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GESTATIONAL DIABETES- A REVIEW

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ABSTRACT

Gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during their third trimester). The word gestational means pregnant. Gestational diabetes is formally defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". It occurs in about 3% to 14% of pregnancies. Gestational diabetes usually reverses after delivery, but necessitate an increased risk for developing gestational diabetes in a future pregnancy. There is also a higher risk for developing diabetes mellitus in the future. Gestational diabetes is caused when the insulin receptors do not function properly. 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. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decrease risks. Most patients are able to manage their blood glucose levels with a modified diet and the introduction of moderate exercise, but some require antidiabetic drugs, including insulin. The food plan is often the first recommended target for strategic management of GDM. Women with unmanaged gestational diabetes are at increased risk of developing type 2 diabetes mellitus.

Keywords: Gestational diabetes mellitus, pregestational, proinsulin, adiponectin

INTRODUCTION

The two most common forms of diabetes are type 1diabetes (diminished production of insulin) and type 2 diabetes (impaired response to insulin and β-cell dysfunction). Both type 1 and type II diabetes lead to hyperglycemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. Type 1 diabetes is subdivided into two types: type 1A, immune-mediated diabetes, and type 1B, idiopathic diabetes. Type 1A diabetes is characterized by autoimmune destruction of beta cells. Idiopathic type 1B diabetes cases of beta cell destruction in which no evidence of autoimmunity is present. Type 1B diabetes is strongly inherited. Type 1 diabetes mellitus (T1DM), previously known as juvenile onset diabetes or insulin-dependent diabetes mellitus (IDDM), This subclass of diabetes mellitus develops as a result of an autoimmune response directed against insulin-producing β cells, located in the pancreas. Type 1 diabetes in which absolute insulin deficiency is present. Due to the destruction of these cells, patients with T1DM require insulin replacement to achieve euglycemia. Onset of this disease generally occurs before age 30, and thus can affect women during their reproductive years. Diabetes mellitus is simply considered as diabetes, a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia).

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Physiology of pregnancy

At the time of pregnancy several physiologic changes may occur. This is a type of diabetes that some women get during pregnancy. Between 2 and 10 percent of expectant mothers develop this condition, making it one of the most common health problems of pregnancy but most often glucose tolerance returns to normal, postpartum. This condition is called gestational diabetes mellitus (GDM). In late pregnancy the fasting serum insulin concentration is almost twice as high as postpartum, both in normal pregnant women and gestational diabetic subject. Normal pregnant women and gestational diabetic women have comparable fasting insulin level. When the body needs additional insulin, the pancreas dutifully secretes more of it. But if your pancreas can't keep up with the increased insulin demand during pregnancy, your blood glucose levels rise too high, resulting in gestational diabetes.

Glucagon secretion is often abnormal in diabetic patients, for which reason it has been proposed that glucagon plays an essential role in the pathogenesis of diabetes. Fasting plasma glucagon is slightly but significantly increased in late-normal pregnancy. The cause of GDM could be a decreased insulin receptor binding to target cells combined with a relative lack of circulating insulin, but the possibility of post receptor defects does also exist

Physiology of Normal Pregnancy

Pregnancy is a state of physiological insulin resistance, and therefore represents a physiological model of beta-cell stress [1,2]. In normal pregnancy insulin sensitivity emerges in the second trimester and progresses over the late third trimester, thereby increasing maternal glucose, free fatty acids and amino acids in order to provide adequate energy to the fetus. In normal pregnancy, insulin resistance leads to an appropriate increase of insulin secretion, and blood glucose levels remain in the normal range. Due to the increasing demand of the developing fetus and increased transplacental nutrition transfer, maternal glucose levels are even lower than in healthy non-pregnant women. Healthy pregnant women have peak glucose levels (70 min postprandially) of approximately 120 mg/dl (6.7 mmol/l).

Table 1: Types of diabetes mellitus

Type 1	Type2	Type 3	Type 4
insulin dependent pancreatic cell dysfunction average age < 30	noninsulin dependent Appears more commonly in adults >40 –obesity positivefamily – insulin resistant	gestational	diabetes mellitus secondary to another disease or drug treatment

Table 2: Classification of Diabetes by risk/outcomes

Pregestional Diabetes (10%)	Gestational diabetes (90%)
Type of maternal diabetes (type 1 or 2)	fetal risks
Metabolic control and timing (early or late pregnancy)	neonatal risks
Maternal vascular complications (retinopathy, nephropathy and/or atheroschlerosis)	maternal risks

WHO diagnostic criteria for hyperglycemia and GDM

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). 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 WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia (WHO, 2006).

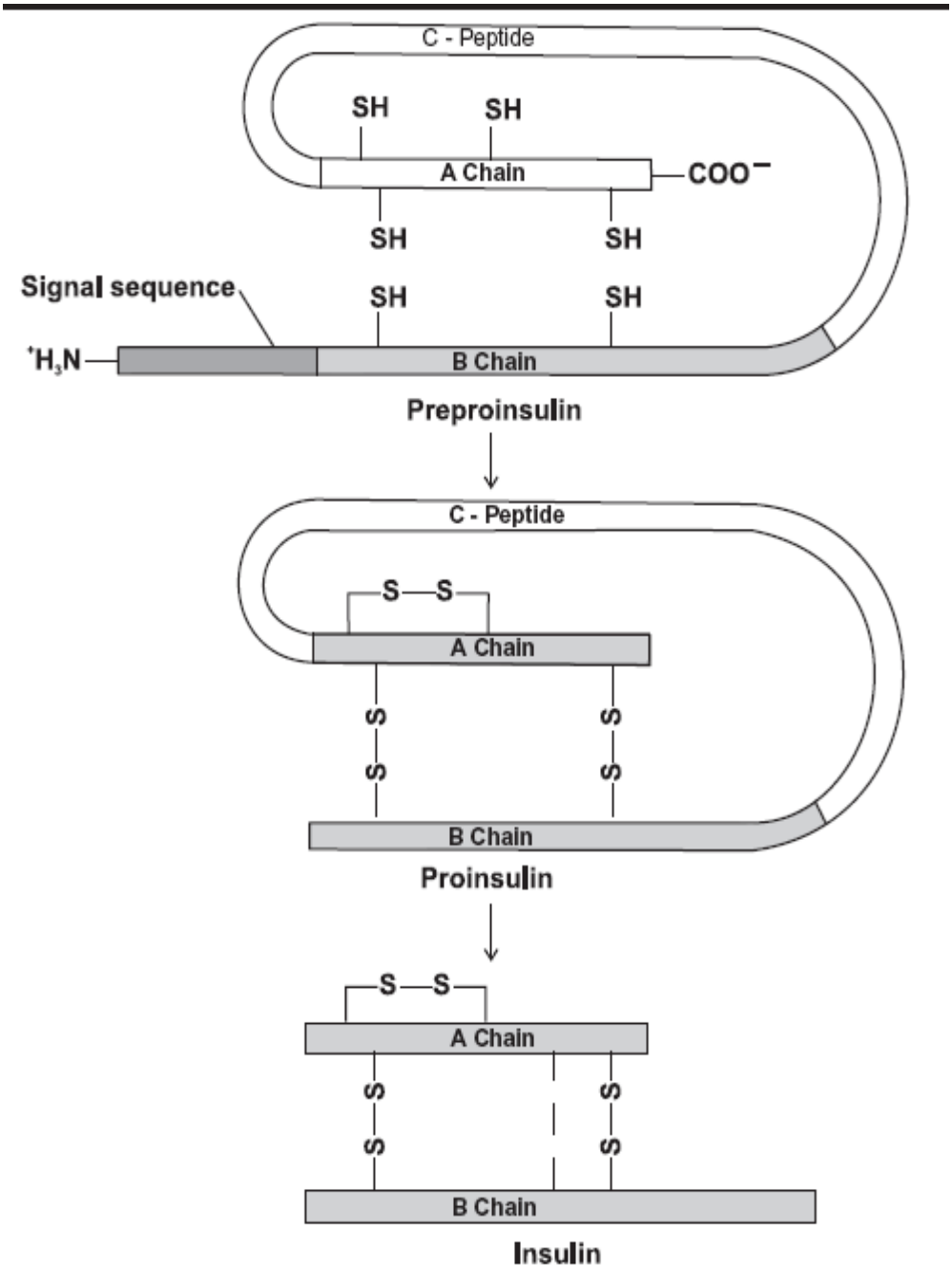
Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl), or
2-h plasma glucose *	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2-h plasma glucose*	≥7.8 and <11.1mmol/l (140mg/dl and 00mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose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

Insulin secretion [3]

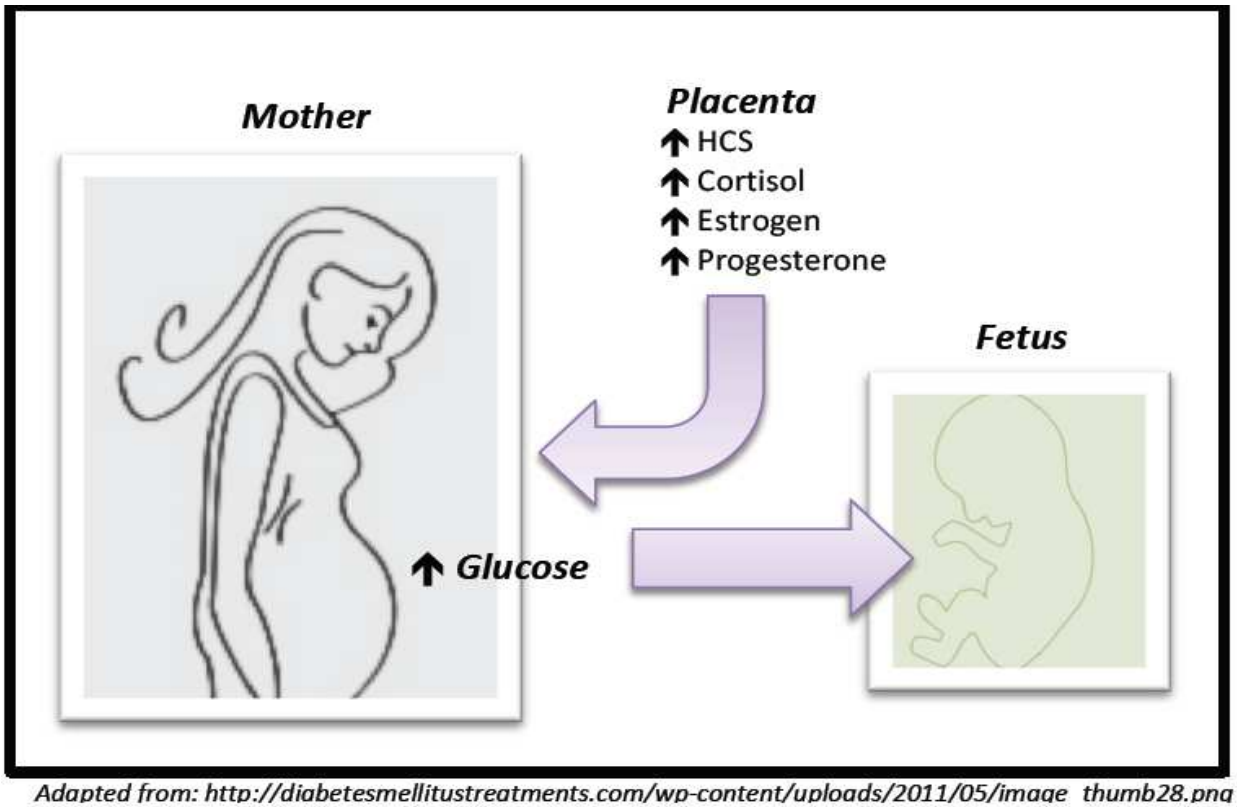
Insulin is secreted from the beta cells in response to various stimuli like glucose, arginine, and sulphonylureas though physiologically glucose is the major determinant. Various neural, endocrine and pharmacological agents can also exert stimulatory effect. Glucose is taken up by beta cells through GLUT-2 receptors. After entering the beta cell, glucose is oxidized

by glucokinase, which acts as a glucose sensor. Glucose concentration below 90 mg/dl do not cause any insulin release. At such sub stimulatory glucose concentrations, K+ efflux through open KATP channels keeps the ß cell membrane at a negative potential at which voltage-gated Ca2+ channels are closed. As there is increase in plasma glucose, glucose uptake and metabolism by the ß and non-sulphonylurea drugs act as insulin secretogogues by closing KATP channels bypassing the ß cell metabolism.



Pathophysiology

1. Insulin resistance increases as pregnancy progresses; insulin sensitivity falls by ~50% in late Pregnancy
2. Increased insulin resistance due to increased maternal adiposity and effects of placental hormones
3. Hormones produced by the placenta: Human chorionic somatomammotropin (HCS), cortisol,estrogen,progesterone
4. As pregnancy progresses and placenta grows, production of hormones increases; thus leading to increased insulin-resistance
5. GDM occurs when insulin secretion is not sufficient to offset the decrease in insulin sensitivity



Adapted from: http://diabetesmellitustreatments.com/wp-content/uploads/2011/05/image_thumb28.png

Pathophysiology of gestational diabetes

In the pathophysiology of GDM we have to consider two main points.

1 Role of feto-placental unit in GDM.

2 Role of the adipose tissue in GDM.

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 [4,5,6]. The insulin resistance of the whole body is increased to about three times that seen in the non-pregnant state [7,8]. The increased resistance is caused by post-insulin receptor events and is brought about by the cellular effects of the increased levels of one or all of the above hormones [9]. 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 [10,11].

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

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 [12, 13, 14, 15]. 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 [16,6].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

It is also considered that human chorionic gonadotropin (HCG) may participate in the development of insulin resistance during pregnancy as it shows higher level in women with GDM in comparison with normal pregnancies [17].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.

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 [18].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[19]. 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 [18,20].

Physiological function 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 [21,22]. 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 [18,23].

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 [18,24].

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 [25].

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 activitie. 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. 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 [26].Barbour et al 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 p85 expression and its interference with PI 3-kinase activity in skeletal muscle[27].

Prolactin

Prolactin level begins to rise at 5-8 weeks of gestation, followed by a progressively increase in its level as pregnancy advances [28]. The increase in prolactin secretion is due the increase in the size and number of maternal pituitary lactotrophs [29] and its secretion from the uterine decidual cells seems to be stimulated by progesterone and insulin (30,31].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 (32). Therefore, prolactin might have no effect on glucose intolerance during pregnancy.

The role of adipose tissue in the development of GDM 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 [33] alpha, interleukin-6, as well as the newly discovered resistin, visfatin, and apelin, are also known to be produced within the intrauterine environment .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 (4). 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 (34) as well as in pregnant women (35).

Adiponectin

Adiponectin is a novel adipocyte secreting protein hormone discovered in 1995/1996 [36].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.* 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[37].

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:

A. General functions

i. Anti-atherosclerotic action: By inhibiting lipid-laden foam cell formation, and inhibiting the inflammatory adipokine, tumor necrosis factor[38,39].
ii. Anti-inflammatory action: By inhibiting the phagocytic activity of macrophages and inhibiting the production of TNF by these macrophages (40).
iii. Anti-oxidant action: By stimulating the endothelial cells to produce nitric oxide (NO).
iv. Anti-tumor action: There is a significant inverse association of adiponectin with postmenopausal endometrial and breast cancer [41,42].

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

1. 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 . adiponectin has indirect insulin-sensitizing effect by decreasing tissue triglyceride (TG) content. 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 . Thus, decreased tissue TG content in muscle may contribute to the improved insulin signal transduction.in skeletal muscle, adiponectin increases expression of molecules involved in fatty acid transport such as CD36, in combustion of fatty-acid such as acylcoenzyme-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.

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.

Effects of adiponectin on lipid metabolism: Adiponectin activates AMP-Kinase (AMPK)and peroxisome proliferator-actvated receptor (PPAR) in the liver and muscle,thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver and muscle . Effects of adiponectin on lipid metabolism: Adiponectin activates AMP-Kinase (AMPK)and peroxisome proliferator-activated receptor (PPAR) in the liver and muscle, thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver and muscle .

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Furthermore, adiponectin decreases lipid synthesis and glucose production in the liver and causes a decrease in glucose and fatty acid concentration in the blood.

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 [43,44,45]. adiponectin is the main adipose-specific protein known to date that despite its excusive production in white adipose tissue, is negatively regulated in obesity. 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

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.

Obese animals and humans show a positive correlation between TNF **α** levels and BMI and hyperinsulinemia [46, 47, 48].

The Diabetogenic action of TNF-α

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 [49], hepatocytes , and skeletal muscl. TNF- **α** activates a pathway that increases sphingomyelinase and ceramides and appears to interfere with insulin receptor autophosphorylation [49]. it has been shown that TNF- **α** promotes serine phosphorylation of insulin receptor substrate (IRS)-1, thus impairing its association with the insulin receptor (50). Elevated levels of TNF- **α** in late

gestation could attenuate insulin signaling, thus causing the decreased insulin sensitivity observed in pregnancy.

Glucose metabolism

The pathophysiology of gestational diabetes involves abnormalities of insulin-sensitive tissue. Beta cell sensing of glucose is also abnormal and is manifested as an inadequate insulin response for a given degree of glycemia. Earlier studies reported that the incidence of islet cell antibodies in women with gestational diabetes as measured by immunofluorescence techniques is between 10% and 35%. Recent studies using specific monoclonal antibodies, however, have found a lower incidence on the order of 1–2% , suggesting a low risk of type 1 diabetes in women with gestational diabetes. Postpartum studies of women with gestational diabetes have demonstrated defects in insulin secretory response and decreased insulin sensitivity [51, 52], indicating typical type 2 abnormalities in glucose metabolism. The alterations in insulin secretory response and insulin resistance in women with a previous history of gestational diabetes as compared with a weight-matched control group may differ depending on whether the women with previous gestational diabetes are lean or obese. Thus in women with gestational diabetes, the metabolic stress of pregnancy may unmask a genetic susceptibility to type 2 diabetes.

INSULIN AND PROINSULIN SECRETION IN PREGNANCY

In late pregnancy, the fasting serum insulin concentration is almost twice as high as postpartum, both in normal pregnant / women and in gestational diabetic subjects. Normal + pregnant women and gestational diabetic subjects have comparable fasting insulin levels,1U2 and fasting serum proinsulin is also similarly elevated in late pregnancy in both groups. During gestation, however, serum insulin rises in parallel with proinsulin in both groups, for which reason the proportion of total insulin immunoreactivity constituted by proinsulin remains constant.

During an OGTT, higher insulin levels are reached in the late-normal and in the GDM pregnancy when compared with postpartum.However, even though the insulin responses in absolute terms are almost similar in the normal women and in the gestational diabetic subjects, the insulin response per unit of glycemic stimulus (the insulinogenic index) is significantly greater in the normal pregnant women than in the gestational diabetic subjects.

GLUCAGON SECRETION IN PREGNANCY

Glucagon secretion is often abnormal in diabetic patients, for which reason it has been proposed that glucagon plays an essential role in the pathogenesis of diabetes. Fasting plasma glucagon is slightly but significantly in-creased in late-normal pregnancy.

In late gestational diabetic pregnancy, fasting plasma glucagon has been reported to be either unchanged or enhanced. However, the fasting molar insulin: glucagon ratio is increased in late normal and in gestational diabetic pregnancy, whereas the opposite finding is a characteristic of insulin-dependent diabetes.

INSULIN RESISTANCE IN PREGNANCY

The insulin resistance (IR) begins activating during the second trimester of pregnancy, when placenta produces hormones (cortisol, placental lactogen, estrogens) preserving pregnancy and blocking action of insulin – the “counter-insulin” effect, and which becomes apparent between 20-24 weeks of pregnancy till the 35th week when the grow of placenta stops.

If the carbohydrate disturbance is developing in the second or the third trimester of pregnancy and returns to norm after childbirth (in majority of cases), the threat of potential diabetes mellitus (of type 2) in mother remains due to preservation of insulin resistance after the childbirth.

If the diagnose of carbonhydrate metabolic disturbance is established in the first trimester of pregnancy then it is a diabetes mellitus which existed before pregnancy but was not diagnosed. Spread of the unstated diabetes among expectant mothers is 0.3%.

In pregnancy, glucose tolerance deteriorates in spite of steadily increasing levels of insulin in plasma.

Increased insulin binding to monocytes, unchanged binding to monocytes, and decreased binding to monocytes and to adipocytes have been reported. In diet-treated gestational diabetic women, increased insulin binding to monocytes was recently found when compared with healthy pregnant controls,whereas in insulin-treated gestational diabetic women, the insulin binding to adipocytes was decreased.

A steady reduction in insulin sensitivity occurs from 18 to approximately 28 weeks gestation. Following delivery, insulin sensitivity returns to pre pregnancy levels. It is unclear how insulin resistance occurs, but several factors are likely to play contributory roles.

Hormones

Sensitivity to insulin decreases progressively during pregnancy and swiftly returns to normal following delivery, strongly suggesting a hormonal association. In particular, human placental lactogen, human placental growth hormone, progesterone, cortisol and prolactin are known to counteract the effects of insulin.[4] Although reproductive hormones are frequently cited as the cause for insulin resistance, changes in hormone concentrations do not directly correlate with insulin resistance.[14] The relationship between such hormones and insulin action may not be simple cause and effect.

Inflammation

Normal pregnancy is a proinflammatory state. Tumour necrosis factor alpha (TNF-a), an adipo-cytokine, has been shown to promote insulin resistance through its prohibitive action on the insulin receptor. Elevation of TNF-a in pregnancy correlates with progressive insulin resistance.[14] Additionally, elevated levels of TNF-a have been found in conditions associated with hyperinsulinaemia such as obesity and type 2 diabetes.[34]However, the degree of increase of TNF-a

levels is very small in comparison with that seen in infection or after major trauma, and neutralization of TNF-a with monoclonal antibodies has no effect on insulin resistance in people with type 2 diabetes, implying that while TNF-a may contribute to insulin resistance, it is by no means the single causative factor.[53]

Adipose-derived hormones

Adiponectin is a globular protein synthesized by adipose tissue. It belongs to a group of hormones, including leptin and resistin, that control local storage and distribution of fat. Low adiponectin concentrations correlate with insulin resistant states.[54] Adiponectin stimulates glucose uptake in skeletal muscle and inhibits hepatic glucose production.

Studies have shown that adiponectin levels decline with advancing gestation in normal pregnancy and are further reduced in gestational diabetes.[55,56] However, the changes are small and unlikely to confer any major effect.

Fat deposition

Pregnancy is associated with increased maternal adiposity and storage of carbohydrate and fat, perhaps as an evolutionary adaptation to facilitate successful lactation. Studies of people with type 2 diabetes have identified that fat deposition within skeletal muscle and liver cells is a major contributory factor to insulin resistance [57].It is unknown whether fat deposition during pregnancy explains the acquisition of insulin resistance.

The risk factors of GDM are as follows

1. Excess body mass, obesity, metabolic syndrome
2. Diabetes mellitus in the relatives of the first relation degree
3. Age over 25 years
4. Disturbance of glucose tolerance in anamnesis
5. Burdened obstetric anamnesis
6. Previous baby with the weight over 4 kg, with big abdominal circumference and the wide shoulder girdle
7. GDM in previous pregnancy
8. Chronic noncarrying of pregnancy (over 3 spontaneous abortions in I or II trimester of pregnancy)
9. Hydramnions
10. Stillbirth
11. Defects of development in previous children.

It is established that 40% of women have one or several risk factors of development of GDM. It is recommended that such expectant women should undergo the glucose tolerant tests with 75g of glucose over the period between 24th-28th weeks of pregnancy.

Table 3: Physiological changes of metabolism in women during pregnancy

Type of metabolism	Glycemia	Characterof origin	changes
Carbohydrate metabolism	a) 4,0 – 5,2 mmol/l on an empty stomach b) ≤6,7 mmol/l postprandial glycemia	a) glycemia level decrease on an empty stomach (not 0,5 – 1,0 mmol/l) b) Glycemia level increase 2 hours later after meal	Accelerated secretion of glucose by kidneys. Decrease of production of glucose by liver. Increased consumption of glucose in the system: mother – placenta – fetus. The climax of rapid absorption of carbohydrate and bradyperistalsis of gastrointestinal tract.
Albumin exchange		Reduction of the quantity of amino – acids circulating in blood	Increase consumption of amino-acids in the system: mother – placenta – fetus.
Fat exchange		Increased decay of fat-acids causing formation of keton bodies. Increase in fat tissue.	Decrease of production of glucose by liver, shortage of carbohydrates in nutrition. Increased formation of pregnancy hormones depending on the period of pregnancy. Increase in food rich in calories and decrease of motional activity.

How to know if a person has gestational diabetes

Gestational diabetes usually has no symptoms. That's why almost all pregnant women have a glucose-screening test between 24 and 28 weeks However, if you're at high risk for diabetes or are showing signs of it (such as having sugar in your urine), your caregiver will recommend this screening test at your first prenatal visit and then repeat the test again at 24 to 28 weeks if the initial result is negative. if you get a positive result on a glucose-screening test, it doesn't necessarily mean that you have gestational diabetes. It does mean that you'll need to take a longer follow-up test (a glucose tolerance test, or GTT) to find out.

Effect of gestational diabetes on pregnancy and foetus

Dietary changes and exercise may be enough to keep your blood sugar levels under control, though sometimes medication is needed, too.If during pregnancy the blood sugar levels are too high, too much glucose will end up in baby's blood. When that happens, baby's pancreas needs to produce more insulin to process the extra glucose. All this excess blood sugar and insulin can cause baby to put on extra weight, particularly in the upper body. This can lead to what's called macrosomia. A macrosomic baby may be too large to enter the birth canal. Or the baby's head may enter the canal but then his shoulders may get stuck. In this situation, called shoulder dystocia, the practitioner will have to use special

maneuvers to deliver your baby. In addition, babies who have excessive fat stores as a result of high maternal sugar levels during pregnancy often continue to be overweight in childhood and adulthood.Shortly after birth, your baby may have low blood sugar (hypoglycemia) because his body will still be producing extra insulin in response to your excess glucose. This is much more likely if your blood sugar levels were high during pregnancy and especially during labor, babys blood sugar will be tested and will be offered IV glucose solution. The risk of newborn jaundice is increased, too.

If your blood sugar control is especially poor, your baby is at risk for polycythemia (an increase in the number of red cells in the blood) and hypocalcemia (low calcium in the blood), and your baby's heart function could be affected as well.

Ways to control gestational diabetes

Eat a well-planned diet. Develop specific meal and snack plans based on your height, weight, and activity level. Your diet must have the correct balance of protein, fats, and carbohydrates, while providing the proper vitamins, minerals, and calories. To keep your glucose levels stable, it's particularly important that you don't skip meals, especially breakfast, and that you avoid sugary items like candy, cookies, cakes, and soda.

Exercise Studies show that moderate exercise also helps improve your body's ability to process glucose, keeping blood sugar levels in check. Many women with gestational diabetes benefit from 30 minutes of aerobic activity, such as walking or swimming, each day

Take medication if necessary. If you're not able to control your blood sugar well enough with diet and exercise alone, your provider will prescribe medication as well. About 15 percent of women with gestational diabetes need medication

Other Additional tests

This testing may include fetal heart monitoring (nonstress tests) and periodic ultrasound tests called biophysical profiles. If you have mild gestational diabetes kept well under control without medication and you have no other problems, you probably won't need any extra testing until about 40 weeks. One or more ultrasounds during the third trimester to monitor baby's growth. One ultrasound in the early part of the third trimester to help assess the need for medication. An ultrasound close to due date, too. If baby seems to be getting very big, labour may be induced before due date, or may be recommended delivering by c-section

Most women with gestational diabetes do not remain diabetic after giving birth.But as many as a third of women who had gestational diabetes will continue to have diabetes or what's known as impaired glucose tolerancea glucose test about six to 12 weeks after delivery. This test requires an overnight fast and can be done at your six-week postpartum visit

To check if you have gestational diabetes, your provider will do two blood tests.

The first test is called a **1-hour oral glucose challenge test** (1-hour OGCT).
You will drink a sugar drink.
An hour later, you will have your blood drawn to test your blood sugar.
If your blood sugar is high, your provider will do a second test. This helps the provider to know for sure whether you have gestational diabetes.
The second test is called a **3-hour oral glucose tolerance test** (3-hour OGTT).
You cannot eat or drink anything but water for at least 8 to 14 hours before the test.
You will have your blood drawn to test your blood sugar.
You will drink a sugar drink.
You will have your blood drawn three more times. This occurs each hour over 3 hours.
There are things you can do to help make sure this second test (3-hour OGTT) is right.

Each of the three days before the test:

Eat foods you normally eat.
Eat at least 10 servings of foods each day such as bread, fruit, and milk. Here is an example of 10 servings:

1 cup milk
1 slice bread
1 dinner roll
1/3 cup cooked pasta
½ cup black beans
1 tortilla
1 cup berries
1 small apple/orange
½ cup corn
3 cups popcorn

8 to 14 hours before the test

It is okay to drink water. Do not eat or drink anything else.

During the test

Drink the sugar drink in less than 5 minutes.
Do not smoke.
Rest Try not to walk a lot.

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