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SERUM LEVELS OF ADIPONECTININE AND LEPTIN IN GESTATIONAL DIABETES MELLITUS - REVIEW

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ABSTRACT:
GESTATIONAL DIABETES MELLITUS (GDM) IS A METABOLIC COMPLICATION OF PREGNANCY. DUE TO THE EPIDEMY OF OVERWEIGHT AND OBESITY IN WOMEN AT REPRODUCTIVE AGE, PREVALENCE OF GDM IS INCREASING WORLDWIDE. GESTATIONAL DIABETES MELLITUS IS A PATHOLOGICAL STATUS CHARACTERIZED BY GLUCOSE INTOLERANCE WHICH IS ONSET OR FIRST RECOGNIZE IN PREGNANCY AND IS ASSOCIATED WITH SHORT AND LONG THERM MATERO-FETAL COMPLICATIONS. UNDERSTANDING THE PHYSIOPATHOLOGY OF GDM IS AN IMPORTANT PROGRESS IN MANAGEMENT OF THESE CASES. BOTH MOTHER AND CHILD PRESENT A HIGH RISK OF DEVELOPING TYPE 2 DIABETES MELLITUS (T2DM), OBESITY AND METABOLIC SYNDROME LATER IN LIFE. GDM COVERS LATENT METABOLIC CHANGES THAT GENERATE A TRANSGENERATIONAL VICIOUS CIRCLE. INSULIN RESISTANCE AND β-CELL DYSFUNCTION ARE INVOLVED IN PATHOGENESIS OF GDM. OBESITY IS A RISK FACTOR OF DEVELOPING GDM. ADIPOSE TISSUE SECRETS ADIPOKINES INVOLVED IN PATHOPHYSIOLOGY OF GDM AND ALSO IN ENERGY HOMEOSTASIS, CARBOHYDRATE AND LIPID METABOLISM. THE PURPOSE OF THIS REVIEW WAS TO ANALYSIS SERUM ADIPOCYTOKINES LEVELS IN PREGNANCIES COMPLICATED WITH GESTATIONAL DIABETES.

KEY WORDS: GESTATIONAL DIABETES, PATHOGENESIS, ADIPOKINES, INSULIN RESISTANCE, B-CELL DYSFUNCTION

BACKGROUND
Gestational diabetes mellitus is a pathological status characterized by glucose intolerance which is onset or first recognize in pregnancy⁷. Epidemiological reports showed

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that prevalence of GDM is estimated to be around 20% of all pregnancies worldwide. The guidelines recommend the 75g 2-hour oral glucose tolerance test (OGTT) as gold standard screening test for diagnosis of GDM. Women with GDM are predisposed to develop type 2 diabetes up to 7 times more than women with normal glucose tolerance in pregnancy. Understanding the physiopathology of GDM will be an important progress in management of GDM because this condition covers latent metabolic changes that generate a transgenerational vicious circle (both mother and child have an increased risk to develop type 2 diabetes, cardiovascular diseases and metabolic syndrome later in life). Essential components involved in the pathogenesis of GDM are insulin resistance (IR) and β-cell dysfunction.

PATHOPHYSIOLOGICAL ASPECTS OF GDM

Pregnancy is characterized by a series of metabolic changes in order to assure the development and grow of fetus. In normal pregnancies maternal tissues develop gradually insulin insensitivity, with a reciprocal increase in insulin secretion by 200%. A reduction of whole body glucose disposal by 50% appear in order to obtain a euglycaemia status.

One of the most common metabolic adaptative mechanism that occur in pregnancy is a temporary increase in insulin resistance, with a peak in the third trimester when the foetal energy demands rise.

In this process of insulin resistance are involved several factors as increased levels of hPL (human placental lactogen), estrogen, progesterone, cortisol, prolactine. The increase levels of placental hormones lead to insulin resistance which determine hyperglycemia. The exceeded glucose is transported across the placenta to the fetus. The insulin resistance stimulate pancreas to secrete insulin which stimulates the breakdown of fat stores and rise the blood glucose and free fatty acid (FFA) concentrations.

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During pregnancy, estrogen, progesterone and adipocyte-derived hormones such as adiponectin and leptin are also suggested to play a role in the development of insulin resistance 15.

Insulin resistance stimulates hepatic gluconeogenesis, reduces glucose uptake in skeletal muscle and adipose tissue, and increase lipolysis in adipose tissue 16. These processes facilitate the lipid metabolism to assure the energy requirements of the mother. Glucose is direct to the foetus in order to promote development 17. In GDM the insulin resistance can not be combated because a relative deficiency of insulin secretion exists. Consequently, hyperglycaemia develops.

Neurohormonal dysfunction is implicated also in pathogenesis of GDM and consists of a complex network of central (cortical centers) and peripheral (satiety and hunger hormones) signals which regulates active energy expenditure, appetite and basal metabolic rate. These factors increase the risk of GDM by influencing adiposity and glucose utilization. The most important regulators of neurohormonal metabolism are adipokines that are secreted by adipose tissue. These include leptin and adiponectin 18.

**ADIPONECTINE**

Adiponectin is a hormone derived from adipocyte and is involved in energy homeostasis. It has an important role in regulating insulin action and glucose homeostasis. In metabolic diseases, such as obesity, type 2 diabetes, cardiovascular diseases and non-alcoholic fatty liver disease, studies have showed that adiponectin levels are decreased.

The most biologically active form of adiponectin regarding glucose metabolism is considered to be high molecular weight (HMW) adiponectin, which consists of large multimers of 12 to 18 subunits 19. Karpe et al. reported that adiponectin gene is located on chromosome 3q27 which is involved in diabetes development 20. Studies have reported an inverse association between low adiponectin levels and insulin resistance, obesity and metabolic dysfunction 21.

Adiponectin has pleiotropic effects on vascular function, cell growth, systemic inflammation, the regulation of energy homeostasis 22.

Lihn et al. showed that adiponectin levels are reduced by pro-inflammatory cytokines suggesting an interaction between inflammation and metabolic dysregulation. Authors also

reported that adiponectin activates fatty acid oxidation and inhibits hepatic glucose production. Similar results are reported by Liu Y et al.

Tao C. et al. revealed that in adipose tissue, adiponectin suppresses the expression of pro-inflammatory cytokines, improves lipid metabolism, glucose homeostasis and insulin sensitivity.

Liu Y. et al showed that in skeletal muscle, adiponectin regulates muscle mass and function and also improves glucose metabolism and insulin sensitivity. Lee Y. et al showed that in pancreas, adiponectin stimulate the insulin secretion by β-cells, promote β-cells survival and viability and reduce β-cells apoptosis.

Tsutomu K. et al. showed that adiponectin is associated with lower levels of fasting glucose, triacylglycerol, low-density lipoprotein (LDL) cholesterol, and higher high-density lipoprotein (HDL) concentration.

Adiponectin plays an important role in gestational metabolic adaptative mechanisms and regulates homeostasis during pregnancy. The main source of circulating adiponectin during pregnancy is adipose tissue. Prepregnancy BMI reflects total subcutaneous and visceral adipose tissue.

A normal adiponectin level in early pregnancy prevents also adverse metabolic outcomes and cardiac dysfunction in offspring. Dietary bioactive compounds such as polyphenols can be a very effective intervention which can improve pregnancy complications. Fruits, vegetables, nuts, tea, cereals, chocolate, olives, spices are rich in polyphenols and are reported to induce adiponectin levels and consequently improve metabolic disorders such as obesity, type 2 diabetes and cardiovascular disease.

Studies have showed that adiponectin concentrations during pregnancy are affected by ethnicity and body mass index. Aye I. et al. showed in their study that using obese mouse models, normalizing adiponectin levels in obese pregnant mice in early pregnancy reduce significantly the effects of maternal obesity on placental dysfunction and foetal overgrowth. This study suggested that adiponectin can have therapeutic potential.

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SERUM ADIPONECTIN CONCENTRATIONS IN GDM

Many studies analysed the role of adiponectin in pathophysiology of GDM. Studies showed that hypoadiponectinemia during pregnancy increase insulin resistance in skeletal muscle and lead to decreased glucose uptake, pancreatic beta cell dysfunction, hyperglycemia and consequently GDM32.

Bao et al. showed that concentration of adiponectin is significantly lower in first and early second trimester in pregnant woman who later had developed GDM. The decrease of adiponectin levels may be associated with the developing of GDM due to decreased insulin sensitivity and anti-inflammatory capability. The risk of GDM is 5-6 times higher in women with hypoadiponectinemia in comparison with women with high levels33. A correlation between significantly hypoadiponectinemia and beta cell dysfunction during pregnancy has been found. This may suggest the use of adiponectin as an early biomarker of the GDM development34.

Hedderson et al. demonstrated that the risk of GDM increased in subjects who had BMI < 25 kg/m2 and hypoadiponectinemia.

Circulating adiponectin levels decrease during pregnancy, reaching the lowest level in the third trimester when maternal insulin resistance is highest35. Each µg per mL decline in maternal adiponectin levels rise the risk of GDM about 20%. Maternal adiponectin is higher in normal pregnant women in comparison with pregnancies complicated with GDM or preeclampsia36. Another conclusion of author is that the reduction in maternal adiponectin levels is an indicator of 4.6 times increased risk of GDM.

Saini et al. showed that adiponectin concentration is lower in GDM and found an inverse relationship between adiponectin level and fasting blood sugar. Tsi et al. reported that in their study the concentration of serum adiponectin was extremely lower in GDM group. They also showed a negative relationship between serum adiponectin levels and development of GDM.

The first line of treatment for GDM is diet. If normoglycemia can not be obtain by diet, insulinoterapy is needed. There are clinical factors that can predict the need of insulin therapy during pregnancy complicated with GDM in order to maintain euglycemia status. These factors are: prepregnancy body mass index (BMI) (especially ≥ 30 kg/m2), early diagnosis (before 24 weeks), high glycosylated hemoglobin values, family history of diabetes mellitus (DM), prior GDM, maternal age (above 30 years).

Retnakaran R. et al. showed that hypoadiponectinemia during pregnancy is associated with postpartum insulin resistance, β-cell dysfunction, and fasting hyperglycemia\(^{37}\). Hypoadiponectinemia during pregnancy and post-partum may predict future development of obesity and type 2 diabetes\(^{38}\).

**LEPTIN**

Leptin is a satiety hormone secreted by adipocytes in response to adequate fuel stores and its function is to decrease appetite and increase energy expenditure. Another leptin function is a regulatory role in energy metabolism, immune system and also is responsible for the inflammatory state associated to obesity. Inflammatory cells release several inflammatory mediators that regulate leptin expression and promote the development of chronic inflammation. Studies suggest that proinflammatory leptin actions might have implications in the pathogenesis of GDM\(^{39}\).

Leptin plays a role in regulation of body glucose homeostasis and has an acute inhibitory effect on secretion of insulin\(^{40}\). Leptin directly affects insulin sensitivity through regulating the insulin-mediated glucose metabolism by skeletal muscle and by hepatic regulation of gluconeogenesis\(^{41}\).

In pregnancy, leptin is expressed by trophoblastic cells from placenta. During pregnancy, leptin increases in parallel with changes in glucose metabolism and maternal fat stores. Laivuori H. et al. showed that in presence of insulin resistance and hyperinsulinemia, an upregulation of adipocyte leptin synthesis occurs in the second half of pregnancy. Consequently, maternal plasma leptin increase\(^{42}\).

Schubring C. et al. showed that maternal leptin concentration increases 2–3 times in comparison with nonpregnant concentration, with a peak around 28 weeks of gestation\(^{43}\).

During pregnancy, maternal serum leptin concentrations increase and are higher in comparison with nonpregnant women. Henson C. et al. suggested that maternal leptin levels are high during pregnancy and peak in the second trimester and also remain elevated until parturition\(^{44}\).

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Substantial increases of leptin concentrations in early pregnancy, before the body weight gain due to progressive gestation, suggest that other factors than increased adiposity mediate maternal leptin levels.

Liu et al. demonstrated that serum leptin level is associated with glucose tolerance during pregnancy and that exists a positive and significant correlation between maternal leptin and fasting insulin levels. Maghbooli et al. showed that leptin concentration is positively associated with insulin level and HOMA index. Mohiti et al. suggested that serum leptin has a negative correlation with insulin in obese diabetic patients but inflammation associated to obesity has an important role in leptin resistance.

**SERUM LEPTIN CONCENTRATIONS IN GDM**

The role of leptin in maternal metabolism, maternal glucose homeostasis regulation, GDM is of great interest for researchers. Data are contradictory.

Studies showed that in gestational diabetes leptin levels are increased and determine a increased size of the placenta and the fetus. Researchers observed that in trophoblasts from gestational diabetic subjects, leptin mediates the increased protein synthesis.

In GDM, serum leptin concentrations are higher than in women with intolerance to glucose (IGT) or non-GDM. Kautzky-Willer et al. reported that maternal plasma leptin concentrations, analysed in third-trimester are higher in GDM women compared with the control group. Similar result observed in other studies. Plasma leptin concentrations did not significantly change at 2nd trimester but decrease at 3rd trimester among GDM women. Other study showed that each 10 ng/ml increase in the leptin concentration in early pregnancy is associated with a 20% increase in GDM risk.

Studies suggest that hyperinsulinemia may regulate placental leptin production. Maternal glucose regulates cord blood leptin levels and this explains why newborns with mothers with GDM have an increased risk of obesity.

Postpartum, in both normal and GDM-complicated pregnancies appear a significant decline of serum leptin. An explanation for the elevation of circulating leptin during pregnancy and GDM can be either increased release of leptin from maternal adipose tissue or placental production of leptin. Circulating leptin decrease after delivery, suggesting that placental production of leptin is one of the main sourse of elevated circulating leptin during pregnancy.

**CONCLUSIONS**

Gestational diabetes mellitus affects an important number of women during pregnancy. Altered concentrations of different adipokines are involved in pathophysiology of GDM. The exact role of adipokines in the pathogenesis of GDM is still unclear. Several adipokines have been analysed during pregnancy and their levels have been evaluated in

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healthy and complicated pregnancies. Studies suggest that adiponectin and leptin are significantly and prospectively correlated with glucose metabolism and cardiometabolic biomarkers. A dysregulation in adipokines concentrations may affect glucose homeostatic processes and increase the risk of GDM.

Adiponectine plays an important role in gestational metabolic adaptative mechanisms and regulates homeostasis during pregnancy. Circulating adiponectin levels decrease during pregnancy, reaching the lowest level in the third trimester when maternal insulin resistance is highest.

Leptin plays a role in regulation of body glucose homeostasis and has an acute inhibitory effect on secretion of insulin. In GDM, serum leptin concentrations are higher than in women with intolerance to glucose (IGT) or non-GDM.

Further analyses are needed in order to completely understand the role of adipokines in pathophysiology of GDM.

CONFLICT OF INTERESTS
The authors declare that they have no conflict of interests.

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