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Gestational Diabetes Mellitus: highlights about biochemical agents that subscribe its physiopathological mechanism during gestational trimesters

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is a common complication in which hyperglycemia goes by physiological state, beneficial to the embryo, to metabolic condition that causes damage to both mother and child. Placental hormones, insulin resistance, visceral fat tissue, dyslipidemia, and other biochemical agentes, subscribe the physiopathological mechanisms that lead to GDM. Nowadays, there are mRNAs, proteins, and even vitamins being associated with GDM risk and its pathophysiology. These new pathways usher a new horizon to discover and describe other important parts of metabolism that play a key role to GDM. With a larger picture of pregnant women metabolism prior and after GDM, better predictors and efficient treatment can be managed.

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Introduction

Pregnancy is a natural process that most women are able to experience during life. Several events happen during gestation in order to maturate the fetus and promote the birth. Although the female body has been prepared to carry pregnancy without the occurrence of any disturbance, there have been many agents that can cause alterations in women physiology, and even to promote diseases[1]. One of the most common complications that can appear during pregnancy is Gestational Diabetes Mellitus (GDM) [2-5].

According to the American Diabetes Association (ADA), GDM is the type of diabetes that is estabilished during the second or third trimester of gestation without records associated with diabetes prior to pregnancy[2]. For the diagnosis, ADA recommends two strategies: the one-step, which requires a 75-g oral glucose tolerance test after 8 hours of fasting; or the two-step, formed by a 50-g nonfasting glucose load test followed by an 100-g oral glucose tolerance test. Both strategies can be performed around the 24th-28th week of pregnancy in order to screen for GDM[2].

In the world, 7 % of all pregnancies are associated with GDM[2], but this number may range from 1 % to above 30 % due to type of studies and their respective populations[3]. In Brazil, specifically, there are 200.000 new cases each year[4]. These numbers highlight how often GDM can happen. However, there are new thresholds for GDM tracking, ADA has decreased the minimum glycemia for GDM diagnosis, and that may increase the number of GDM in the next years[2,5].

The hyperglycemia during gestation is a result of a set of factors, among which the activities of some hormones, for example, human chorionic somatomammotropin, growth hormone, and corticotropin releasing hormone, all these hormones are produced by the placenta[5]. Thus, as the placenta grows throughout the gestation, the serum levels of these hormones increase, with concomitant increase in the plasma glucose values, which start to match frank hyperglycemia, establishing the GDM. This scenario is reached between the 24th and the 28th week of pregnancy, and that is why there is consensus of testing for GDM during this period[2]. Besides that, studies with earlier weeks of pregnancy could not find strong relations to predict GDM[2,3,5].

Moreover, there are some risk factors very associated with GDM. Women above 40 years of age have twofold increased risk than those below 30 years. Male fetus and twins also seem to increase GDM prevalence, but information regarding these associations are not well stabilished[5]. The increase of GDM cases is also related to comorbidities, such as genetic risks, and lifestyle of most populations, which is commonly based in high fat and high caloric diets, and sedentary behaviours. And, the most common risk factors are a previous pregnancy with GDM and family history of Type 2 Diabetes Mellitus[4,5]. These last risks are strongly related to GDM, because of several genetic pathways that can be inherited and can cause damage to glucose metabolism[6]. Then, it is necessary to point that the disturbance in carbohydrates metabolism is not only caused by placenta hormones, but also by marginal insulin secretory capacity and impaired insulin sensitivity[2].

Among the main problems, GDM can lead to pre eclampsia, macrosomia, congenital malformation, and cesarean[2,3,5]. All of these complications increase risk of death during pregnancy and birth for the woman and the child[3,5]. After birth, GDM is considered a sign to future Diabetes Mellitus and cardiovascular diseases for puerperal women. In addition, children are also at increased risk of becoming obese adults and/or with other metabolic disorders, and, if female, to have higher risk to develop GDM when pregnants[1,7].

A woman that had GDM needs to be accompanied by a health team, since needs to have her blood glucose levels monitored, and needs to have the risk range assessed for other metabolic injuries and cardiovascular diseases, as well as her child [1,2,7]. So even if GDM is resolved after birth, complications for both the mother and the fetus (and the unborn child and adult)[7,8], studies

and a better understanding of the biochemical agents that can corroborate to its development are necessary, in order to also identify updates on new analytes, which are gaining importance in this pathophysiology.

First Trimester

At the first trimester of gestation, pregnancy is accompanied by several alterations for the female human body[9], but risk for GDM is not certain, because there is a lack of studies that establish possible thresholds during this period[2,9,10]. Even though there is not a specific time-period for GDM occurrence, progressive increase in glycemia might start as soon as the placenta is formed[11-13].

There is a trend to consider women prone to GDM due to family history and previous gestations with GDM. Thus, studies consider women without these factors as low-risk[14], and women with at least one of factors, as high-risk[15]. In addition, there are those with family history for dyslipidemia and obesity, which are also considered to be high-risk due to the relation of these conditions to Type 2 Diabetes Mellitus prevalence [14,15].

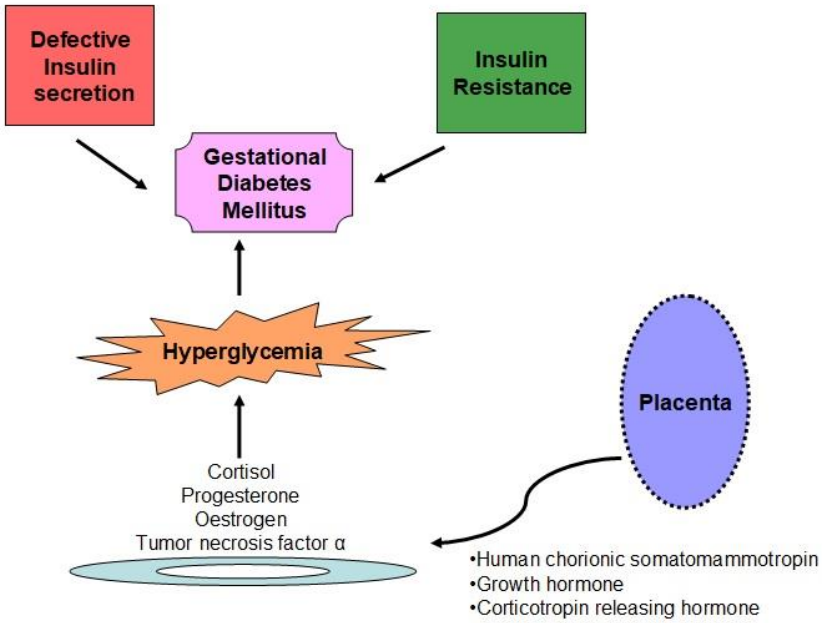

Figure 1. Most common explanation for Gestational Diabetes Mellitus etiology.

Low-risk women can present hyperglycemia during fasting, but case control studies showed that the levels of glycemia for GDM women though higher than control women are often lower than ADA threshold to GDM, and that might be why is difficult to diagnose it in earlier stages[16]. Moreover, other variables such as body mass index (BMI), systolic and diastolic blood pressure, fasting insulin, insulin resistance index (HOMA-IR), glycosilated hemoglobin (HbA1c), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), and triglycerides (TG) are also prone to be higher in women that develop GDM than the ones that do not, but levels are not higher than the necessary for diagnosing any dysfunction of metabolism, in the first trimester[2, 16].

As some highlights, systolic blood pressure for women that develop GDM range from 100 mmHg to 122 mmHg, diastolic blood pressure varies from 64 mmHg to 80.2 mmHg; fasting glucose is below 85 mg/dL; TC is below 150 mg/dL, LDL-c is below 100 mg/dL, and TG is below 150 mg/dL[16]. However, it is interesting to note that studies have reported that even with fasting glycemic levels below 100 mg/dL, pregnant women in the first trimester present significant higher

values of plasma glucose than in other gestational periods[16,17]. This understanding is important to the biochemical evaluation of GDM, because the fasting blood glucose has a higher relationship with insulin resistance, which may be developing in women in the first trimester, generating hyperinsulinemia, that acts as an adaptation to the increased demand for insulin. Thus, all this occurs before the damage to pancreatic β-cells and the consequent development of established hyperglycemia, in the more advanced stages of pregnancy[17, 18].

Hyperinsulinemia is associated to alterations in the lipid and lipoproteic profile; and, in the pregnancy, this resembles to a more atherogenic profile, which can be under-identified in the first trimester[16], since the alterations in the serum levels of lipids occur mainly in the second half of the gestational period[2]. However, in the first trimester, even without quantitative alterations, it is possible to note dysfunction in the lipid metabolism and to estimate its impact on development of the GDM[14-18]. Moreover, most of the variables are related to lipid metabolism, or can be a consequence of its complications, and in the first trimester, one tool to magnify the tracking through serum lipids quantification is the TG/high-density lipoprotein cholesterol (HDL-c) ratio[14]. Since this technique associates two lipid variables, it becomes more sensible to signaling dyslipidemia, and it can act as ***a valuable index for estimating the risk of GDM in the first months of pregnancy[14].***

Furthermore, the TC/HDL-c ratio is another tool more sensible than brute values of TC and HDL-c, separately[14]. Oxidative stress is identified as one of the main causes that link the lipid alterations and GDM[14-18]. Oxidative stress seems to cause impaired insulin sensitivity, reduced insulin receptor numbers and lower exteriorization of receptors in cell membranes. Thus, decreasing insulin activity[16]. And, damage in pancreas cells, specifically in β-cells, is also considered to occur in the presence of oxidative stress. Therefore, it causes not only a decrease in the activity of this hormone, but also a lower production of insulin[15].

BMI has also been considered in the evaluation of the risk for GDM[9]. However, studies have shown that abdominal visceral adipose tissue depth (VAD) is more reliable and may predict insulin resistance, impaired tolerance glucose, and GDM, in the first trimester[19]. For high-risk women, there are other markers than can be associated with the occurrence of GDM. BMI, C-reactive protein (CRP), sex hormone binding globulin (SHBG), adiponectin, and 1,5 anhydroglucitol (1,5AG)[15]. For high risk women, the values are often discrepants than control groups, and meet diagnose criteria[15]. However, these biochemical agents are also in low-risk women, and are independent factors to subsequent GDM, nevertheless with lower sensivity than found in high-risk women. Adiponectin and 1,5AG are the strongest related to GDM. Women pregnants with lower concentrations of 1,5AG has 40 % more risk to GDM, and though the adiponectin is produced by fat tissue, this hormone is related to reduction in dyslipidemia and insulin resistance, with the decrease of adiponectin presenting a 3.3 odds-ratio to GDM[14].

Other biochemical agent very important in the first trimester, that subscribes the physiopathology of GDM, is the pregnancy-associated plasma protein A (PAPP-A) [20]. This molecule is synthesized by the placental syncytiotrophoblast, and it has an association to the insulin-like growth factors (IGF). PAPP-A catalyzes the cleavage of the three binding proteins to IGF, promoting the release of active IGF. Normal levels of PAPP-A are related to good gestational development, however low levels of this protein in the first trimester are associated to metabolic complications, including GDM with future problems of health linked to chronic diseases for both mother and child. This emphasizes that is very important to investigate these biochemical agents and these metabolic conditions in the estimative of the risk for GDM, in the early months of pregnancy[16,19,20].

Second and Third Trimesters

Placental hormones activity increases glycemia in a physiological event to maintain fetus maturation[2, 21, 22]. Nonetheless, there are some cofactors that induces higher liberation of glucose in bloodstream, leading to GDM[23]. In these gestational stages, second and third trimesters, there is a progressive development of GDM with a potentiation of hyperglycemia[24]. It has been proposed that a greater injury in the pancreatic β-cells may occur through the relationship between hyperglycemia and the increased serum levels of the platelet-derived growth factor (PDGF)[25]. Higher blood concentrations of this biochemical agent, of this molecule, raise its signaling in the pancreatic β-cells, and thus it provokes higher breakdown of glucose tolerance, and lower gene expression to proteins linked to insulin synthesis. Hyperglycemia is more often to appear during the 24th and the 28th week of pregnancy[2]. And, this hyperglycemia already characterizes GDM[1-3,18].

Dyslipidemia usually also begins around the 24th and the 28th week of pregnancy, and it is established, mainly, in the second half of the gestational period[21]. This dyslipidemia is marked by increase in TG levels, in free fatty acids, small and dense LDL particles, and lowers cholesterol concentrations of high-density lipoproteins (HDL-c), that is the type of dyslipidemia found in other metabolic diseases, such as metabolic syndrome[2, 21].

Obesity, diagnosed by BMI, is well associated with GDM in the second and third trimesters. BMI is becoming less usefull lately, but another obesity parameter, fat tissue depth, has great association with GDM, as well as in the first trimester[19]. Literature provides that vaste fat tissue reduces adiponectin concentrations, and is a sign of hypertriglyceridemia, hypercholesterolemia, and dyslipidemia, in general[19,21]. Besides that, obesity is associated with oxidative stress, chronic inflammation, and reduction of insulin sensitivity[26].

Moreover, placental hormones increase glycemia progressively during pregnancy, because of placental growth follows fetal growth. There are hyperglycemia, increase in hydrolysis of triglycerides into free fatty acids, and aminoacids turnover. A small list of these hormones contains cortisol, progesterone, oestrogen, human chorionic somatomammotropin, growth hormone, corticotropin releasing hormone, and tumor necrosis factor α[5]. Though these hormones and events seem to cause diverse pathophysiologies, they are actually physiological steps to fetal maturation[27]. However, GDM occurs when these events find the presence of an organism with impaired insulin production due to genetic conditions or oxidative stress in pancreas, and impaired peripheral function of insulin receptors. This has been the classic mechanism to explain GDM[2,5].

Another mechanism associated to placental hormones are the extracellular vesicles released by placenta in plasma of pregnant women, another horizon for important investigations[28]. Some studies found that concentrations of these particles in pregnant plasma range from 1.0 x 10^9 particles / mL in the first trimester to 1.5 x 10^9 particles / mL in the third trimester. These exosomes may contain residues of placental hormones, and maintain hormones availability for a longer time, increasing their acitivities. Other possibility lies on chronic inflammation caused by non recognition of vesicles by the pregnant women antibodies. Thus, this is another pathway that begins to be investigated, but seem to hold important details to understand GDM pathophysiology[28].

Family hystory, inherited characeristics, are also very associated with GDM, but some genes has been studied[29-31]. There are several studies that associate maternal or family history of diabetes mellitus, obesity, and dyslipidemia with GDM, but these studies classify gene relation with historic records, there is not particular genetic markers studied[2,5,29-31]. This occurs in all the stages of gestational period, but it has been more observed after the first trimester. One specific marker, miR-330-3p, a circulating microRNA that is associated with insulin secretion, is increased in women that develop GDM[32]. The

strong association of this microRNA may be a better source for prediction of GDM, and could reduce cesarean birth[32].

Glutatione S-Transferase (GST) M1 and T1 gene polymorphisms were also investigated, but were not related to GDM[33]. These ubiquitous molecules play a role of becoming toxic (increasing apoptosis and oxidative stress) in higher concentrations, such as during pregnancy, but this hypothesis is not confirmed, because of low relation between GST concentrations and GDM. However, serotonin, another protein was found decreased during parturition, and this was related to downregulation of gene expressions for pancreas health (Gene otology and KEGG pathway), and upregulation of gene expressions associated with reduction in islets mass (Cdc25c, Cdc20, Aurkb, Ccna2, Rps6kb1, Ccnb2, Ccnb1 and Cdkn1a)[33]. This mechanism could reduce risk for hyperinsulinemia, another promoter of macrosomia and perinatal risks, but studies associate the decrease in pancreas mass to loss of pancreas function, causing impaired insulin production, which is very serious in the later gestational stages[33].

In addition, a last molecule, vitamin D, has been found reduced in women with GDM, mainly in the second and third trimestres[34]. There is not specific responses to its action, but other perinatal outcomes are also related to lower levels of this vitamin[34,35]. Other possibilities to explain GDM lies on ethnicity[31], physical inactivity[36], dietary composition, hypertension, and polycystic ovarian syndrome[5]. As family history[30], these aspects are mentioned, but new studies investigating pathways are needed to clarify the possible mechanisms, such as protein signaling and mRNAs expression. Thus, it is very interesting to note that there is a wide range of old and new molecules that can provide a guide in the managing of GDM.

Table 1. New biochemical agents with possible relation to Gestational Diabetes Mellitus development.

First Trimester	Second and Third Trimesters
SHBG	mRNAs markers of pancreas disorder
Adiponectin	Vitamin D
1,5AG	Placental exosome
PAPP-A	Dyslipidemia
Hyperinsulinemia	Serotonin

SHBG: ***platelet-derived growth factor***; 1,5AG: ***1,5 anhydroglucitol***; PAPP-A: ***pregnancy-associated plasma protein A***.

Conclusions

Pregnancy has had high risk to GDM development. Placental hormones are the main cause of hyperglycemia, with lipid and insulin metabolism playing key roles to the development of GDM in the classic mechanism. Lately, new biochemical agents are being associated with GDM pathophysiology, and there are some specific to earlier stages of pregnancy and others to later stages. Earlier markers are directly related to glycemia, such as SHBG, adiponectin, 1,5AG, and PAPP-A. For later stages, mRNAs markers of pancreas disorder, vitamin D, and extracellular vesicles released by placenta might track and present higher risk to dysfunction in insulin metabolism. Thus, GDM is a multifactorial disorder, in which several metabolic routes play an important role, and need to be considered in order

to promote quality of life to the women that have this alteration during pregnancy and their children.

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