Mini Review

Risk of Imminent Transformation of Diabetes Mellitus Postpartum in Women who covered with Gestational Diabetes: Physiology and Perspectives of Treatment

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Introduction

In the last 30 years the incidence of obesity has increased alarmingly and almost on a par with the Metabolic Syndrome, which evolves into Type 2 Diabetes Mellitus (DM2) [1]. In 2012, the International Diabetes Federation (IFD) estimated that more than 371 million people lived with this disease and that 4.8 million people die because of its worldwide [2]. The frequency of DM2 in Mexico, from 1998 to 2012, has seen a trend towards an increase of 4.7%, from a morbidity rate of 342.1 to 358.2 cases per 100 thousand inhabitants, specifically in 2012, 418,797 patients were reported. diagnosed with diabetes (which represents 0.4% of the Mexican population), 59% of the cases were female, being the age group of 50-59 years of age the most affected, with a morbidity rate of 1,237.90 cases per 100,000 inhabitants [2-6]. The prevalence of Gestational Diabetes Mellitus (GDM) varies according to the geographical area and is closely linked to the human ethnic type [3]. It is reported that in regions such as the United States, it is more frequent among the Latino, Hispanic, and Native American population., African American and Asian. The prevalence is around 5% of the general population in regions such as Pakistan, Belgium, Denmark, Estonia, Ireland, South Korea, South Africa, and United Kingdom and is around 10% of the general population for Italy, Turkey, Brazil, USA, and Australia. The prevalence is very high in

regions such as Bermuda and Nepal with 20%. In a recent report of the International Diabetes Federation estimates that 16% of births around the world in 2013 had complications due to Gestational Diabetes [3,4]. With the consensus of the new criteria for DG issued by both the American Association of Diabetes (ADA) as the European Society for the Study of Diabetes Mellitus the prevalence of the global DG will be around 18% by 2015 [1,3].

In Mexico, a frequency that varies between 4 and 14% has been described, depending on the literature [6]. The rate of cases that convert from DMG to DM 2 is still high (up to 40%) and the effect of the treatments offered is not complete. A risk of up to 7 times more of suffering from DM 2 was found in patients with a history of GDM [4]. Breastfeeding during the first 6 months postpartum promotes beneficial effects in the product preventing overweight or obesity by 20% [5]. In the study (ACTOS), the use of pioglitazone in prediabetic patients decreased the conversion to DM 2 by 72% at a dose of 45 mg per day [6]. Gestational Diabetes Mellitus affects 14% of pregnancies annually, and approximately 90% of cases of diabetes in pregnant women are considered as Gestational Diabetes Mellitus. GDM is defined as failure to tolerate glucose that begins during pregnancy. Many risk factors for developing GDM are similar for DM2, including obesity, family history for diabetes, high risk

ethnic group, other additional risk factors are increase in maternal age, history of birth of macrosomic products as well as history of DMG in previous pregnancies [7,8].

GDM appears mainly in women with easily identifiable risk factors such as: pregnancy changes that increase insulin resistance, their glucose levels affect the development of the fetus and can be a cause of macrosomia [7,8]. Changes in the maternal physiology during pregnancy are due to storage of energy in the fatty tissue that from the end of the second trimester has adjustments for it to be released and can be derived to the growing fetus [3,7]. Normal pregnancy is considered a diabetogenic stage or of progressive resistance to insulin due to changes in the pattern of insulin secretion and its modifications in its sensitivity and action [9,10]. This hormone resistance of pregnant women seems to be due to a combination of maternal adiposity and desensitizing effects of insulin [11,12].

Various substances produced by the placenta (placental lactogen, placental growth hormone, prolactin, corticotropin-releasing hormone-cortisol, insulins, alpha tumor growth factor, interleukin 6, adiponectin's (leptin, resistin and visfatin) as evidenced by the rapid reduction of resistance almost 24 hours after delivery [11,12]. It is known that in normal pregnancy there are hormonal and metabolic changes mediated by hormones of the placenta, in particular TNF-α and other factors related to previous obesity such as the case of low molecular weight adiponectins and genetic predisposition, causing a decrease of insulin sensibility [11,12]. If the decrease in insulin sensitivity decreases by 50%, then the blood supply of insulin for available body glucose decreases, so that pregnant women have to increase their pancreatic secretion of insulin by 50% [9,10]. If this does not occur, there is a lack of carbohydrate intolerance related to pregnancy or DMG [9-11].

In a study published in 2013 by Bonde L et al. A decrease in endogenous GLP-1 incretin (glucagon like peptide-1) secretion was observed among women with DG at 2hrs after a standard load of 75 gr. of glucose, in the case of incretin GIP (glucagone like peptide) remained unchanged. The latter corresponds to that observed by Lencioni C. et al. in 2011, it was observed that the secretion of GLP-1 is significantly lower in patients with DG compared with women with euglycemic pregnancy both during and after pregnancy, evidenced in a glucose tolerance curve with 100 grams of glucose [10-12]. There is a high risk of having DM2 once having had DG at some time after delivery even when euglycemia is reached. In a Danish study it was found that 40% of women who suffered from DG treated with diet developed DM2 10 years after pregnancy. Compared with women between 30 to 60 years of age, women who suffered from DG have the risk of developing DG 10 times more [12]. In a systematic review of 20 studies, there was a risk of up to 7 times more of suffering from DM2 in patients who had GD compared with those with euglycemic pregnancy [13].

The progression of normal glucose tolerance (TNG) to diabetes is mediated by a transition state called glucose intolerance (IG). Important properties of breastfeeding have been found such as: facilitating the elimination of meconium, facilitate the production of lactobacilli in the intestine, immunoglobulins (lactoferrin, IgA,

oligosaccharides, lymphocytes and macrophages) cover the inner lining of the digestive tract preventing the adherence of bacteria, viruses, parasites and thus avoiding allergic processes, growth factors stimulate the maturation of the child's own systems, such as the maturation of the digestive tract, its volume and osmolarity are appropriate for the kidney of the RN, nutritional superiority, immediate availability and ideal temperature, immunological support, promotes neural maturation, and prevents malnutrition [11,12].

Breastfeeding during the first 6 months of postpartum promotes beneficial effects in the product preventing overweight or obesity up to 20% [12]. However, the results are controversial, since the strict attachment to breastfeeding and the time of breastfeeding during the evaluation periods is not specified [11,12]. In the case of patients with normal blood glucose and who have GI, and in patients with impaired fasting glucose (GAA), insulin resistance and beta cell dysfunction are metabolic alterations that exist and that they share with patients already developed Diabetes Mellitus 2 (DM2) and that trigger the conversion. In the initial phases of insulin resistance there is an increase in insulin secretion by beta cells, creating a state of hyperinsulinism, however the function of beta cells is impaired [9-12].

In the case of GAA, it also constitutes an intermediate metabolic condition between TNG and the development of DM2, it is an entity different from GI but together they coined the term "Prediabetes" accepted by the American Diabetes Society (ADA). The pathophysiology of both conditions has differences as well as their impact on atherosclerosis.

In GAA, the hepatic resistance to insulin is increased and the initial insulin response in a glucose tolerance test is decreased (0-30min). When hyperglycemic clamp techniques and intravenous glucose tolerance tests are applied, the first phase of absent secretion is observed, but in the late 60 to 120 min phase the sensitivity to muscle insulin is practically normal and the serum glucose returns to normal. 2 hrs. In GI there is moderate to severe muscle resistance to insulin and there is an alteration in insulin secretion in the initial and late phase when a glucose tolerance test (CTG) is performed. The standard gold for evaluating insulin resistance is to calculate the insulin secretion/insulin resistance index (disposition)/G IR. Patients who have GI have 3-4 times the risk of developing DM2, in prospective epidemiological studies it has been observed that 40% of patients in follow-ups for 5 years develop DM2 when presenting GAA and IG without intervention [8-10].

Therefore, the strategies of change of the state of life and pharmacological treatment that impacts these two conditions is rational to think that they will contribute to inhibit the progression of the IG and GAA to DM2 [14].

To improve insulin resistance, a diet and aerobic program have been proposed as strategies; these strategies have shown a reduction in the progression of GAA and IG to DM2 in 4 articles [14-16]. Both in the Finish Diabetes prevention program and the Lanmark DPP study (dipeptidyl peptidase), it was observed that interventions in caloric intake, promotion of weight loss and aerobic

activity reduced the incidence of new cases in 58% after a follow-up of 2.8 and 3.2 years respectively. However, the improvement in effective sensitivity to insulin has not been satisfactory, which is why a series of pharmacological interventions have been carried out to improve it.

The use of metformin plus weight loss has been used in the Landmark DDP study and the Diabetes Program for Indians with a decrease in the incidence of conversion to DM2 of 31%, however as in the case of modifications of the lifestyle does not stop the damage in the beta cell and therefore the effective progression to DM2 [15,17]. The thiazolidinediones act as activator of the peroxisome proliferation receptors (PPAR-y) as well as intervene in the two metabolic alterations observed in patients with IG and GAA, namely insulin resistance and pancreatic beta cell dysfunction. No statistically significant differences were found in the improvement in insulin resistance and pancreatic beta cell function between pioglitazone, troglitazone, rosiglitazone. In the case of troglitazone, a similar effect was observed in glycemic control and insulin sensitivity compared with the other thiazolidinediones discussed and it has been observed that the incidence of IG conversion and patients suffering from Gestational Diabetes (GD) in a 23 % and was more efficient when compared against placebo, metformin or changes in lifestyle. In the DREAM study, there was a decrease in the incidence of DM2 from IG to DM2 attributed to rosiglitazone in 62% and improvement in beta function through the measurement of the insulin secretion/insulin resistance index. Pioglitazone and troglitazone have shown a decrease in the incidence of MD2 in patients with GI who had a history of GD [15,17].

In the ACTOS Now study, a decrease in the incidence of DM2 was observed in patients with GI of 72% attributed to the pioglitazon.27 The inconvenience with the management of thiazolidinediones although they improve the metabolic alterations that share IG and GAA and that trigger the conversion of DM2, is the water retention, the weight/fat gain. However, in a study conducted in Canadians, rosiglitazone 2 mg daily plus 1000 mg daily of metformin was used in patients with GI found a decrease in conversion to DM2 in 71%, without statistically significant differences in weight gain and water retention [18].

Analog incretins are one of the innovative treatments for patients with DM2 and together they have been called GLP-1 analogs (glucagone like peptide-1). The oral consumption of glucose produces an increase in insulin secretion 3 to 4 times higher compared to intravenous glucose instillation, this is called "incretin effect", and is mediated by 95% by the secretion of GIP (glucagone like peptide) and GLP-1 secreted through the L and intestinal cells respectively.

GLP-1 also inhibits gastric emptying, has anorexic effect, produces gradual weight loss, decreases endothelial oxidative stress, and in vitro studies have also observed decreased apoptosis of pancreatic beta cells [19]. A study conducted with GLP-1 followed for 3 years showed in patients with DM2, the sustained reduction of glycosylated hemoglobin (Hb-g) as well as weight reduction and improvement of beta function. GLP-1 does not produce

hypoglycaemia since insulin secretion is based on the presence of hyperglycemia [20]. In a clinical trial it was observed that GLP-1 after treatment continued for 3 years produced an improvement in the response of beta cells to glucose [21]. According to the differences in the pharmacokinetics and pharmacodynamics of GLP1, Liraglutide is considered the analogue with the best effects on the other GLP-1. There is no study to evaluate its effectiveness in prediabetes states. A very important limitation in the groups of medicines used for prediabetes states, is the lack of sustainability of the inhibitory effect of the conversion of glucose intolerance and impaired glucose in fasting (GAA) to DM2 after leaving the use of medication to weigh to continue with an adequate lifestyle [21-23].

A new group of drugs called GLP 1 analogues showed that its effect is favorable on glycosylated hemoglobin, with a decrease in body weight maintained over time and with a low risk of hypoglycemia, a favorable metabolic profile on lipids and also pressure adequate systolic blood pressure in diabetic patients [24-26] and its use in obese prediabetic patients decreased the conversion to DM 2 by 84% to 96%. Liraglutide at a subcutaneous dose of 1.8 mg per day was the most effective dose in studies conducted to control obesity [27,28]. Therefore, long-acting GLP-1 could be drugs of choice in order to avoid conversion of IGT to DM type 2, because it modifies the pathophysiology of the disease, resulting in the progressive deterioration of pancreatic beta cells in addition to decreased body weight maintained over time and with a low risk of hypoglycemia, with a favorable metabolic profile over lipids and systolic blood pressure.

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