 277: 25863-6.

Kuhl C, HornnesPJ, Andersen O. (1985). Etiology and pathophysiology of gestational diabetes mellitus. *Diabetes*, 34 (2): 66-70.

Kühl C. (1991). Aetiology of gestational diabetes. *Baillieres Clin Obstet Gynaecol*., 5: 279–92.

Kuhl C. (1998). Etiology and pathogenesis of gestational diabetes. *Diabetes Care*, 1 Suppl. 2:B19-26.

Kuhl C. (1975). Glucose metabolism during and after pregnancy in normal and gestational diabetic women. 1. Influence of normal pregnancy on serum glucose and insulin concentration during basal fasting conditions and after a challenge with glucose. *Acta Endocrinol (Copenh)*, 79(4):709–719.

Lacroix MC, Guibourdenche J, Frendo JL, et al. (2002). Human placental growth hormone--a review. *Placenta*, 23 Suppl A: S87-94.

Laham N, Brennecke SP, Bendtzen K, Rice GE. (1994). Tumor necrosis factor α during human pregnancy and labor: maternal plasma and amniotic fluid concentration and release from intrauterine tissues. *Eur J Endocrinol.*, 131: 607–614.

Lee JH, Bullen JW, Stoyneva VL, Mantzoros CS. (2005). Circulating resistin in lean, obese, and insulin-resistant mouse models: lack of association with insulinemia and glycemia. *Am. J. Physiol. Endocrinol. Metab.*, 288 (3): E625–32.

Lee JH, Chan JL, Yiannakouris N, et al. (2003). Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J. Clin. Endocrinol. Metab.*, 88 (10): 4848–56.

Lepercq J, Challier JC, Guerre-Millo M, et al. (2001). Prenatal leptin production: evidence that fetal adipose tissue produces leptin. *J Clin Endocrin Metabol*, 86: 2409–2413.

Letchworth AT, Chard T. (1972). Placental lactogen levels as a screening test for fetal distress and neonatal asphyxia. *Lancet*, 1(7753):704-6.

Lewandowski KC, Stojanovic N, Press M et al. (2007). Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. *Diabetologia*, 50:1033–1037.

Ling PR, Bistrian BR, Mendez B, Istfan NW. (1994). Effects of systemic infusions of endotoxin, tumor necrosis factor, and interleukin-1 on glucose metabolism in the rat: relationship to endogenous glucose production and peripheral tissue glucose uptake. *Metabolism*, 43:279–284.

Maeda K, Okubo K, Shimomura I, et al. (1996). cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1(AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun*., 221(2):286-9.

Maeda N, Funahashi TTF, Kihara S, et al. (2005). PPARγ Ligands Increase Expression and Plasma Concentrations of Adiponectin, an Adipose-Derived Protein. *Diabetes*, 50(9): 2094-2099.

Maffei M, Halaas J, Ravussin E, et al. (1995). Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med.*, 1:1155–1161.

Maiorana A, Chiara Del Bianco, Cianfarani S. (2007). Adipose Tissue: A Metabolic Regulator. Potential Implications for the Metabolic Outcome of Subjects Born Small for Gestational Age (SGA). *Rev Diabet Stud*, 4(3): 134-146.

Mantzoros C, Petridou E, Dessypris N, et al. (2004). Adiponectin and Breast Cancer Risk. *The Journal of Clinical Endocrinology & Metabolism*, 89(3): 1102-1107.

Masuzaki H, Ogawa Y, Sagawa N, et al. (1997). Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med*., 3:1029 –1113.

McIntyre HD, Zeck W, Russell A. (2009). Placental growth hormone, fetal growth and the IGF axis in normal and diabetic pregnancy. *Curr Diabetes Rev*, 5(3):185-9.

McLachlan KA, O'Neal D, Jenkins A, Alford FP. (2006). Do adiponectin, TNF alpha, leptin and CRP relate to insulin resistance in pregnancy? Studies in women with and without gestational diabetes, during and after pregnancy. *Diabetes Metab Res Rev.*, 22(2): 131-8.

McTernan PG, Fisher FM, Valsamakis G, et al. (2003). Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. *J. Clin. Endocrinol. Metab.*, 88 (12): 6098–106.

Meier U and Gressner AM. (2004). Endocrine Regulation of Energy Metabolism: Review of Pathobiochemical and Clinical Chemical Aspects of Leptin, Ghrelin, Adiponectin, and Resistin. *Clinical Chemistry*, 50: 1511-1525.

Meral C, Tascilar E, Karademir F, et al. (2010). Elevated plasma levels of apelin in children with type1 diabetes mellitus. *Journal of Pediatric Endocrinology and Metabolism*, 23(5): 497–502.

Merviel P, Muller F, Guibourdenche J, et al. (2001). Correlations between serum assays of human chorionic gonadotrophin (hCG) and human placental lactogen (hPL) and pre-eclampsia or intrauterine growth restriction (IUGR) among nulliparas younger than 38 years. *Eur J Obstet Gynecol Reprod Biol.*, 95(1): 59-67.

Metzger BE. (1991). Organizing Committee: Summary and recommendations of the Third International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes,* 40:197-201.

Milan G, Granzotto M, Scarda A, et al. (2002). Resistin and adiponectin expression in visceral fat of obese rats: effect of weight loss. *Obes. Res.*, 10 (11): 1095–103.

Milasinovic L, Djurdjevic J, Dokmanovic-Djordjevic M, et al. (1997). Prolactin levels in pregnant women with glucose intolerance at full-term delivery. *Med Pregl*, 50: 269-73.

Mills NC, Gyves MT, Ilan J. (1985). Comparisons of human placental lactogen mRNA levels from placentas of diabetics and normal term. *Mol Cell Endocrinol.*, 39(1):61-9.

Monga A and Baker P. (2006). Physiology of pregnancy, In: Obstetrics By Ten Teachers, Philip N Baker, pp 48-62, A Hodder Arnold Publication, ISBN-13: 978-0340816653.

Muoio DM, Dohm GL, Fiedorek FT, et al. (1997). Leptin directly alters lipid partitioning in skeletal muscle. *Diabetes*, 46 (8): 1360-1363.

Nagaev I, Smith U. (2001). Insulin resistance and type 2 diabetes are not related to resistin expression in human fat cells or skeletal muscle. *Biochem. Biophys. Res. Commun.*, 285 (2): 561–4.

Nakano Y, Tobe T, Choi-Miura NH, et al. (1996). Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. *J Biochem.*, 120:803–812.

Nathan DM. (2009). International Expert Committee 'in the American Diabetes Association' Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care*, 32(7): 1327–1334.

Ouchi N, Kihara S, Arita Y et al. (2000). Adiponectin, an adipocyte-derived plasma protein, inhibit endothelial TNF-a signaling through a Camp-dependent pathway. *Circulation*, 102: 1296-1301.

Ouchi N, Kihara S, Arita Y et al. (1999). Novel modulator for endothelia adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation*, 100: 2473-2476.

Ouchi N, Kihara S, Arita Y, et al. (2001). Adipocyte-derived plasma protein, suppresses lipid accumulation and class A scavenger receptor expression in human Monocyte-derived macrophages. *Circulation*, 103: 1057-1063.

Pagano C, Pilon C, Olivieri M et al. (2006). Reduced plasma visfatin/pre B-cell colony enhancing factor in obesity is not related to insulin resistance in humans. *J Clin Endocrinol Metab*, 91:3165–3170.

Pawson T. (1995). Protein modules and signalling networks. *Nature*, 373: 573–580.

Pena AS, Belobrajdic DP, Wiltshire E et al. (2009). Adiponectin relates to smooth muscle function and folate in obese children. *Int J Pediatr Obes*., 15: 1-7.

Perz M, Torlińska T. (2001). Insulin receptor--structural and functional characteristics. *Med Sci Monit*., 7(1): 169-77.

Petridou E, Mantzoros C, Dessypris N, et al. (2003). Plasma adiponectin concentrations in relation to endometrial cancer: a case control study in Greece. *J Clin Endocrinol Metab*, 88:993–997.

Polderman KH, Gooren LJ, Asscheman H, et al. (1994). Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Meta,* 79: 265–271

Qiu C, Williams MA, Vadachkoria S, et al. (2004). Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. *Obstet Gynecol*, 103(3): 519-525.

Rieck S, Kaestner KH. (2010). Expansion of beta-cell mass in response to pregnancy. *Trends Endocrinol Metab*., 21 (3): 151-8.

Rui L, Aguirre V, Kim JK, et al. (2001). Insulin/IGF-1 and TNF-α stimulate phosphorylation of IRS-1 at inhibitory Ser^{307} via distinct pathways. *J Clin Invest*., 107:181–189.

Ryan EA and Enns L. (1988). Role of Gestational Hormones in the Induction of Insulin Resistance. *J Clin Endocrinol Metab*., 67: 341-347

Scherer PE, Williams S, Fogliano M, et al. (1995). A novel serum protein similar to C1q, produced exclusively in adipocytes. *Biol Chem*., 270(45):26746-9.

Schoonjans K, Staels B, Auwerx J. (1996). The peroxisome proliferator activated receptors (PPARs) and their effects on lipid metabolism and adipocyte differentiation. *Biochim Biophys Acta.,* 1302*:* 93–*109.*

Shalayel MH, Elrobh MS, Idris SA, Mohammed MS, and Ahmed SA. (2010). Prolactin and insulin estimates in pregnancy with glucose intolerance. Pak J Med Sci, 26 (1): 102-106.

Shali MT, Roberto R, Pedro K J, et al. (2009). Visfatin in human pregnancy: maternal gestational diabetes vis-à-vis neonatal birthweight. *Journal of perinatal medicine*, 37(3): 218-31.

Shao J, Catalano PM, Yamashita H, et al. (2000). Decreased insulin receptor tyrosine kinase activity and plasma cell membrane glycoprotein-1 overexpression in skeletal muscle from obese women with gestational diabetes mellitus (GDM): evidence for increased serine/threonine phosphorylation in pregnancy and GDM. *Diabetes*, 49: 603–610.

Sherwood L. (2010) The Peripheral endocrine glands In: *Human Physiology from Cells to Systems* (7th edition), Brooks/Cole. ISBN: 13:978-0-495-39184-5.

Shulman GI. (2000). Cellular mechanisms of insulin resistance. *J. Clin Invest*., 106: 171-176.

Statnick MA, Beavers LS, Conner LJ, et al. (2000). Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. *Int J Diabetes Res*, 1: 81-8.

Steppan CM, Bailey ST, Bhat S, et al. (2001). The hormone resistin links obesity to diabetes. *Nature*, 409(6818): 307-12.

Tapan S, Tascilar E, Abaci A, et al. (2010). Decreased plasma apelin levels in pubertal obese children. *Journal of Pediatric Endocrinology and Metabolism*, 23: 1039-1046.

Tatemoto K, Hosoya M, Habata Y, et al. (1998). Isolation and Characterization of a Novel Endogenous Peptide Ligand for the Human APJ Receptor. *Biochemical and Biophysical Research Communications,* 251: 471-476.

Telejko B, Kuzmicki M, Wawrusiewicz-Kurylonek N, et al. (2010). Plasma apelin levels and apelin/APJ mRNA expression in patients with gestational diabetes mellitus. *Diabetes Res Clin Pract*., 87(2):176-83.

Thamer C, Machann J, Tschritter O et al. (2002). Relationship between serum adiponectin concentration and intramyocellular lipid stores in humans. *Horm Metab Res*., 34: 646-9.

Tsao TS, Murrey HE, Hug C, et al. (2002). Oligomerization state-dependent activation of NF-kappa B signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30). *J Biol Chem*., 16 (33): 29359-62.

Tsuchida A, Yamauchi T, Kadowaki T. (2005). Nuclear receptors as targets for drug development: molecular mechanisms for regulation of obesity and insulin resistance by peroxisome proliferator –activated receptor gamma, CREB-binding protein, and adiponectin. *J Pharmacol Sci*., 97: 164-70.

Uvena J, Thomas A, Huston L, Highman T, Catalano PM. (1999). Umbilical cord leptin and neonatal body composition. *Am J Obstet Gynecol*., 180:S41.

Valsamakis G, McTernan PG, Chetty R, et al. (2004). Modest weight loss and reduction in waist circumference after medical treatment are associated with favorable changes in serum adipocytokines. *Metab. Clin. Exp*., 53 (4): 430–4.

Vendrell J, Broch M, Vilarrasa N, et al. (2004). Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. *Obes. Res.,* 12 (6): 962–71.

Vickers MH, Gilmour S. (2009). 20-kDa placental hGH-V has diminished diabetogenic and lactogenic activities compared with 22-kDa hGH-N while retaining antilipogenic activity. *AJP – Endo*, 297 (3): E629-E637.

Ward CW, Lawrence MC. (2009). Ligand-induced activation of the insulin receptor: a multi-step process involving structural changes in both the ligand and the receptor. *Bioessays*, 31 (4): 422–34.

Way JM, Görgün CZ, Tong Q, et al. (2001). Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor gamma agonists. *J. Biol. Chem*., 276 (28): 25651–3.

Weyer C, Funahashi T, Tanaka S, et al. (2001). Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close association with Insulin Resistance and Hyperinsulinemia. *The journal of Clinical Endocrinology & Metabolism*, 86: 1930-1935.

Worda C, Leipold H, Gruber C, et al. (2004). Decreased plasma adiponectin concentrations in women with gestational diabetes mellitus. *Am J Obstet Gynecol,* 191*:* 2120–*2124.*

Xiang AH, Peters RK, Trigo E, et al. (1999). Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes. *Diabetes*, 48: 848–854.

Yamauchi T, Hara K, Kubota N et al. (2003). Dual roles of adiponectin/ Acrp30 in vivo as an anti-diabetic and anti-atherogenic adipokines. Curr Drug Targets Immune Endocr *Metabol Disord*, 3: 243-254.

Yamauchi T, Kamon J, Ito Y, et al. (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*, 423(6941):762-9.

Yamauchi T, Kamon J, Waki H et al. (2001). The fat driven-hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med.*, 7: 941-946.

Yokota T, Oritani K, Takahashi I et al. (2000). Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood,* 96: 1723-1732.

Yool MJ, Lee GY, Chung J et al. (2006). Adiponectin Increases Fatty Acid Oxidation in Skeletal Muscle Cell by Sequential Activation of AMP-Activated Protein Kinase, p38 Mitogene-Activated protein Kinase, and Peroxisome Proliferator- Activated Receptor a. *Diabetes*, 55: 2562-2570.

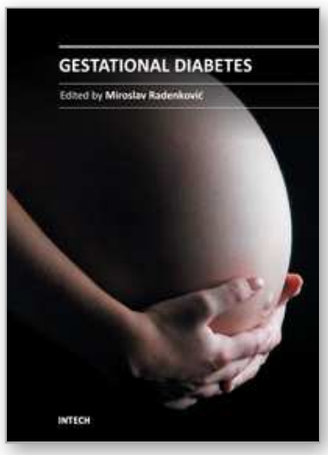
Zeghari N, Vidal H, Younsi M, et al. (2000). Adipocyte membrane phospholipids and PPAR-gamma expression in obese women: relationship to hyperinsulinemia. *Am J Physiol Endocrinol Metab.,* 279*:* E736–*E743.*

Zhang B, Berger J, Hu E, et al. (1996). Negative regulation of peroxisome proliferator-activated receptor-gamma gene expression contributes to the antiadipogenic effects of tumor necrosis factor-alpha. *Mol Endocrinol.,* 10: 1457–1466.

Zhang Y, Proenca R, Maffei M, et al. (1994). Positional cloning of the mouse ob gene and its human homologue. *Nature*. 372: 425– 432.

Zhang XJ, Wang Z, Li HH, Yu L, Gao S. (2010). Association between both resistin, visfatin and insulin resistance as well as β cell function in the first-degree relatives of type 2 diabetes mellitus. *Zhonghua Liu Xing Bing Xue Za Zhi*, 31(12):1393-1396.

Zwick E, Bange J, Ullrich A. (2001). Receptor tyrosine kinase signalling as a target for cancer intervention strategies. *Endocr. Relat. Cancer*, 8 (3): 161–173.



Gestational Diabetes

Edited by Prof. Miroslav Radenkovic

ISBN 978-953-307-581-5
Hard cover, 382 pages
Publisher InTech
Published online 02, November, 2011
Published in print edition November, 2011

Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen