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UPDATES ON GESTATIONAL DIABETES

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Abstract: **Introduction** - Gestational diabetes mellitus refers to hyperglycemia diagnosed during the second or third trimester of pregnancy. Its prevalence ranges from <1% to 28% depending on the country and diagnostic criteria. **Goals** - literature review updating concepts, diagnosis and new therapeutic possibilities in gestational diabetes. **Methodology** - bibliographic review, with descriptors: diabetes and pregnancy, high risk pregnancy, prenatal care, oral hypoglycemic agents and postpartum care. **Results** - the increase in sugar consumption parallels the increase in overweight, gestational diabetes and type 2 diabetes mellitus over the past four decades. Universal screening associated with lifestyle changes (diet and exercise) is the main approach during pregnancy. Metformin gained definitive space, preceding the introduction of insulin. Telemonitoring must be encouraged. Postpartum control, which is much neglected, is fundamental in the screening of type 2 diabetes. **Conclusions – Some** very well-defined points: Universal screening is mandatory, there are still some divergences in the methodology used (fasting or test with load), changes in life habits and physical exercise are fundamental in control. However, they are difficult to adhere to this. Metformin is a reality that must be in all protocols, follow-up in the postpartum period is fundamental, and must be considered in the long term, due to the relationship with type 2 diabetes in the future of patients. Consider remote monitoring adequate with promising results.

Keywords: "Diabetes and pregnancy", "risk pregnancy", "prenatal", "oral hypoglycemic agents" and "puerperium".

INTRODUCTION

Physiological changes in pregnancy can lead to a predisposition to serious metabolic disorders. Insulin sensitivity initially increases in the first trimester, but then declines to a plateau of approximately 56% by the end of the third trimester. This is partially driven by placenta-derived hormones such as cortisol, glucagon, and especially human placental lactogen.[1]

Women, as a rule, also have a decreased renal buffering capacity, as their increased ventilation causes respiratory alkalosis and renal bicarbonate loss, making them prone to acidosis. Significant metabolic disorders occur in pregnant women and are usually treated the same as in the non-pregnant population and result in rapid resolution without fetal compromise. The location of care is critical, depending on the gestational age, medical and obstetric requirements at the time of presentation. A multidisciplinary team experienced in dealing with pregnant women at risk, including endocrinologists, obstetricians, intensivists, and obstetric anesthetists, must be present.[1]

Gestational diabetes mellitus (GDM) refers to hyperglycemia diagnosed during the second or third trimester of pregnancy. The prevalence of GDM in 173 countries ranges from <1% to 28% depending on country and diagnostic criteria.[2]. It is estimated that more than 5% of all pregnancies in Europe are complicated by GDM. Women who had GDM during pregnancy are at a very high risk of developing type 2 diabetes (T2D) later in their lives. Their risk is almost 10 times greater than in women who have not had GDM.[3.4]

However, the risk of T2D after GDM was reduced in women who performed pre and postpartum diet and physical activity, both of which are effective in health care to avoid these dangerous and costly complications caused by the metabolic complication.

GDM is associated with an increased risk of pregnancy with preeclampsia, congenital malformations, macrosomia, muster dystocia, and neonatal death. Women with GDM are at

increased risk of cardiovascular events, and their children are predisposed to the future risk of obesity and T2DM.[2,4,5]

Evan et al.[3] recently concluded, in qualitative research, that there are perceptions around GDM that, if not addressed, are likely to compromise the effect of lifestyle interventions. For example, although many women know that there is an association between GDM and T2D in their future, they may not understand this risk as GDM has minimal and transient impact on their lives. If it's short-lived and easily controllable, they often don't realize the potential consequences. The authors also hold health professionals accountable, accepting it as a fact without consequences, and creating "postpartum abandonment"[3]

In normal pregnancy, the placenta produces the human placental lactogen hormone (hPL), which increases insulin resistance. In addition, the amount of insulin produced by the mother's body also increases, but if this production is insufficient, GDM can occur. Patients in whom this happens are given insulin until their blood glucose levels are sufficiently controlled. As insulin resistance progressively increases before delivery, the insulin dosage is increased as needed. In some patients, insulin dosage is decreased, but no studies to date have reported perinatal prognosis in the context of reduced insulin requirements during pregnancy.[6]

Some recent findings allow us to better explain the pathophysiology of GDM. Chemerin is one such example. It is an adipokine secreted mainly by adipose tissue and initially discovered in psoriasis studies, and which stimulates the adhesion of macrophages to extracellular matrix proteins, promoting chemotaxis leading to the recruitment of these macrophages at the site of inflammation. In addition to an inflammatory mediator, chemerin has also been shown to promote the pathogenesis of obesity and metabolic diseases such as T2D.[7]

In the context of diabetes, chemerin exacerbates glucose intolerance, reduces serum insulin levels, and causes resistance to insulin secretion. In the mouse model, a significant reduction in chemerin levels during pregnancy was documented. [7] In contrast, a human pregnancy study by Garces et al.[8] highlighted a higher serum level of chemerin in women with GDM. A fraction of pregnant women is thought to show the GDM phenotype due to inadequate pancreatic β-cell compensation that leads to the development of insulin resistance and increases hepatic glucose production.

To corroborate this observation, Wang et al. [7] in a study in China, examining more than 700 pregnant women with GDM and comparing them with metabolically healthy patients, found higher plasma chemerin levels in individuals with GDM.

GOALS

PRIMARIES

Conduct a literature review updating concepts, diagnosis and new therapeutic possibilities in gestational diabetes.

SECONDARY

To propose an update to the protocol of the Hospital de Clínicas de Teresópolis in the chapter that addresses endocrinopathies during pregnancy.

METHODS

The methodology used was a bibliographic review, for the last ten years of publications in the main research sources, using the following descriptors: diabetes and pregnancy, risk pregnancy, prenatal care, oral hypoglycemic agents and postpartum care.

The criteria used were articles from the last 10 years in Portuguese, English and French,

with a preference for new concepts and studies that presented a series of cases.

RESULTS

UPDATE ON RISK FACTORS FOR GDM

An increase in sugar consumption parallels an increase in the incidence of overweight, GDM and type 2 diabetes mellitus over the past four decades. Guidelines for the prevention of obesity, cardiovascular disease and T2D recommend limiting the intake of added sugars. The 2015 Dietary Guidelines Advisory Committee advocates limiting added sugars, a subset of free sugars, to 10% of total intake. [9]

Mussa et al. [9] in a recent literature review, did not find any studies, where the purpose was to examine the association between free sugars from solid sources and excess weight or the onset of diabetes during pregnancy. The authors designed a retrospective study of female participants (12–50 years) from the 2004–2005 *Canadian Community Health Survey*, with data from 2017.

Out of 6,305 participants, 2,505 (40%) were overweight, defined as a BMI ≥ 85th percentile under age 18 and a BMI ≥ 25 kg/m2 for adults. Free sugars from solid sources were associated with lower odds of being overweight (RR = 0.80, 95% CI 0.70-0.92); free sugars from liquid sources were associated with higher odds of being overweight (RR = 1.20, 95% CI 1.07–1.36). There were 113 cases of GDM among the 1,842 women who gave birth (6.1%). Free sugars from solid sources were associated with lower odds of GDM (RR = 0.56, 95% CI 0.36–0.85). The authors concluded that GDM is related to free sugars from liquid sources (juices, soft drinks) but not to sugars from solid sources at any of the examined limits.[9]

In Germany, a universal GDM screening program was introduced for all pregnant women. A screening test with 50 g of glucose load ('pre-test') must be performed and if the values are ≥135 mg/dL (7.5 mmol/L), we are diagnosed with T2D. GDM is diagnosed if glucose levels are ≥92 mg/dL (5.1 mmol/L) fasting, ≥180 mg/dL (10 mmol/L) after 1 hour, or ≥153 mg/dL (8, 5 mmol/L) after 2 hours.[4]

Women with diagnosed GDM are recommended to have a glucose tolerance test 6-12 weeks postpartum. The National Health Guidelines, in the German country, indicate reference to a center for screening and diagnosis, treatment and postpartum care. The patient is recommended to check glucose metabolism every 2 years. In case of changes in glucose levels, intensive counseling on lifestyle measures to prevent overt diabetes is recommended, and the benefits of lactation are especially emphasized.[4]

EFFECTIVENESS OF LIFESTYLE CHANGES

Currently, a healthy lifestyle recommendation (diet and exercise) is the main approach in GDM in pregnancy. It is recommended that women with GDM consume a low glycemic index diet (less than 55) and limit carbohydrate intake to 35-45% of total energy intake. Carbohydrate intake must be divided into three medium meals and two to four snacks. In addition, daily physical activity must be performed for approximately 30 minutes. Studies have reported that 70-85% of women with GDM maintain glucose levels with these simple lifestyle changes. However, the effectiveness of lifestyle intervention in managing GDM can be challenging, as only 16-55% of pregnant women adhere.[2]

Studies have consistently reported that overall obesity predicts GDM. However, other obesity phenotypes such as central obesity and adiposity may have differential associations, as the risk factors for GDM are less well known.

Alwash et al. [10] carried out a systematic review including research articles from 1985

to February 2020 with a cohort study design that reported an association between obesity and GDM. Results from twenty studies met the inclusion criteria representing data from approximately 50,000 women of reproductive age with a 7% prevalence of GDM.

A meta-analysis of 14 datasets revealed that the three types of obesity were significantly associated with an increased risk of GDM. Furthermore, visceral adiposity was a stronger risk factor for GDM than other obesity phenotypes (RR = 3.25, 95% confidence interval = 2.01-5.26) versus RR = 2.73, interval 95% confidence interval = 2.20-3.38 for general obesity and RR = 2.53, 95% confidence interval = 2.04-3.14 for central obesity.

The findings of this study suggest that general obesity, central obesity and visceral body fat were associated with an increased risk of GDM. The authors confirm that prenatal control must be rigorous in terms of changes in eating habits and in the process of losing calories through physical exercise. [10]

CURRENT AND NEW DRUG TREATMENT PROPOSALS

A consensus led by Dinicola et al. [11] and published recently, issued some new concepts about the use of inositol in the control of DGM. Myo-inositol (myo-Ins) and D-chiro-inositol (D-chiro-Ins) are natural compounds involved in many biological pathways. Since the discovery of its involvement in endocrine signal transduction, myoIns and D-chiro-Ins supplementation has contributed to clinical approaches in the improvement of many gynecological and endocrinological diseases.

Currently, both myo-Ins and D-chiro-Ins are effective and well-tolerated alternative candidates to replace classical insulin, and are useful treatments in the prevention and treatment of metabolic and reproductive disorders such as polycystic ovary syndrome (PCOS), diabetes Gestational Mellitus (GDM) and male fertility disorders such as sperm abnormalities.

Given the complexity of inositol-related mechanisms of action, many of its beneficial effects are still under scrutiny. Therefore, research continues to try to discover new roles and emerging mechanisms that may allow us to adapt inositol therapy and use it in other medical areas, hitherto unexplored. Based on the physiological role of inositols and the pathological implications of altered ratios of myo-Ins to D-chiro-Ins, inositol therapy can be designed with two different goals: (1) to restore the physiological ratio of inositol; (2) changing the ratio for specific effects. [11]

Although metformin is increasingly being used in women with type 2 diabetes during pregnancy, there is little data on the benefits and harms of its use on pregnancy outcomes for these women.

But, as research with drugs during pregnancy dictates, there were several studies in animals that were published to endorse the use of metformin in the control of GDM. We cite the work of Schoonejans et al. [12], who accepted the premise that obesity is not only associated with adverse metabolic and cardiovascular events in adult women, but, when present during pregnancy, also has consequences in exposed offspring with risk of obesity, insulin resistance, type 2 diabetes and syndrome metabolic. Obese women are four times more likely to develop GDM.

Metformin is the first-line pharmacological treatment for GDM in many countries, including the UK, where lifestyle interventions are ineffective and its use is increasing worldwide. [13] In pregnancy, metformin improves glucose tolerance in GDM and treatment is associated with less gestational weight gain compared with insulin or placebo in GDM or obese glucose-tolerant women, respectively.

Its oral administration, lack of cold storage requirement, and cost-effectiveness also make it more appropriate than insulin for use in low-resource social situations. However, metformin readily crosses the placenta, and follow-up of offspring in human randomized controlled trials investigating maternal metformin treatment remains sparse, with few studies reporting offspring outcomes beyond childhood.

In the model of the article cited above, females are fed a diet high in fat and sugar before mating and, consequently, are obese, hyperleptinemic and hyperinsulinemic at conception and develop glucose intolerance in pregnancy. These animals received metformin and this intervention increased adipocyte hyperplasia in male offspring, but not in females. [12]

Feig et al. [14] investigated the effects of adding metformin to a standard insulin regimen on neonatal morbidity and mortality in these pregnant women. In this prospective, multicenter, international, randomized, parallel, double-masked, placebo-controlled study, the authors randomly selected pregnant women with type 2 diabetes at 25 centers in Canada and four in Australia to receive metformin 1000 mg twice daily or placebo, added to insulin. Women were eligible if they had T2D, took insulin, had a viable singleton pregnancy, between 6 and 22 weeks plus 6 days of gestation. They were protocolled to check fasting blood glucose before the first meal of the day, before the last meal of the day and 2 h after each meal.

At study visits, blood pressure, body weight, drug tolerance, need for hospitalization, changes in insulin doses, and severe hypoglycemic events were controlled for.

Between May 25, 2011 and October 11, 2018, 502 women were recruited, 253 (50%) in the metformin group and 249 (50%) in the placebo group. Compared with women in the placebo group, women treated with metformin achieved better glycemic control, required less insulin, gained less weight, and had fewer cesarean deliveries. They found no significant difference between groups in hypertensive disorders. Compared with those in the placebo group, infants exposed to metformin weighed less, had a lower incidence of macrosomia, with reduced adiposity measures.

The most common adverse event reported by pregnant women was gastrointestinal. In short. we found several maternal glycemic benefits and neonatal adiposity in the metformin group. Along with reduced maternal weight gain and stable insulin dosing with improved glycemic control.

Inadequate glycemic control in pregnant women with GDM is warranted. Recent data strongly support its link to altered gut microbiota. For example, the decrease in Sutterella, Bacteroides and Phascolarbacterium are positively correlated with lipopolysaccharide (LPS) biosynthesis in pregnant women with GDM. The increase in pathogenic possibilities in the decline of the microbiota and LPS, as well as the reduction of short-chain fatty acids, can impair the integrity of the intestinal epithelial barrier and induce inflammatory reactions. These factors upregulate the expression of pro-inflammatory markers and suppress the expression of anti-inflammatory markers. [2]

Sutterella is positively correlated with C-reactive protein levels. Furthermore, gut microbiota dysbiosis is linked to overproduction of oxidative stress species (ROS), elevated lipid peroxidation and oxidative stress markers, in addition to reduced antioxidant markers. Inflammation, oxidative stress reactions and metabolic pathways are associated with insulin resistance, and may explain abnormal lipid and glucose metabolism in pregnant women. [2]

Probiotics are defined as "live

microorganisms which, when properly administered, confer a health benefit on the host". Certainly, probiotic effects can be influenced by a number of factors, including lifestyle and dietary intake. [2]

Hasain et al. [2] performed a meta-analysis to summarize the effects of probiotics on GDM, focusing on lifestyle intervention in addition to metabolic, inflammatory, and oxidative stress outcomes in pregnancy. They involved 10 randomized controlled trials with 594 participants. The meta-analysis indicated that probiotic supplementation reduced fasting blood glucose by 3.10 mg/dL. Probiotics also reduced the level of inflammatory markers (high sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α and malondialdehyde), incidence of macrosomia and hospitalization of the newborn. The authors admitted the suggestion that probiotics may have positive effects on metabolism, inflammation, oxidative stress, and neonatal outcomes in women with GDM. Future studies are needed on a larger scale to determine clinical significance.

As the use of probiotics still leaves the literature divided on their indication in the DMG, we consulted an article by Okesene-Gafa et al. [15] who based their studies on the assessment of the safety and efficacy of probiotics in the treatment of women with GDM in child outcomes.

The authors proposed a meta-analysis supported by randomized controlled trials (RCTs) comparing the use of probiotics versus placebo/standard care for the treatment of GDM. The main results in RCTs (695 pregnant women with GDM) when compared with probiotics versus placebo were identified.

The trial was uncertain whether probiotics have any effect compared with placebo in hypertensive disorders of pregnancy, (RR = 1.50, 95% confidence interval 0.64 to 3.53) and cesarean sections (RR = 0.64), 95% CI 0.30 to 1.35). There was no conclusion as to whether probiotics have any effect, when compared to placebo, in inducing labor (RR = 1.33, 95% CI 0.74 to 2.37). For other secondary maternal outcomes, there are no differences between probiotics and placebo, with postpartum hemorrhage; pregnancy weight gain and total gestational weight gain; fasting glucose or need for extra pharmacotherapy (insulin). Probiotics appear to be associated with a slight reduction in triglycerides and total cholesterol.

However, in the probiotic group, compared to the placebo, there was evidence of a reduction in markers of insulin resistance and insulin secretion. Probiotics have been associated with small benefits on relevant inflammatory biomarkers such as C-reactive protein, interleukin 6 (IL-6) and the malondialdehyde marker of oxidative stress. [15]

Regarding the offspring of these patients, there were no significant differences between probiotics and placebo in the risk of macrosomia (RR = 0.73, 95% CI 0.35 to 1.52) or childhood hypoglycemia (RR = 0.85, CI 95 % 0.39 to 1.84). No studies reported differences in primary outcomes such as perinatal (fetal/neonatal) mortality or sensorineural impairment. There was evidence of a reduction in childhood hyperbilirubinemia with probiotics compared with placebo.

Even though there were no adverse events reported by any of the trials, the authors conclude that there is still a lack of robust evidence indicating the routine use of probiotics in GDM. [15]

ADVANCES IN PRENATAL CARE

One of the main ways of monitoring pregnant women with GDM, in times of a pandemic by SARS COVID 19, was the use of telemedicine using the digital model DiabCare Tirol. Moazen et al. [16] followed 27 patients who joined the diabetes outpatient program

in Tyrol, Austria during the year 2020.

Analysis of patient outcomes was used to examine the effects of integrated care that involved telemonitoring support, and compared these with results from some controlled clinical trials with face-to-face consultations. The feasibility of the digital treatment model was confirmed in practice, as the trend analysis of the 27 GDM patients involved showed significantly improved glycemic control. The benefits of telemonitoring with integrated care to support conventional therapy cannot be dispensed with, especially in times of a pandemic. The authors encouraged the continuation of this strategy in the post-pandemic period, still requiring a greater number of patients for effectiveness to be achieved.

The results show a better monitoring of glycemic levels in the group followed by telephone. The incidence of low birth weight, macrosomia, prematurity, premature rupture of membranes, post-cesarean hemorrhage, perinatal asphyxia, malformations and admission to a perinatal tertiary unit were not significantly different between the two groups. The conclusion of this trial makes it possible to value the remote monitoring of patients with GDM, despite being as efficient as the traditional model, it needs a larger sample to reinforce this observation.

Although experts recommend universal screening for gestational diabetes, there is no consensus on which of the two recommended screening approaches must be used. The most accepted method today is the valuation of fasting blood glucose at any time during pregnancy, where a value greater than or equal to 92mg% is considered positive for the prognosis of GDM.

Hillier et al. [18], however, performed a randomized trial comparing one-step screening (i.e., a glucose tolerance test in which the blood glucose level was obtained after oral administration of a 75 g glucose load in the fasting state) with two-step screening (a glucose challenge test in which the blood glucose level was obtained after oral administration of a 50 g glucose load without fasting, followed, if positive, by an oral glucose tolerance test with a fasting glucose load of 100 g in all pregnant women attended.

The results of the comparative study enrolled 23,792 women in a randomized fashion. A total of 66% of women in the one-step group and 92% of those in the two-step group adhered to screening. Gestational diabetes was diagnosed in 16.5% of women assigned to the one-step treatment and in 8.5% of those assigned to the two-step approach (unadjusted relative risk, 1.94; 97.5% confidence interval [CI], 1.79 to 2.11). The respective incidences of the primary outcomes were as follows: babies large for gestational age, 8.9% and 9.2% (RR = 0.95; 97.5% CI, 0.87 to 1.05); perinatal composite outcome, 3.1% and 3.0% (RR = 1.04; 97.5% CI, 0.88 to 1.23); gestational hypertension or preeclampsia, 13.6% and 13.5% (RR = 1.00; 97.5% CI, 0.93 to 1.08); and primary cesarean section, 24.0% and 24.6% (RR = 0.98; 97.5% CI, 0.93 to 1.02). Despite more diagnoses of gestational diabetes with the one-step approach than with the two-step approach, there were no significant differences between groups in the risks of primary outcomes related to perinatal and maternal complications. [18]

ACTION AFTER CHILDBIRTH

In Scotland, most women receive health care from the National Health Service (NHS), which is funded by the government. [3] Women who are diagnosed with GDM are referred to their family doctor after delivery for a 13-week glycated hemoglobin test, although initially not all women attend. Then, 11 home visits are scheduled (*Universal Health Visiting Pathway*), eight in the first year of life and

three between 13 months and 3 to 5 years. [3]

Evans et al. [3] in order to evaluate this model of postpartum follow-up, carried out a study in Scotland through interviews with two health visitors, three nurses, two general practitioners, two diabetes consultants and two obstetricians. The results showed broad support from all participants and general consensus that these visitors would be key. Regarding time, later visits approximately 6 to 8 months after delivery were considered more appropriate.

Another proposal for the postpartum period comes from the review by Whelan et al. [19] who started from the data that up to 70% of patients diagnosed with GDM will develop type 2 diabetes throughout their lives. Mitigating this postpartum progression, when patients are already connected to routine medical care, is essential to optimizing patients' lifelong health. Both lifestyle modification and metformin were investigated as options to reduce the risk of type 2 diabetes in patients with a history of GDM.

The current model for postpartum testing and care of patients with GDM has been shown to have low acceptance rates. Similarly, intervening with postpartum lifestyle modification did not result in a significant reduction in diabetes risk in prospective studies. The authors, after this review, and based on large prospective studies indicated that metformin may be a useful addition to lifestyle modifications to prevent progression to diabetes. They agree that further studies are needed to determine which individuals with GDM are most likely to benefit from this drug. [19]

Greiner et al. [4] stated that in the densely populated region of the North Rhine (Germany), approximately 40% of women with GDM seen in specialized clinics attend the postpartum consultation. The percentage of participation in diabetes screening 6-12 weeks postpartum differs widely (6%–100%, median 48%), presumably due to different scheduling strategies, eg digital appointment or at discharge.

A multicenter study of three German clinics with specialist diabetes and pregnancy services shows 51% participation in post-treatment GDM overall. However, the authors report large differences between centers, which may be due to population composition as well as differences in the care environment. Although the authors do not know the proportion of women in Germany who are tested between 6–12 weeks postpartum with other healthcare providers, the authors assume that the participation rate in postpartum glucose testing is lower across the country compared to with registration fees during prenatal care.

But the main concern that we must have in the future of patients who have had a GDM, from the postpartum period onwards, are the rates of progression to type 2 diabetes mellitus (DM2).

For this purpose, Vounzoulaki et al. [20] published an important systematic review and meta-analysis with selected articles from January 2000 and December 2019. The inclusion criterion was postpartum follow-up for at least 12 months, with 20 studies involving 1,332,373 subjects (67,956 women with GDM and 1,264,417 controls). The overall relative risk for T2DM was nearly 10-fold higher in women with previous GDM than in healthy controls (RR = 9.51, 95% CI 7.14 to 12.67, P < 0.001).

Within populations of women with previous GDM, the cumulative incidence of T2DM was 16.46% (95% CI - 16.16% to 16.77%) in women of mixed ethnicity, 15.58% in a predominantly non-white population. and 9.91% in the white population. These differences were not statistically significant between subgroups (white versus mixed populations P=0.26; white versus non-white

populations P=0.54). Analyzes showed that study effect size was not significantly associated with mean study age, body mass index, year of publication, and duration of follow-up.

Women with a history of GDM appear to have an almost 10-fold greater risk of developing T2DM than those with normoglycemic pregnancies. The magnitude of this risk highlights the importance of intervening to prevent the onset of T2DM, especially in the first few years after pregnancy.[20]

DISCUSSION

As mentioned earlier, the anti-insulin effect of placental lactogenic hormone (hPL) increases maternal blood glucose levels, allowing the fetus to use glucose as a nutrient. As hPL is produced by the placenta until delivery, insulin requirements in patients with GDM generally increase, but in exceptional situations, some cases may lead to a decrease in this insulin requirement. Kawarai et al. [6] retrospectively examined data from patients with GDM who received insulin and gave birth between April 2019 and March 2020.

In two patients whose insulin dosage was significantly reduced, a syndrome of hemolysis, elevated liver enzymes and low platelet counts or acute fatty liver of pregnancy developed with emergency cesarean section. The authors suggest that a decrease in insulin requirement in pregnant women with GDM may predict maternal abnormalities due to placental dysfunction, such as severe preeclampsia.

We cannot ignore the emotional aspects that GDM causes, not only in the pregnant woman, but also in the family group involved with these patients. Parsons et al. [21] published a meta-analysis of 16 qualitative studies and found significant data related to women with GDM who experienced feelings of shock, annoyance, denial, fear and guilt at diagnosis, as well as a loss of normalcy and personal control.

Of the three previous studies conducted in the UK, two included participants with primarily white ethnicity. [22] Although these studies were locally representative, they do not reflect the general population of GDM, which is predominantly of Asian, Black and African and Caribbean women. [21]

There is a lack of information on maternal-fetal outcomes in patients with GDM and concomitant COVID-19. However, Violante-Cumpa et al. [5] presented the case of a 20-year-old primigravidae with GDM and COVID-19.

The patient was evaluated in a basic health unit with a complaint of cough for 6 days. She went because of hyperglycemia. The patient had a medical history of obesity (BMI of 31.6 kg/m at conception), at 30 weeks of gestation, already having a diagnosis of GDM at the 27th week of gestation with a BMI of 34.8 kg/m at the time of evaluation. The patient was treated with NPH 20 IU insulin twice daily with poor adherence and without self-monitoring of blood glucose for economic reasons. Her vital signs were normal and she did not need supplemental oxygen; however, what was notable was acanthosis on the back and sides of the neck and groin. There were clinical data of hyperandrogenism (acne, hirsutism, etc). At this time, blood glucose was 203 mg% and glucosuria was 500 mg/dL. In view of her respiratory symptoms, a SARS-CoV-2 PCR test was positive. Fasting and basal plus regimen were started with a dose of 20 IU of NPH insulin and betamethasone for fetal lung maturation (12 mg intramuscularly).

The fetus was monitored with cardiotocography (CTG). After 10 h, the fetus showed signs of fetal distress on the CTG, and a cesarean section was performed. The newborn weighed 2,630 g (P > 97%) with an Apgar score of 1/3. The newborn was then transferred to the NICU, where he was tested

for SARS-CoV2 with a negative result. The newborn remained hypotensive and acidotic and died three days after delivery. The insulin regimen was changed to NPH 10 IU, but two days after delivery, she had two episodes of asymptomatic hypoglycemia (65 mg/dl and 62 mg/dl). It was decided to withhold the basal insulin regimen and continue glucose monitoring without additional insulin therapy. The patient was isolated for five days in the hospital with no supplemental oxygen and no sign of respiratory distress. She was discharged with an indication to continue in home isolation and was scheduled for an oral glucose tolerance test and follow-up at 8 weeks.

As the pandemic has evolved, these cases may be associated with negative outcomes in certain high-risk groups. The prevalence of COVID-19 in pregnant women varies by series, with an overall rate of 10% (7–14%). As the prevalence of GDM varies between 7.5 and 11.6% in large case series, the literature is still limited to case reports or small case series. [5]

Even so, we can observe an increased risk of hospitalization (5.4 times), ventilation (1.7 times) and ICU admission (1.5 times), but there was no difference in terms of mortality. Older age (>35 years) and comorbidities (obesity, chronic hypertension, and preeclampsia) are risk factors associated with a more severe clinical presentation of COVID-19 in a pregnancy with a worse maternal-fetal prognosis, such as preterm delivery, fetal distress and cesarean delivery. In the case reported above, there was no vertical transmission and the newborn died from a cardiac anomaly. [5]

But a great deal of controversy was caused by the article by Pillay et al. [23] on the validity of universal screening for DMG. The purpose of the communication was to update the 2012 review on screening for GDM in the United States of America.

A total of 76 studies were included: 18 randomized controlled trials (RCTs) with 31,241 patients, 2 non-randomized intervention studies with 190 patients, 56 observational studies with 261,678 patients. In 5 RCTs (n = 25,772), 1-step screening versus 2-step screening was significantly associated with increased likelihood of GDM (11.5% vs 4.9%) but no better health outcomes. Fasting glucose tests with cut-off points of 85 and 92 mg/dL had sensitivities of 88% and 81% and specificities of 73% and 82%, respectively.

Regarding the decision to treat or not, there was no divergence with everything that is currently accepted. Treatment was significantly associated with a decreased risk of cesarean deliveries (RR = 0.70 [95% CI, 0.54-0.91]); muster dystocia (RR = 0.42 [95% CI, 0.23-0.77]); macrosomia (RR, 0.53 [95% CI, 0.41-0.68]); large for gestational age (RR, 0.56 [95% CI, 0.47-0.66]); birth injuries (RR = 0.33 [95% CI, 0.11-0.99]); and admissions to the neonatal intensive care unit (RR = 0.73 [95% CI, 0.53-0.99]).

The authors dispute the certainty of the need for universal screening, stating that direct evidence on screening versus no screening remains limited. However, they were incisive in stating that after 24 weeks of gestation, treatment of gestational diabetes was significantly associated with improved maternal and perinatal health outcomes.

CONCLUSIONS

This literature review shows that the universal incidence of gestational diabetes has been increasing over the decades, however, despite this increase, it is possible to see that new drugs are gaining ground with good results, such as metformin and inositol. Life changes and physical exercise are fundamental in controlling the condition, although they are difficult to adhere to.

Postpartum follow-up is essential, and

long-term follow-up must be considered, due to the relationship between GDM and type 2 diabetes in the patients' future.

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