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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«Η επίπτωση της αλλαγής τρόπου ζωής με δίαιτα και άσκηση στην εμφάνιση σακχαρώδη διαβήτη κύησης σε γυναίκες υψηλού κινδύνου»

ΠΑΠΑΓΙΑΝΝΗ ΕΙΡΗΝΗ
ΔΙΑΙΤΟΛΟΓΟΣ – ΔΙΑΤΡΟΦΟΛΟΓΟΣ

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« The effect of change of life with diet and exercise in the drawing of gestational diabetes mellitus in women who have a high risk of disease »

ΕΥΧΑΡΙΣΤΗΡΙΟ ΣΗΜΕΙΩΜΑ

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Περίληψη

Ο σακχαρώδης διαβήτης κύησης (GDM) είναι μια δυσανεξία στους υδατάνθρακες που σχετίζεται με την εγκυμοσύνη και εμφανίζεται ως επί το πλείστων στο δεύτερο και τρίτο τριμήνου της εγκυμοσύνης. Τις τελευταίες δεκαετίες παρατηρήθηκε αύξηση του επιπολασμού του σακχαρώδη διαβήτη κύησης κατά τη διάρκεια της εγκυμοσύνης, η οποία μπορεί να είναι επακόλουθο πολλών και διαφορετικών παραγόντων κινδύνου όπως είναι τα αυξημένα επίπεδα παχυσαρκίας, οι λανθασμένες διατροφικές συνήθειες που ακολουθούνται από γυναίκες και η έλλειψη σωματικής δραστηριότητας πριν ή κατά τη διάρκεια της εγκυμοσύνης. Ως εκ τούτου, είναι σημαντικό να διερευνηθεί πώς η τροποποίηση της διατροφικής συμπεριφοράς, είτε όσο αφορά τα μεμονωμένα θρεπτικά συστατικά είτε τα γενικά διατροφής πρότυπα αλλά και τη σωματική δραστηριότητα ως ανεξάρτητο παράγοντα ή σε συνδυασμό με τη διατροφή, μπορεί να συμβάλει στη μείωση αυτού του επιπολασμού σε γυναίκες που παρουσιάζουν υψηλό κίνδυνο για εμφάνιση της νόσου του σακχαρώδη διαβήτη κύησης.

Λέξεις κλειδιά: σακχαρώδης διαβήτης κύησης, διατροφή, άσκηση, διατροφικά πρότυπα και σακχαρώδης διαβήτης κύησης, άσκηση και σακχαρώδης διαβήτης κύησης

ABSTRACT

Gestational diabetes mellitus (GDM) is an emerging pregnancy-related intolerance to carbohydrates during the 2nd and 3rd trimesters of pregnancy. In recent decades there observed an increase in the prevalence of GDM during pregnancy, which may be linked to several risk factors such as increased levels of obesity, erroneous dietary patterns followed by women and lack of physical activity before or during pregnancy. Therefore, it is important to investigate how dietary behavior modification, either regarding individual nutrients or overall nutrition patterns and physical activity alone or in combination with nutrition, may help reduce this prevalence in women showing high risk for gestational diabetes mellitus.

Keywords: gestational diabetes mellitus, nutrition, exercise, dietary patterns and GDM, exercise and GDM.

CHAPTER 1

1.1 Introduction

Diabetes mellitus is a haeterogenous disorder, characterized by hyperglycemia which results either from decreased insulin secretion, or from decreased insulin action. Uncontrolled chronic hyperglycaemia is associated with long-term dysfunction or destruction of organs such as eyes, kidneys, nerves, heart and blood vessels. Diabetes is a chronic, complex illness that requires continuous medical intervention not only for good glycemic control but also for the improvement of many other factors that contribute to chronic diabetic complications and impair quality of life. There are different types of diabetes mellitus (DM) such as type 1, type 2, gestational diabetes mellitus, pancreatic and other types.

Life style changes, with diet and exercise, are the cornstone for diabetes management. Weight management is important for good glycemic control in patients with type 2 diabetes. Carbohydrate control through diet is also important for patients with type 1 diabetes for controlling hyperglycaemia. Additionally, both the amount and the type of food affect the postprandial glucose levels. [1]

1.2 Gestational diabetes mellitus.

Carbohydrate disorder occurring for fist time during pregnancy, after the 24-28 week of gestation[2]. The definition of the GDM, also includes women with pre-existing diabetes who have not yet been diagnosed, but also those who developed it during pregnancy (especially during the third trimester of pregnancy) [3]. Continuously over the years, a large number of pregnant women worldwide develop gestational diabetes mellitus (GDM). The incidence of GDM is around 18%, depending on the diagnostic criteria used. [4]

Symptoms of GDM are the same as those of diabetes outside pregnancy, ie polyuria, polydipsia, nocturia, sensitivity to vaginal infections and failure to obtain the expected weight for pregnancy.

The presence of gestational diabetes results in unwanted effects to both the fetus and the mother, such as macrosomia, need for caesarean section, jaundice, tetanus, pre-eclampsia, premature labor, hypertension, choriomannicitis, and even endometrial death. There is also a greater risk of obesity for the child and diabetes for both. [1, 5]. Surveys have shown that women with elevated glucose levels, although not meeting the criteria for gestational diabetes mellitus, are equally at risk of prematurity, macrosomia, and choriomagnunitis [6]. Women suffering from gestational diabetes mellitus have a 7-fold greater risk to obtain type 2 diabetes later in their life compared to women who have a normal glycemic profile [7]. Increased risk is affected by factors such as race, obesity and the presence of history of diabetes or gestational diabetes [8].

1.3 Pathophysiology and Symptoms

The GDM is usually diagnosed after the twentieth week of pregnancy, when placental secreted hormones, such as, placental lactogens, placental growth hormone, cortisol and progesterone, which exert opposite effects of that of insulin on glucose metabolism, are significantly increased and are likely to be the triggers of these physiological changes [9] [10].

In the development of a normal pregnancy, insulin does not bring the same efficacy in transferring glucose from the blood to the mother's tissues so that she can supply the baby with the necessary nutrients. [11]. This resistance to insulin increases as pregnancy progresses and the GDM occurs when insulin secretion is not able to overcome this resistance [9]. Women with adequate insulin secretion during pregnancy outweigh this resistance to insulin by producing more endogenous insulin to maintain blood glucose concentrations within normal limits. However, other women are unable to produce enough insulin to overcome the increase in insulin resistance, resulting in glucose intolerance. Increasing insulin resistance in normal pregnancy, especially during the third trimester, helps respond to the increased demand for nutrients for fetal development and promotes fetal development by increasing maternal glucose delivery [10]. For women with GDM, however, higher maternal insulin resistance may lead to maternal hyperglycemia, increased glucose transfer from the placenta to the fetus,

hyperinsulinemia and accelerated fetal growth [12]. Typically, maternal insulin resistance induced in pregnancy disappears immediately after the birth of the baby.

It is widely observed that in an unseen or poorly controlled gestational diabetes mellitus, hyperglycaemia is connected with signs such as polyuria (increased urination frequency), polydipsia (increased thirst), blurred vision and fatigue, although a lot of women do not present any symptoms [13].

Glucose abnormalities are often repeated in subsequent pregnancies. Pregnant women with GDM run a high risk of developing diabetes in the future. The cumulative incidence of diabetes after diagnosis of GDM varies according to the maternal body mass index (BMI), nationality and time from pregnancy, and may reach high levels such as 60% [14]. When glucose abnormalities persist after giving birth to a woman with a GDM, she probably had pre-pregnancy diabetes, particularly if the RSV diagnosis taken place before 20 weeks of gestation and glucose levels were significantly elevated during pregnancy and in which case its diabetes is again categorized as manifest diabetes.

1.4 Risk factors

In recent decades the incidence of GDM has increased, with a tendency to continue alongside the rise in obesity and type 2 diabetes [15]. It is ambiguous whether the increased rates in obesity can influence the percentage of women diagnosed with obvious diabetes during pregnancy in relation to transient glucose intolerance caused by pregnancy. The risk factors for the GDM, identified by observational studies, include maternal BMI of 30 kg / m², body inactivity [16], maternal age [17], nationality (Hispanics, Africa, the Americas, South and East Asia, women from the Pacific Islands have a higher risk than women of other nationalities). Low dietary fiber diets and / or high glycemic load have been proved to enhance the risk for GDM. [18]. Women who had a previous pregnancy with a baby with ~~a~~ macrosomia (birth weight of 4,000 gr or more) are also at increased risk for GDM, or have already had a CVD, or have a background or family of first degree diabetes or have polycystic ovarian syndrome [19]. In addition, overweight, obesity and metabolic syndrome [20], or excessive weight gain during pregnancy are important risk factors for the development of GDM [21] [22]. The more the risk

factors the higher the risk for GDM while women at moderate GDM risk do not meet all the criteria of low risk women but lack two or more risk factors for GDM. Low risk for GDM has a young (≥ 30 year old), non-Hispanic, white, with normal BMI (≥ 25 kg / m^2), without history of previous glucose intolerance or adverse pregnancy related to GDM and first degree relative with a known type of diabetes [23][24]. Risk factors for developing GDM mellitus can be divided in modifiable and non-modifiable (table 2) [25] [26].

Table 1. Risk Factors

Modifiable risk factors	Non-modifiable risk factors
Obesity before pregnancy or rapid weight gain during pregnancy	Age over 30 years of age
Underweight women (<50 kg)	A race particularly prone to diabetes such as (South Asia, South America, Africa, Spain, Atlantic islands, indigenous Australian breeds)
More than four pregnancies	Polycystic ovary syndrome
Hypertension	Family history of Type II diabetes mellitus or gestational diabetes
Dyslipidemia	An individual history of glucose or diabetes mellitus
Use of glucocorticoids in pregnancy	Multiple pregnancy
Women who smoked before pregnancy	Have a newborn with overweight (macrosomia) in a previous pregnancy and / or cesarean section
Glucosuria (++ or more in general urine)	Poor Obstetricity: automatic miscarriages, endometrial death, baby macrosome (birth weight 4 kg or more)

1.5 Diagnosis

There does not seem to be an international consensus on the control point, the screening method and the optimal limits on the diagnosis and intervention of GDM. DIPSI (Diabetes in Pregnancy Study Group India) [27] is a non-fasting glucose tolerance (OGTT) oral test with 75g of glucose with a cut off of ≥ 140 mg /dl after 2 hours, while WHO Health Organization [2] recommends an OGTT fasting where the woman is fasting before the test is provided a 75 g glucose load, by measuring the blood glucose concentration after the first and the second hour

with a cut off plasma glucose ≥ 140 mg /dl after 2 hours. Finally, ACOG [28] proposes a 2-step procedure, GCT with glucose 50g non-fasting if the value> 7.8 mmol /l, accompanied by 3 hours OGTT to confirm the diagnosis.

Adoption and use of these recommendations in medical practice worldwide will help to drive a significant change that will lead to an increased diagnosis of GDM in several countries in need, and subsequently several changes and challenges for healthcare systems. In addition, studies carried out have shown significantly higher prevalence of GDM using these criteria than previously used techniques (including WHO), while other studies confirm the existence and consequently increased incidence of unwanted pregnancies in women who have been diagnosed [29]. The classification and diagnostic criteria for GDM according to various European and global associations are shown in Table 2 for comparison.

Table 2. Diagnostic criteria for the GDM with the corresponding glucose values

Guidelines	Fasting glucose Mg/dl (mmol/l)	Glucose challenge	1-hour plasma glucose Mg/dl (mmol/l)	2-hour plasma glucose Mg/dl (mmol/l)	3-hour plasma glucose Mg/dl (mmol/l)
WHO 1999*	≥126 (7.0)	75 g OGTT	Not required	≥ 140 (7.8)	Not required
ACOG **	≥95(5.3)	100gOGTT	≥180(10.0)	≥155 (8.6)	≥140 (7.8)
Canadian Diabetes Association***	≥95(5.3)	75 g OGTT	≥191(10.6)	≥ 160(8.9	Not required
IADPSG****		75 g OGTT	≥180(10.0)	≥ 153 (8.5)	Not required
DIPSI*		75 g OGTT	Not required	≥140 (7.8)	Not required

*** A value sufficient to diagnose**
**** Two or more values required for diagnosis**
***** Two or more values are required for diagnosis**
****** A value is sufficient for diagnosis**

As stated above, for several years now any level of glucose intolerance which was first identified in pregnancy has been defined as diabetes mellitus, without the physician concerned whether or not this condition would exist before or after pregnancy [30]. This delimitation and by extension, the definition made it easier to have a common method for the detection and classification of the disease, even though it confuses the medical practice with inaccurate data.

The increasing disease of obesity and diabetes has resulted in an increase in the incidence of type 2 diabetes in women of reproductive age and an increase in undiagnosed pregnant women with type 2 diabetes [31]. Therefore, due to the increased number of non-diagnosed pregnant women with type 2 diabetes, all pregnant women who were at high risk of developing GDM during their initial prenatal screening were screened for the disease on the basis of standard diagnostic criteria [32].

All women found to be positive for diabetes using regular diagnostic criteria after examinations during the first three months of pregnancy should be included in the category of women with pre-existing diabetes (type 2 diabetes or, very rarely, type 1 diabetes or unilateral diabetes). Subsequently, women diagnosed in the first trimester of pregnancy with prediabetes are advised of their lifestyles until these changes can decrease their chances of developing type 2 diabetes and mayde GDM, although further research in this part is considered necessary [33]. GDM is diabetes which diagnosed for the first time in the second or third trimester of pregnancy, which did not exist as type 1 or type 2 diabetes. The 75 G OGTT diagnostic criteria for GDM diagnostic criteria as well as those used to screen people with GDM in the two-step approach were not derived from data collected during the first half of pregnancy. it should also be noted that in the early stages of pregnancy the diagnosis of GDM with FPG or OGTT values is not data based [34]. In conclusion, it is understood that women who developed GDM during pregnancy are at increased risk for type 2 diabetes immediately after pregnancy. For this reason, and since there are disease recruitment procedures, you may find it necessary for women who have had GDM during their pregnancy to have lifelong screening for all types of diabetes[35-39].

Gestational diabetes mellitus carries risks for the mother, fetus and newborn. The study of Hyperglycaemia and Unwanted Pregnancy (HAPO) [40], an extensive multinational cohort study, which included data from 23,000 women, showed that in the first 24 weeks of pregnancy, the risk of unpleasant symptoms for both the mother and the fetus initially and the baby subsequently continued to increase although maternal glucose levels were within the range previously considered normal for pregnancy. These data led the researchers to re-examine the diagnostic criteria for GDM. Therefore, GDM can now be diagnosed with one of the two strategies listed below.

1. One-step strategy with 75g OGTT
2. Two-step strategy with 50g (non-fasting) screen followed by a 100g OGTT for those

who screen positive.

The various diagnostic criteria for the disease will determine the degree of maternal hyperglycemia and the risk of the mother and fetus, resulting in conflicting opinions from experts on the best strategies for diagnosing GDM.

One-step strategy

The IADPSG defined the diagnostic criteria for GDM in pregnant women who were 24 to 28 weeks pregnant and participated in the HAPO study as fasting one hour and two hours mean PG values over a 75-g OGTT. In the median fasting 1 hour and 2 hours of the population the study showed that the probability of adverse effects increased by 1.75 times compared to the estimated odds. In conclusion, in the one-step strategy, the researchers expected to see an increase in the event of GDM (from 5-6% to 15-20%), since with only a non-physiological value they could diagnose the disease[41]. This anticipated increase in the incidence of the above-mentioned disease could create significant problems in the cost of medical care and additionally characterize abnormal pregnancies as many of those previously categorized as normal.

In a follow-up study, a follow-up study found that women with GDM who were categorized with one step strategy compared with women who were undiagnosed were 3.4 times more at risk for prediabetes and type 2 diabetes, children who were born were in danger of developing obesity and increased body fat. As a result, women categorized with GDM benefit from the unpleasant consequences of the disease in the future [42]. However, the ADA recommends these diagnostic criteria in order to optimize pregnancy outcomes, because these criteria were created on the basis of pregnancy approval and not based on predictions of what might happen after GDM.

Several intervention studies with a sample of women who had lower levels of hyperglycemia show positive results for children with GDM. It should be noted that these women were diagnosed with previous criteria for GDM. The data from these studies also showed moderate benefits [43] [44]. It should be noted here that in these two studies that ≥80% of pregnant women undergoing mild treatment for GDM would only be able to follow advice on a modified lifestyle. In these two studies, glucose values well above the threshold set by the IADPSG and in one trial, the two hours of PG threshold (140mg / dL [7.8 mmol / L]) was lower than the cutoff recommended by the IADPSG. (153 mg / dL [8.5 mmol / L]) [44]. It should be

mentioned here that no data have been presented comparing the results of the above non-randomized controlled trials for GDM and its treatment based on the IADPSG criteria in relation to the pre-existing criteria. Studies should also be conducted to investigate the future risk in women treated with low levels of hyperglycemia as a reference to the development of another type of diabetes. In conclusion, there is an urgent need to conduct research to determine with tangible evidence the rate of follow-up and treatment of women with GDM characterized by the one stage strategy [45] [46].

Based on the results of the study (HAPO) [47] as mild degree dysgeusia which has the negative effects and high prevalence of type 2 diabetes to have international consensus constitutes the IADPSG criteria, although the controversy persists. The IADPSG criteria are the only ones that based on the results could diagnose and treat GDM earlier, thus reducing the complications of the fetus and mother that come from the GDM. This practice is superior as it is simple to execute, patient-friendly and results are correct and consistent with international consensus.

Two-step strategy

After all this data, about six years ago, a study team was convened by the National Institutes of Health (NIH) to study the diagnostic criteria for GDM [48]. This board consisted of 15 members each representing a field such as obstetrics/gynecology, maternal fetal medicine, pediatrics, endocrinology, biostatistics and other fields. The team decided that a two-step strategy in order to investigate GDM, which used a one hour 50g glucose (GLT) test, followed by 100g three hours OGTT for those women who showed a positive result, would be better. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135 or 140 mg/dL for the 1 hour 50g GLT [49]. The team compared GLT cutoffs of 130 mg /dL (7.2 mmol / L) and 140 mg/dL (7.8 mmol / L) [50]. The highest cut yielded 70-88% sensitivity and 69-89% specificity, while the lowest cut yielded 88-99% sensitive and 66-77% specific. Data on a cutoff of 135 mg/dL are limited. As for other screening tests, the choice of a cut is based on the exchange between sensitivity and specialization [51].

The decision in favor of the 2-step strategy, according to NIH researchers, was based on the lack of robust data from clinical studies that presented the positive results of a one-step strategy combined with the negative effects on health care and the costs it would likely incur.

creating a group of women with GDM. Also, in the 50g GTL test, women do not have to fast to be able to do it, which makes it much easier and simpler. Treatment of higherthreshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births[52], and shoulder dystocia, without increasing small-for-gestational-age births. ACOG concludes in favor of the two-step strategy but also states that the one-step strategy can diagnose GDM [49]. The same organization recommends one of two sets of diagnostic thresholds for OGTT 3h-100g [53, 54]. Each of these two is supported on various mathematical transformations of the initial suggested thresholds, which used whole blood and non-enzymatic methods to determine glucose. An upcoming analysis of the data from a randomized clinical trial for the diagnosis and treatment of mild GDM [55] presented data supporting that patients who met only lower thresholds[53] were equally as good as those with higher thresholds[54]. As far as the two-stage strategy is concerned, it is advisable to study the limits based on the table 3 below [39].

Table 3— Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.
The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.
If the plasma glucose level measured 1 h after the load is 130 mg/dL, 135mg/dL, or 140mg/dL (7.2mmol/L, 7.5mmol/L, or 7.8mmol/L, respectively), proceed to a 100-g OGTT.
Step 2: The 100-g OGTT should be performed when the patient is fasting.
The diagnosis of GDM is made if at least two* of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h during OGTT) are met or exceeded:

	Carpenter-Coustan (86)	or NDDG (87)
Fasting	95 mg/dL (5.3 mmol/L)	105 mg/dL (5.8 mmol/L)
1h	180 mg/dL (10.0 mmol/L)	190 mg/dL (10.6 mmol/L)
2h	155 mg/dL (8.6 mmol/L)	165 mg/dL (9.2 mmol/L)
3h	140 mg/dL (7.8 mmol/L)	145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *ACOG notes that one elevated value can be used for diagnosis (82).

In conclusion, according to the latest guidelines published by the ADA (American diabetes association) for the diagnosis of gestational diabetes mellitus, the one-step strategy of 75g glucose OGTT is suggested, which should take place from the 24th to the 28th week of pregnancy and the final decision on the diagnosis of GDM is obtained if one of the values in OGTT was ≥5.1-10.0-8,5mmol/L [56].

1.6 Screening for GDM

The frequency of the GDM ranges from 1% to 18% depending on the sample population and the diagnostic criteria used [57] [58] [59]. At present, there is a lack of coherence in terms of control procedures and diagnostic criteria among and within the same countries. As mentioned above, there are various diagnostic methods and no uniformly acceptable international diagnostic criteria. Universal screening is encouraged due to the absence of pre – identified risk factors in 50% of cases [60]. However, in some places around the world, only higrisk women are screened considering risk factors[61].

Table 4. Detection procedure (screening) GDM

Risk	Clinical features	Detection test
High (one of the clinical features required)	• Obesity • Diabetes in a 1st degree relative • History of glucose disorder • Persistent glycosuria • A previous macrosomal infant	• Directly • Repeat at 24-28 weeks of gestation if a GDM has not yet been diagnosed
Medium	• Non-inclusion in high or low risk groups	• 24-28 weeks of gestation
Low (all clinical features required)	• Age <25 years • Low risk ethnicity • Absence of diabetes in a 1st degree relative • Normal weight before pregnancy • No history of impaired glucose tolerance • Free obstetrical history	• Not required

1.7 Impact of Gestational Diabetes Mellitus on health

The GDM is related to an increased incidence of several abnormalities during pregnancy including pre-eclampsia and the requirement for childbirth or caesarean section [62] [19]. Also, women who develop GDM are at increased risk of developing GDM in future pregnancies [63] and have a significantly increased risk of developing Type II diabetes later in life. The consequences for the fetus may consist of macrosomia, which in turn could probably be associated with negative effects on the mother in childbirth, such as uterine and perineal rupture [19]. Older babies are at increased risk of birth injury including perinatal asphyxia and shoulder dystonia, bone fractures and the common motor nerve [64]. These infants are at an alarming rate of developing Type 2 diabetes, hypertension, obesity and metabolic syndrome in the forthcoming years [57] [65]. Additionally, children born from mothers with GDM are in danger of developing hypoglycemia [62], respiratory distress syndrome, polycythaemia (increased red blood cell counts), hyperbilirubinaemia, and premature birth[19] [40] [66]. Therefore, if not treated, the GDM may be linked with an enlarging risk of perinatal mortality.

1.8 Management of gestational diabetes mellitus

Treatment for GDM begins with the combination of diet, exercise and weight gain control, depending on pre-pregnancy weight. The continuous monitoring of glucose levels is also necessary and the aim for blood glucose is: (objectives proposed by the Fifth International Gestational Diabetes Laboratory Conference).

- Fasting 95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial 140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial 120 mg/dL (6.7 mmol/L)

Several studies show that about 85% of women with GDM (depending on the population of origin), using the «Carpenter-Coustan» criteria or the National Diabetes Data Group, are able

to monitor the progression of the disease only by varying their lifestyle.

Medical Nutrition Therapy

The practices used nowadays to prevent and treat GDM are aimed at modifying the diet, exercise or combination of these two.

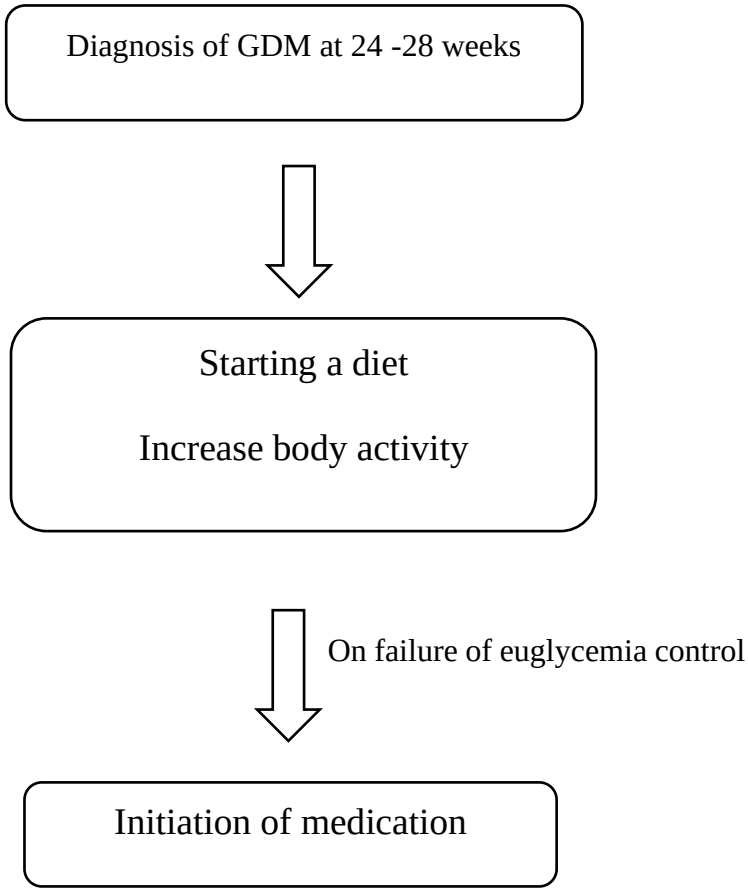
The term medical nutrition for GDM means a personalized nutrition program organized in collaboration with a pregnant woman and a dietician who is aware of the nutritional management of GDM [67] [68]. The diet programme should supply the woman with sufficient calories to promote the health of both the mother and the fetus, while ensuring the desired glycemic goal and weight gain during pregnancy To date, there has been no research that identifies the sufficient number of calories needed and should be taken by a woman with GDM or to suggest that the needs of these women are different from those of pregnant women without GDM. In addition, the dietary plan should be established on the basis of the Dietary Reference Intakes (DRI). The dietary intake threshold for all pregnant women includes 175g of carbohydrates, 71g of protein and 28g of fiber.

Also, physical activity is important in the management of gestational diabetes mellitus. For this reason, each pregnant woman should contact a qualified trainer with knowledge for pregnant women as well as information on the GDM. The exercise plan should be tailored to the needs of the woman and include at least 3 times a week 45 minutes of moderate intensity exercise.

Pharmacological Treatment

If life style changes fail to achieve glycemic control in women with GDM, initiation of pharmacological treatment is needed. The first recommended agent for GDM in the US is insulin. Lifestyle modifications and insulin treatment for women with GDM has been shown to improve perinatal outcomes in two large randomized trials, as summarized in a review by the US Preventive Services Group [69]. While individual RCTs support the restricted efficacy of metformin [70] [71] and glyburide [72] in reducing glucose levels for the cure of GDM, these agents are not proposed as first-line treatment for GDM because they are known to pass through the placenta and there is no data on the safety of the infant [73]. In addition, in two RCTs, gliburide and metformin failed to provide satisfactory glycemic control in women and women with GDM respectively (23% and 25-28% respectively [74] [75] [76].

Algorithm of treatment of GDM



CHAPTER 2 - Aim of the study

The GDM occurs when glucose intolerance is first recognized during pregnancy, irrespective of whether the condition may have occurred before or after pregnancy (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003). Prevention is preferred than therapy and, in this notion, recognizing factors associated with the development of the GDM could potentially assist reducing its incidence and results.

Based on the literature, overweight and obesity as well as dietary habits and sedentary life during pregnancy can lead to numerous complications to the mother and fetus, including gestational diabetes [77] [78] [79] [80].

For this reason, recognizing the nutritional factors at the current stage associated with the development of gestational diabetes mellitus may have made it possible to reduce its incidence and its consequences.

This review is conducted to examine in the literature whether early modification of lifestyle (diet and physical activity) of pregnant women, can lead to the onset of gestational diabetes mellitus.

CHAPTER 3

NUTRITION AND GESTATIONAL DIABETES MELLITUS

3.1 Diet and Prevention of GDM

3.1.1 Energy Recruitment

A study of 399 participants aimed to improve eating habits and reduces the caloric intake of women at high risk of developing gestational diabetes mellitus has shown that women have indeed improved their eating habits, but without clarifying if these women showed a lower incidence of disease [81].

Overweight, obese and severely obese women have two, four and eight times higher risk of developing GDM, respectively, compared to women with normal weight [82]. Also, Torloni et al. [83] concluded that for every 1 unit of BMR growth before pregnancy, the GDM prevalence was increased by 0.92%. Finally, a systematic review of Morriset et al. [17] showed that there is a correlation between weight gain during pregnancy and the risk of developing GDM, regardless of woman's BMR before pregnancy. It is therefore understood that weight gain is an aggravating factor for the emergence of GDM, which will be discussed further in the next chapter.

3.1.2 Macronutrients

A study involving 32 women, of whom 14 had recurrent gestational diabetes mellitus and the other 21 with non-recurrent GDM concluded that women with GDM recurrence consumed 38.4% (by patient’s history) and 41.4% (by food record) of their total fat intake compared to 34.1% and 33.1% of non-recurrent GDM women, respectively [50].

Two prospective studies conducted in GDM showed statistically significant differences in the association between total fat consumption and GDM. The first prospective study, collecting data from 1698 women with food frequency questionnaires and classified them in three

categories (GDM, glucose tolerance - IGT, normal glucose tolerance) found that the overall prevalence of IGT and GDM was 2.6% and 5.2%, respectively. It was also observed that white, married and older women had IGT and GDM. In addition, women with IGT and GDM received more calories from fat than carbohydrates. Also, one of the models studied showed that the risk for IGT increases by 7% and the risk for GDM by 6% for every percentage increase in fat [26]. The same results appeared in Nurses' Health Study II, concluding that replacement 5% of colories from carbohydrate with total fat led to increase the risk of GDM [84].

In a study conducted in 504 Caucasian overweight pregnant women, 126 of whom had gestational diabetes mellitus, 84 had impaired glucose levels and 294 were healthy volunteers, it was found that saturated fatty acids consumption> 30% was associated independently with the development of glucose intolerance in pregnancy [25].

A study conducted in Chinese population involving 171 women, 56 of whom had GDM, 38 IGT and 77 had normal glucose levels, showed that increased intake of polyunsaturated fatty acids was associated with a reduced frequency of IGT during pregnancy. This finding also had serious implications for women at high risk for GDM [85].

As shown in a study analyzed above, high intake of n-3 compared to n-6 fatty acid intake is protective in the onset of gestational diabetes mellitus. Conversely, reduced PUFA consumption was associated with impaired fasting glucose levels in non-obese women without a history of DM [25].

Based on the above data, it seems that fat consumption has a positive correlation with the incidence of gestational diabetes mellitus in women at high risk.

Studies on cholesterol intake and its correlation with gestational diabetes mellitus showed a consistently increased of risk for GDM with higher cholesterol intake [84] [86-88]. Two of these studies with a sample number of 13475 women and 3754 women, respectively, showed a significant increased risk for women who received 300 mg of cholesterol per day or more [26, 84]. More detailed, in the study of Golzalez - Clemente et al. data were collected from 335 Caucasian pregnant women and it was estimated that an increase in cholesterol intake by 50mg / 1000kcal was associated with an average increase of 88% in the risk for GDM [87]. As is evident, therefore, the consumption of cholesterol is positively associated with the appearance of GDM.

In the study of Moses et al. [89], which was analyzed previously, showed that women who reduced their carbohydrate consumption had a higher degree of GDM. Additional data on

carbohydrate consumption were also obtained from the study by Saldana et al. [26], who in one of the models studied showed that adding 100 calories to their carbohydrate diet was associated with a 12% reduction in IGT and a 9% reduction in GDM. As found above carbohydrate consumption is not directly linked to an increase in GDM incidence.

Zhang et all. examined data from 758 cases with GDM at a depth of 8 years of follow-up and concluded that for every 10g / day increase in total fiber intake was associated with a 26% risk reduction for GDM. Also, high nutritional glycemic load was positively associated with GDM risk, while the combination of high glycemic load and low cereal intake was associated with a 2,12 times greater risk for GDM compared to reciprocal diet [84]. The beneficial property of fiber in reducing the chances of developing gestational diabetes mellitus is confirmed by Bo et all. team and Moses et all. team as well [89].

In conclusion, the above studies showed that women who decreased carbohydrate intake had higher rates of GDM, while those who increased their consumption decreased their chances of GDM. Additionally, fiber also plays an important role in the diet of pregnant women as the increase in their daily intake was associated with a decrease in the incidence of GDM. In terms of fat, it appeared that an increase in total fat in the daily diet of women had negative effects on the incidence of the disease. In particular, it was found that consumption of SFA and PUFA was positively correlated with the development of glucose tolerance, whereas consumption of n-3 polyunsaturated fatty acids was negatively correlated. Finally, the data on cholesterol suggest that any increase in women's consumption is positively correlated with an increased likelihood of developing GDM. It appears that obese and overweight women are more likely to develop GDM, and also when a woman gain body weight fast during pregnancy is positively associated with the onset of the disease.

The studies above provide data on individual nutrients taken by humans in their daily lives. However, it should be understood that no diet contains only one nutrient. For this reason, it is more appropriate to look at dietary patterns that research and provide data for a whole nutrition plan.

3.1.3 Type of Diet

The Nurses' Health Study II collecting data from 10 different Mediterranean countries with a sample of 13100 women showed that women without GDM had a higher level of commitment to the Mediterranean diet (consists of high intake of fruit, vegetables, bread, and cereal and low consumption of meat, eggs, cheese, and dairy products) than among those with GDM [90]. Similar findings from 21,376 women proved that adherence to the DASH diet reduces by 34% the risk for GDM, to aMED by 24% and to aHEI by 46% [91]. Nevertheless, it should be mentioned that the diagnosis of GDM in these researches was not made by OGTT, but by self-reporting, and that dietary assessment was made some years preceding pregnancy.

Also, an observational study (N=1076) [90] was conducted to investigate a likely association between the incidence of the GDM and the standard diet of the Mediterranean diet. The researchers hypothesized that the Mediterranean diet can improve glucose tolerance and reduce to some point the impact of the GDM. Indeed, women with GDM in this study had less degree of glucose intolerance than those in previous studies. The association of high total fat intake with risk both DMII and GDM which has been found in a lot of studies (N=338, N=721) [92] [93] [94] confirmed the findings of this study, in which the adhesion to a standard diet. Mediterranean diet is associated with a lower incidence of GDM and a better degree of glucose tolerance, even in women without GDM. A new evidence is not only the relationship of adherence to the Mediterranean diet with a lower incidence of GDM but also a better degree of glucose tolerance in pregnant women without GDM.

Based on a non-systematic review, epidemiological data provide indications that diet can play a role in the development of GDM, and that higher fat intake and lower carbohydrate intake may be associated with increased risk of GDM [95].

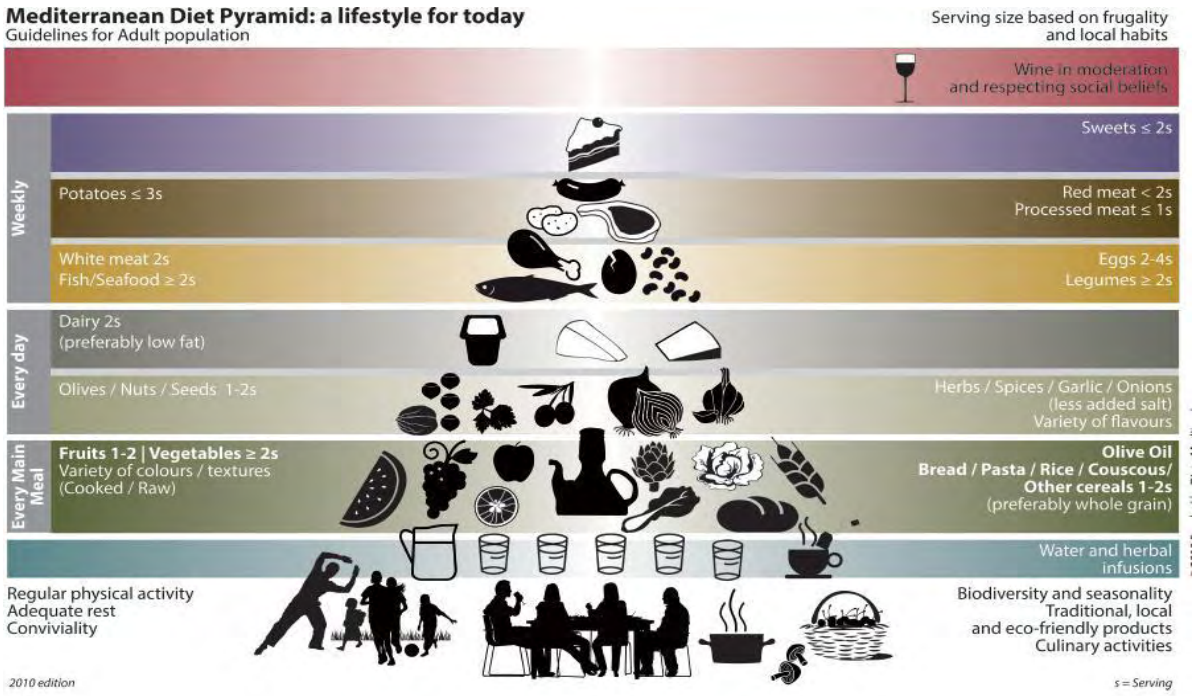
Zang et al. conducted a study in 13110 women and tried to relate the Western diet to the risk for GDM. It was concluded that low compliance with a healthy diet (characterized by low intake of fruits, green leafy vegetables, poultry and fish) and high consumption of the Western diet (characterized by high intake of red meat, processed meat, refined cereal products , sweet, French potato and pizza) were associated with increased GDM risk [96].

From a dietary standpoint, an overall diet rich in vegetables, fruits, legumes, whole grains, nuts, eggs, fish and low-red and processed meat, refined cereal products and full dairy can be beneficial for risk reduction for GDM [90, 91]. These correlations are adjusted for major

confounding factors, including maternal age, ethnicity, parity, GDM history, family history of diabetes, lifestyle, BMI, and energy intake.

Smaller risk for GDM was reported in studies containing dietary interventions promoting a balanced diet [97], but not for supplemented food products or dietary advice [98].

«Mediterranean diet pyramid today» [99]



In conclusion, the literature review of dietary patterns showed that a healthy diet such as the Mediterranean diet that include vegetables, fruits, legumes, whole grains, nuts, eggs, fish and low-red and processed meat, refined cereal products and full dairy have beneficial effects on the occurrence of fasting glucose disorders and therefore for GDM.

CHAPTER 4

4.1 Gestational Diabetes Mellitus and Exercise

Based on the literature, physical activity has been shown to help reduce fasting glucose, fasting insulin and insulin resistance regardless of weight loss [100]. Research has shown that women who have regular physical activity during pregnancy exhibit 55% less chance of developing GDM than those who have a sedentary lifestyle [101] .

There are growing data from observational studies showing that pre-pregnancy and early pregnancy exercise is associated with a reduction in insulin resistance [66], and therefore a reduction in the risk of developing GDM [102] [103] [104]

A cross-sectional study conducted in 1052 women with GDM and 10,351 healthy women concluded that women who exercised 5 days per week 3 months before pregnancy had 31% lower odds of GDM compared to women who exercised less than one day. Moreover, women who exercised 1–4 days per week had 7% lower odds of GDM. No association was observed between pre-pregnancy physical activity and GDM risk [103].

In a randomized clinical trial conducted in 150 overweight and obese pregnant women <12 weeks of gestation following a cycling exercise program (exercise 3 times/week for 30 mininus per session or more in a cycling program begun within 3 days of randomization until 37 weeks of gestation) and 150 women in a control group (continuing their usual daily activity) concluded that exercise by bicycle that started in early pregnancy and was performed at least 30 minutes, 3 times/week, was associated with a significant decrease in the incidence of gestational diabetes in overweight /obese pregnant women [105].

Findings from the Omega study conducted in 3209 women and comparing pre-pregnancy and early pregnancy period concluded that physical activity in both periods was associated with a 46% reduced risk of GDM compared with women who did not exercise in these periods [106].

A study carried out in the Spanish population in 152 women, 33 of whom were diagnosed with GDM and 119 with glucose tolerance disorder, had no significant association between GDM risk and occupational and active living in prepregnancy, early pregnancy, and midpregnancy or with change in levels of household / caregiving, occupational, and active living activities from prepregnancy to during pregnancy. Physical activity was assessed in early pregnancy and midpregnancy via a modified version of the Kaiser Physical Activity Survey

(KPAS) designed specifically to assess physical activity in women and validated for use during pregnancy. Questions in the KPAS are grouped into four domains: (1) household/caregiving, (2) occupational activities (3) active living habits and (4) sports/exercise. However, after the controlling for age and pre-pregnancy body mass index, women ranked in the highest quadrant had a reduced risk for GDM compared to those in the lower quadrant [107].

A group of researchers presented a series of epidemiological studies in which they compared recreational physical activity with the occurrence of gestational diabetes mellitus [102]. The first study looked at questionnaires from 900 women and found that women who participated in any recreational physical activity during the previous year of conception had a 56% reduced prevalence for GDM appearance, those who participated more than 4 hours per week in recreational Physical Activity had a 76% risk reduction, while those who continued any recreational physical activity and during early pregnancy reduced the risk of GDM by 69%. In the second study, where the information was again gathered through a questionnaire, the beneficial action of the exercise to reduce the risk for GDM was verified. In addition, a dose response relationship has been identified between the various measures of exercise volume in the first half of pregnancy and the reduction in risk [9].

In the study by Dempsey et al. involving 155 pregnant women with GDM and 386 healthy pregnant volunteers, information on the type, intensity, frequency and duration of physical activity during the previous year from pregnancy and the first 20 weeks of gestation was collected. Women who participated in any physical activity during the first 20 weeks of pregnancy reduced the risk of developing GDM by 48% compared to inactive women. Also, a statistically significant difference was found in women with daily stair climbing, when compared to no stair climbing, was associated with a 49-78% reduction in GDM risk. Physical activity performed by women during the previous year from pregnancy was also significantly associated with a reduction in risk for GDM. Finally, women who reported physical activity both during the previous year and at the beginning of pregnancy showed a greater reduction in risk [108] [109] [110].

CHAPTER 5

5.1 Combined diet and exercise intervention

Many of the existing studies examine the evaluation of nutritional counseling only and exercise interventions only to prevent GDM and have revealed vague findings [111] [112]. A review including samples from three other studies, resulted in the fact that while a low glycemic index diet appeared to be beneficial for certain maternal effects such as lower maternal fasting glucose concentration and infant such as risk reduction [9] [89], the evidence was limited and not high-quality [112].

Hawkins at al. in a clinical study carried out in a total of 68 women, failed to show statistically significant results although the lifestyle intervention group managed to increase its physical activity relative to the standard care group. Of course, in both groups there was an increase in total calorie intake and percentage of calories from fat, and the intervention team managed to increase fiber intake in the first half of pregnancy without this being statistically significant [113].

Later, however, it appeared that an early behavioral intervention in overweight / obese pregnant women may reduce the appearance of GDM. This is evidenced by a case-control study with a sample of 270 pregnant women with BMI ≥25kg / m2 of which 95 were placed in the cases, monitored by a dietician and gynecologist and followed a low-glycemic-index diet (1700-1800kcal / day) plus 30 minutes of walking 3 times/week or more. Among cases and controls the weight gain was similar but the GDM was lower in cases (21.5%) compared to the controls (32.7%) [114].

Another study (N=293), designed as a randomized controlled trial, created an intervention team with 96 women who received hypocaloric, low-glycemic, low-saturated fat diet and physical activity recommendations, and a standard care group who received lifestyle advices regarding healthy nutrition and exercise. In the intervention group the incidence of GDM was reduced to 18.8% compared to the standard care group who achieved a frequency of 37.1%, while the disease rate in the first group was 12.5% compared to the second 41.8% [115]. This finding comes to confirm another study with 269 women, 155 of those entered the intervention team and received individualized counseling on dietary, physical activity and weight control from trained study nurses, and had one group meeting with a dietitian. After the analyzes, it

was shown that the incidence of GDM was 13.9% in the intervention group and 21.6% in the control group also women in the intervention group increased their leisure time physical activity more and improved their dietary quality, compared with the women in the control group, which suggests that moderate exercise in combination with dietary intervention in women at increased risk of developing GDM may reduce this risk [116].

All the above data indicate that the combination of healthy eating and exercise is negatively associated with the appearance of GDM. More specifically a mild physical activity (30min-3times / week or more) in combination with a balanced diet such as Mediterranean diet (1700-1800kcal) can reduce the incidence of GDM.

CHAPTER 6

6.1 Weight gain in pregnancy and Gestational diabetes mellitus

Avoiding excessive weight gain during pregnancy is an important weapon in preventing GDM. This is because it is likely that excess weight gain, which leads to increased body fat deposition, may decrease insulin sensitivity. [117] [22].

New guidelines for overweight and its management by health scientists and pregnant women were published in 2009 by the Institute of Medicine. These new guidelines present a series of specific recommendations for overweight women as well as specific rates of permitted weight gain every week of pregnancy from the second trimester onwards. [118]. The data have shown that about half of women have experienced excessive weight gain since the publication of IOM guidelines [119].

As is well known, pregnant women are screened for GDM in the second trimester of their pregnancy depending on the diagnostic criteria and the country of residence. But weight gain may already have affected insulin sensitivity, so researchers are interested in studying the relationship between first weight gain before GDM and the subsequent risk for GDM. Also, it is not yet clear whether avoiding weight gain at the beginning of pregnancy is associated with a reduced risk for GDM. This can be explained in part by the intensive management of weight gain that has been shown to be successful in limiting pregnancy weight gain in advanced pregnancy resulting in a similar overall increase in pregnancy weight among women in a pregnancy complicated from GDM and women without GDM [120].

Brunner et al. [121] studied the possible correlation between excessive weight gain before testing for the GDM, according to IOM criteria and GDM risk. This study showed that women who gained normal weight during pregnancy compared to those who had increased their weight before the GDM test were associated with an increased risk of GDM. Based on the above, it is understood that there is a need to prevent weight gain during the period before conception.

In conclusion, the above study showed that among women of normal weight and overweight / obese women, the sudden and high weight gain had the same effects on the risk of GDM. This puts researchers in mind as it seems that women's weight before pregnancy does not play a role,

but only its excessive growth in the early stages of pregnancy.

CHAPTER 7

Summary – Conclusions

From the above thesis, which deals with gestational diabetes mellitus, we conclude that this literature review confirms the possibility of preventing GDM through different dietary and exercise interventions in pregnant women at high risk of developing GDM. This study also confirms the existence of many different strategies used to intervene in the lifestyle of women in studies designed to prevent GDM. Therefore, it becomes difficult to present a specific dietary pattern and physical activity plan that contribute to the intake of GDM in the high-risk categories for the onset of the disease. It should be noted, however, that there were several studies that did not observe statistically significant results between the intervention and control groups.

As for the studies selected in the present thesis, these were mainly dietary and physical activity interventions because they have been reported to be the most effective type of intervention to prevent GDM. At the same time, however, it was necessary to refer to epidemiological studies in a bibliographical reference.

In addition, this study identifies the urgent need for future mothers to communicate with healthcare providers such as obstetricians, midwives, nutritionists, and trainers to provide advice on the prevention or management of risk factors for GDM. Since, as mentioned, changes in lifestyles can offset the risk factors for gestational diabetes mellitus.

Further larger sample observation studies are needed to monitor and evaluate eating habits before and during pregnancy and their effects on glycemic indexes as well as studies that will take into account both physical activity and dietary intake in assessing the association between lifestyle and risk of GDM, using physical activity measuring tools designed specifically for pregnant women.

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