Obstetrica şi Ginecologia LXV (2017) 193- 197 **Review article**

THE ROLE OF ADIPOKINES IN THE DIAGNOSIS OF GESTATIONAL DIABETES

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Abstract

Gestational diabetes (GD) is one of the most common complications of pregnancy and can lead to significant risks to the mother and fetus. Gestational diabetes is defined as glucose intolerance that develops or is diagnosed during pregnancy. The incidence of this disease varies from 0.6 to 20%, depending on the diagnostic criteria used, with an increasing trend over the past years. GD occurs when an inadequate secretion of the beta-pancreatic cells fails to compensate for the decrease in peripheral insulin sensitivity, a phenomenon characteristic of pregnancy. Typically, GD is diagnosed at 24-28 weeks of gestation by performing OGTT, according to the diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). Apparently, GD can develop very early in pregnancy, and can negatively impact on both fetus and mother. Recent studies have evaluated the role of several adipokines in GD, especially that of leptin, adiponectin, TNF-á and resistin. Adipokines are a group of proteins secreted by adipocytes, whose secretion is altered in obesity, contributing to metabolic and vascular changes. At present, there is growing concern for early detection of GD using various biochemical genetic markers, or various metabolites involved in the pathophysiology of gestational diabetes. Early detection would allow rapid initiation of appropriate treatment. Moreover, if a link between the pathophysiological mechanisms of GD and those of obesity could be proven, this would open up new opportunities for the prevention and treatment of these conditions.

The aim of this review is to provide an overview of these adipokines, as well as of their regulatory mechanisms and potential contribution to the onset of GD. The evidence so far shows that adiponectin and leptin are most likely involved in the pathophysiology of this disease.

Rezumat: Rolul adipokinelor în diagnosticul diabetului gestaţional

Diabetul gestaţional (DG) este una dintre cele mai frecvente complicaţii ale sarcinii şi care duce la riscuri considerabile materne şi fetale. Diabetul gestaşional este definit ca intoleranţă la glucoza aparută sau diagnosticată prima dată în timpul sarcinii. Incidenţa afecţiunii este diferit raportată între 0,6-20% in funcţie de criteriile de diagnostic utilizate, procentul fiind în creştere. Apariţia DG se datorează unei secreţii necorespunzătoare a celulelor beta-pancreatice, secreţie care nu reuşeşte să compenseze scăderea sensibilităţii periferice la insulina, fenomen caracteristic sarcinii. In mod clasic depistarea DG se face la 24-28 SA utilizând TTGO, conform criteriilor de diagnostic ale International Association of the Diabetes and Pregnancy Study Groups (IADPSG). Se pare că DG poate sa apară foarte precoce în sarcina cu influenţe negative asupra fătului şi mamei. Studiile recente au evaluat rolul mai multor adipokine in DG, printre care cele mai studiate au fost leptina, adiponectina, TNF-α şi resistina. Adipokinele sunt un grup de proteine secretate de către adipocite, a caror secreţie este modificată în obezitate şi contribuţie la apariţia modificărilor metabolice şi vasculare. Preocupările recente sunt pentru depistarea precoce a DG utilizând diverşi markeri biochimici, genetici sau diferiţi metaboliţi cu rol în fiziopatologia DG. Depistarea precoce ar permite un tratament rapid şi adecvat şi dacă există legături între mecanismele fiziopatologice ale DG si respectiv ale obezităţii, se deschid noi posibilităţi de prevenţie şi tratament al acestor afecţiuni. Acest review îşi propune să ofere o imagine de ansamblu asupra acestor adipokine, mecanismele de reglare şi contribuţia potenţială în apariţia DG. Dovezile de până acum arată că adiponectina şi leptina sunt cel mai probabil implicate în fiziopatologia acestei boli.

Cuvinte cheie: diabet gestaţional, adiponectină, leptină, obezitate

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KEY WORDS: gestational diabetes, adiponectin, leptin, obesity

Introduction

Gestational diabetes (GD) is one of the most common complications of pregnancy and can lead to significant risks to the mother and fetus (1). Gestational diabetes is defined as glucose intolerance that develops or is diagnosed during pregnancy. The incidence of this disease varies from 0.6 to 20%, depending on the diagnostic criteria used, and it seems that the percentage is increasing (2). Typically, GD is diagnosed at 24-28 weeks of gestation by performing OGTT, according to the diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). Various studies have shown that GD onset may occur very early in pregnancy, with negative effects on the fetus and mother (1). At present, there is growing concern for early detection of GD using various biochemical genetic markers, or various metabolites involved in the pathophysiology of gestational diabetes. To this end, adipokines have been studied, especially Adiponectin (AN) and Leptin (L). Adipokines are proteins secreted by adipocytes and are involved in many endocrine and metabolic processes, such as insulin secretion, insulin resistance regulation, a number of inflammatory processes, as well as body weight regulation. As a result, AK also interfere with glycolysis processes, (4,5). The starting point of the studies regarding the role AK playin the pathophysiology of GDwas the connection existing between GD and obesity.

Adiponectin

Adiponectin (A) is a plasma protein secreted exclusively by the adipose tissue. It decreases in obesity, and circulates in serum as multimers. The high molecular weight form is the most active one, and it is responsible for most peripheral effects (14). AN is involved in regulating inflammatory processes and lipid metabolism by reducing fat deposits due to stimulation of lipid oxidation and inhibition of lipolysis. With respect to glucose metabolism, AN increases insulin sensitivity, decreases glycogenogenesis and glucose uptake, thus beingin inverse relationship with the metabolic syndrome (10,20,21). AN synthesis is inhibited by the beta-adrenergic stimulus, glucocorticoids and TNF-α. Low AN levels were also found in Diabetes mellitus type 2, obesity, insulin resistance, hypertension and left ventricular hypertrophy (9).

In normal pregnancy, maternal AN levels decrease progressively and there is an inverse correlation with BMI and obesity (14). The decrease in AN levels in pregnancy correlates with beta-pancreatic cell dysfunction and increased insulin resistance, and it may therefore be a marker of GD (15). Lower AN levels determined in the first trimester of pregnancy may be a prediction marker for gestational diabetes. Studies on changes occurring in pregnancy and on the relationship with GD are still inconclusive.

AN slows down fetal weight gain by reducing placental insulin effects and transplacental amino acid transfer (6). In such circumstances, decrease in AN levels in patients with GD may cause fetal macrosomia. This decrease is also suspected to be a cause of fetal macrosomia in patients without GD (26,27). Low values of this protein may persist after delivery and may contribute to the progression from GD towards diabetes mellitus type 2 (28,29,30).

A recent meta-analysis evaluating 27 trials, has studied the correlation existing between the maternal serum concentrations of 3 adipokines (AN, L, TNF-α) and GD onset. The results of this meta-analysis show elevated Leptin and TNF-α levels and decreased AN levels in patients with GD, compared to those with physiological pregnancy, which suggests that imbalance in pro and anti-inflammatory cytokine expression may contribute to impaired glucose homeostasis in GD(16).

Another meta-analysis of 9 prospective studies shows a decrease in AN levels in the first trimester in pregnant women who will develop GD (13). A decrease in AN levels may have early predictive value for the development of GD, independently of BMI (10,22,23,24). One prospective study showed that patients with low AN levels in the first trimester of pregnancy had increased risk of

developing GD even when returning to a normal BMI (25).

A cohort study published in 2017 by Ida Naslund Thagaard et al. performed on 2590 pregnant women in the first trimester of pregnancy, monitored the maternal serum level of AN and L. Patients were divided into 3 groups, according to their weight: normal weight, moderate obesity and severe obesity, and the results showed a low level of AN in patients who developed GD in all three groups. By contrast, Leptin associated with GD only in severely obese patients. The AN / L ratio associated with GD in patients with BMI <35 kg/m2, but not in those with severe obesity. The importance of the AN/L ratio equals that of the AN, although it is lessprecise in patients with higher degrees of obesity. Leptin has little contribution, since its level only increases in the group of severely obese patients [32].

In conclusion, adiponectin decreases in obesity, pregnancy and GD, in the pathophysiology of which it appears to be involved and, being a predictive marker of this condition.

Leptin

Leptin is a protein hormone primarily involved in insulin secretion, glucose utilization, neoglucogenesis and fatty acidmetabolism (7,8,9). It is released into the circulation by the adipose tissue, proportionally with the body's fat reserves (8). A low level of L causes a feeling of hunger, while an increased L level correlates with a feeling of satiety and an increased rate of the basal metabolism. Obesity and pregnancy are associated with leptin resistance and inadequate action of this protein at the level of the hypothalamic receptors (9). The amount of circulating L is directly proportional to the volume of adipose tissue. In obesity, one can also notice central resistance to the action of increased L levels (6). In pregnancy, leptin levels increase in the first part of the pregnancy, independently of the weight gain of the pregnant woman. In normal pregnancy L levels are 2-3 times higher than in non-pregnant women, reaching a maximum at about 28 weeks of gestation. Placenta has been shown to produce large amounts of leptin mRNA and is rich in L-receptors (8). Increased L-secretion at the placental level appears to play an important role in fetal growth. In such circumstances, L is involved in the pathophysiology of GD by decreasing insulin secretion by Beta-pancreatic cells (6). It also affects the hypothalamic functions, causing changes in appetite, weight gain and energy use, all of which lead to the development of GD (6). Hyperleptinemia in GD amplifies the proinflammatory state of pregnancy by increasing cytokines such as IL-6 and TNF-alpha, which increase even more the level of L (9).

Various studies show increased leptin concentrations in pregnant women with gestational diabetes (17,18,19). However, there is also one study on pregnant women with GD that does not report this (10). Qiu et al. (11) report a close correlation between the growth of L levels in the first trimester and GD. The risk of GD was 20% higher in the case of pregnant women with hyperleptinemia, regardless of the preconception weight of the pregnant woman.

A study by Kirwan et al. (12) shows increased L levels before conception and throughout the pregnancy in a reduced number of patients with GD (8) compared to pregnant women without GD.

A recent meta-analysis showed significant increases in leptin levels (above 7.25 ng / mL) in pregnant women with GD in the first trimester and early in the second trimester (13). The exact role played by adiposity in increasing L levels in pregnant women with GD is yet unknown.

Skvarca et al determined the AN and L values in pregnant women and studied their correlation with insulin resistance. Insulin resistance was evaluated using the HOMA-IR assessment model (a simple and non-invasive method for estimating insulin resistance during pregnancy using glucose and insulin). The authors have found a close correlation between HOMA-IR and L-concentrations, but no correlation with AN levels (5). The study conducted by Lapass shows that the release of AK and especially of resistin, L and AN is altered in GD, compared to that in pregnant women without pathology.

In conclusion, the studies conducted so far have not clearly established the effects of BMI/ pregestive adiposity and weight gain during pregnancy,

on leptin level changes. Thus, further prospective studies are required to determine the predictive ability of leptin in GD.

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