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CONSEQUENCES OF GESTATIONAL DIABETES MELITTUS IN PREGNANT WOMEN AND FETUS: AN INTEGRATIVE REVIEW

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Abstract: Introduction: During pregnancy, a woman's body changes to shelter and maintain the baby. In this process, the pregnant woman can develop gestational diabetes mellitus (GDM) as a result of the increase in blood glucose levels. Risk factors for GDM include overweight, advanced maternal age, history of GDM in previous pregnancies, and preeclampsia. To diagnose it, it is necessary to test fasting plasma glucose, if it is greater than or equal to 92 mg/dl, but less than 126 mg/dl, the diagnosis of gestational diabetes is made. After the diagnosis has been made, it is important that the pregnant woman undergoes treatment correctly to avoid the consequences of the disease for the mother and baby. **Methodology:** this study used an integrative literature review as a method. The search took place in the PubMed, Scielo and VHL databases. The data collected is from 2015 to 2021 in Portuguese and English. Gestational diabetes, diagnosis, treatment, newborn and complications were used as keywords. **Results**: the final analysis sample consisted of 10 articles in the English language between 2018 and 2021, 7 from PubMed, 2 from Scielo and 1 from the VHL. **Conclusion**: it was possible to understand during the work the seriousness of the main consequences of GDM for both the newborn and the mother. For the fetus, macrosomia, neonatal hypoglycemia, respiratory and cardiovascular morbidity, congenital anomalies, spontaneous abortions, prematurity and neonatal death can be observed. For the mother, there is an increased risk of developing type 2 diabetes mellitus, the need for a cesarean section, neoplasms, ophthalmic, psychiatric, kidney diseases, eclampsia and pre-eclampsia, postpartum complications such as hemorrhages.
Keywords: Gestational diabetes; diagnosis; treatment; newborn; complications.

INTRODUCTION

During pregnancy, a woman's body goes through countless physiological changes to receive the fetus and meet its demands. In this context, an important change is insulin sensitivity, which changes during pregnancy depending on maternal-fetal needs (PLOWS et al., 2018).

As a result of gestational physiological changes, women can develop gestational diabetes mellitus. This disease is characterized by maternal hyperglycemia diagnosed during the current pregnancy. The increase in glucose levels causes important consequences for both the fetus and the mother, requiring it to be diagnosed in time and treated correctly (PORTUGUESE SOCIETY OF DIABETOLOGY, 2016).

Oliveira et al. (2016) reports that

> Gestational diabetes mellitus (GDM) is considered the most common metabolic disorder in pregnancies, and its prevalence varies from 3% to 13% of all pregnant women, varying according to the population assessed and the criteria used.

Among the maternal consequences arepremature labor, operative delivery, and increased risk of type 2 diabetes mellitus. In children, the risks are trauma during birth with a risk of dystocia, hypoglycemia, excessive intrauterine growth and insulin resistance (PLOWS et al., 2018).

Risk factors for gestational diabetes (GDM) include overweight, obesity, advanced maternal age, excessive central body fat deposition, family history of diabetes in first-degree relatives, previous gestational diabetes, excessive fetal growth, hypertension, pre-eclampsia, polycystic ovary syndrome, short stature and dyslipidemia (BRAZILIAN DIABETES SOCIETY, 2019).

According to the Portuguese Gestational Diabetes consensus, to make the diagnosis of gestational diabetes mellitus, fasting plasma

glucose must be determined. If this blood glucose level is greater than or equal to 92 mg/dl, but less than 126 mg/dl, the diagnosis of gestational diabetes is made.

Once GDM is diagnosed, the patient must begin treatment to reduce complications caused by the disease. Treatment ranges from non-pharmacological measures such as dietary re-education to pharmacological measures such as the use of insulin therapy.

According to the Brazilian Diabetes Guideline, pregnant women must receive individualized guidance on their diet. In general, 40 to 55% carbohydrates, 15 to 20% proteins and 30 to 40% fats must be distributed.

For pregnant women who use insulin, guidance on doses, times and administration is important. Meals must be distributed so that the patient does not have episodes of hypoglycemia, especially at night. Because of this, supper is of fundamental importance (BRAZILIAN DIABETES SOCIETY, 2019).

Given the importance of the consequences of gestational diabetes mellitus both for the mother during pregnancy and childbirth and for the child during birth and development, this study aims to carry out an integrative review of publications from 2015 to 2021, regarding the importance of gestational diabetes mellitus prophylaxis to avoid maternal and fetal complications.

OBJECTIVE

GENERAL OBJECTIVE

Understand the importance of gestational diabetes prophylaxis to avoid short and long-term complications for the pregnant woman and baby.

SPECIFIC OBJECTIVES

Identify the risk factors, forms of diagnosis and treatment of gestational diabetes mentioned in the references consulted.

Identify the consequences of gestational diabetes for the pregnant woman and the newborn mentioned in the references consulted.

LITERATURE REVIEW

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes mellitus (GDM) is defined according to the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) as hyperglycemia during pregnancy that can occur at any stage of pregnancy, being more frequent after of 24 weeks (FEDERATION, 2019).

In a study carried out by the International Diabetes Federation (IDF), it was estimated that 20.4 million (15.8%) of live births in 2019 suffered some type of hyperglycemia. Of these 20.4 million, 83.6% are caused by gestational diabetes mellitus. The estimate of live births affected by hyperglycemia during pregnancy for 2030 is 18.3 million and 2045 is 18 million (FEDERATION, 2019).

The Brazilian Diabetes Society reports that

> A study in the population of the United States of America revealed that, in the early 2000s, diabetes *mellitus* type 1 (DM1) was present in 7% of pregnancies complicated by diabetes, while diabetes *mellitus* type 2 (DM2) appeared in 4.7% of them (BRAZILIAN DIABETES SOCIETY, 2019).

Gestational diabetes mellitus is classified as a subtype of hyperglycemia that differs from diabetes during pregnancy, presenting glycemia values that are intermediate to normal glycemic values and those that exceed the limits of non-pregnant patients.

Added to this issue, this disease is also characterized by insulin resistance, dysregulation of adipokines, altered lipid metabolism, mild inflammation and increased circulating fatty acids (TUMURBAATAR et al., 2017).

PATHOPHYSIOLOGY OF GDM

Pregnancy is a state of multiple metabolic changes. Initially, there is an increase in insulin sensitivity that promotes the uptake of glucose for the fetus' demand. Placental hormones promote a state of insulin resistance and, as a result, blood glucose is elevated, which is transported to nourish the fetus. This resistance also promotes the endogenous production of glucose and the lysis of fat stores. As a result, there is an increase in the concentration of glucose and fatty acids in the blood (PLOWS et al., 2018).

Insulin resistance is associated with pancreatic beta cell dysfunction during pregnancy. These cells function to store and release insulin, which in turn helps transport glucose from the blood to target cells. Therefore, when these cells do not respond adequately to glycemic load, beta cell dysfunction is said to occur. (PLOWS et al., 2018).

Hormones antagonistic to insulin, such as progesterone and estrogen, will promote hyperplasia of pancreatic beta cells and this will increase the insulin response to the glycemic load, favoring an increase in glycogenesis, lipogenesis and also the increase in deposits of glycogen, triglycerides and proteins, essential substances in fetal development (KUNZENDORFF et al., 2017).

In a later phase, insulin release increases and glucose concentrations are also elevated. If the release of insulin is not sufficient for the glycemic load, hyperglycemia will occur, causing harmful effects for both the fetus and the pregnant woman. This maternal hyperglycemia triggers fetal hyperglycemia, due to glucose being transported to the fetus through the placenta. The fetus responds to this stimulus with excessive insulin production, leading to fetal hyperinsulinemia (REIS et al., 2019).

RISK FACTORS

Pre-gestational risk factors for the development of gestational diabetes mellitus include poor diet, sedentary lifestyle, obesity and hormonal changes during pregnancy itself, since glucose is the main source of energy for the fetus and the maternal body needs it. adapt to this increase in glycemic load (CARVALHO et al., 2019).

DIAGNOSIS

According to the Portuguese Gestational Diabetes consensus in an analysis of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study and the criteria of International Association of Diabetes and Pregnancy Study Groups (IADPSG) found that for the diagnosis to be made correctly, all pregnant women must, at their first prenatal consultation, undergo a fasting plasma glucose test.

If the blood glucose level is greater than or equal to 92 mg/dl, but less than 126 mg/dl, the diagnosis of gestational diabetes is made. Pregnant women who have a fasting result greater than or equal to 126 mg/dl or occasional plasma glucose greater than 200 mg/dl must be diagnosed with diabetes mellitus prior to pregnancy. Pregnant women who obtained a result lower than 92 mg/dl, at 24 to 28 weeks of gestation, must take the oral glucose tolerance test with 75 g of glucose (PORTUGUESE SOCIETY OF DIABETOLOGY, 2016).

For the oral glucose tolerance test, the pregnant woman ingests a solution of 75 grams of glucose diluted in 250-300 ml of water. Blood is collected at 0:00, 1:00 and 2:00. If the result is a fasting blood glucose level greater than or equal to 126 mg/dl or in the 2nd hour greater than or equal to 200 mg/dl, diabetes during pregnancy is diagnosed and treatment is carried out as previous diabetes. To diagnose gestational diabetes at midnight, the result must be between 92 and 125 mg/

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dl, in the 1st hour greater than or equal to 180 mg/dl and in the 2nd hour between 153 and 199 mg/dl (PORTUGUESE SOCIETY OF DIABETOLOGY, 2016).

MATERNAL-FETAL CONSEQUENCES

Exposure of fetuses to intrauterine hyperglycemia has short- and long-term consequences for both the baby and the mother. For the newborn, in the short term, they include excessive intrauterine growth as the main repercussion and hyperinsulinemia and hypoxia also occur (PLOWS et al., 2018).

Due to glucoseflow through the placental barrier, the fetus increases insulin production to try to control this hyperglycemia. Insulin, however, acts as a growth hormone, increasing the likelihood of macrosomia (ALEJANDRO et al., 2020). Fetal hyperinsulinemia can lead to increased fetal myocardial thickness. This is possible even when the pregnant woman has adequate control of her glycemia (OLIVEIRA et al., 2016).

Glucose has a high affinity for oxygen, making it possible for the fetus to enter into intrauterine hypoxia. If this occurs, the fetus will respond with an increase in the production of red cells – polycythemia – to try to capture as much oxygen as possible. This condition causes the fetus at birth to have neonatal jaundice (PLOWS et al., 2018).

In addition to neonatal jaundice, as soon as the baby is born he may have hypoglycemia, due to the abrupt reduction in the amount of glucose available. This condition can occur in 25% to 50% of newborns born to mothers who already had diabetes prior to pregnancy and between 15% to 25% in mothers with GDM. Hypoglycemia may be responsible for poor neurological development, with the WHO recommending blood glucose tests in symptomatic newborns or those who have a mother with GDM (DUARTE et al., 2019).

The main long-term complications are related to nutritional adaptations. These babies have greater difficulty feeding correctly, have a high risk of obesity and glucose intolerance in childhood and early adulthood (REIS et al., 2019).

According to Duarte et al. (2019), in a cross-sectional cohort study with 409 pregnant women with positive screening for diabetes mellitus, cases of neonatal hypoglycemia and hyperbilirubinemia were observed in 2.2% of these pregnant women.

Just like the newborn, the mother has both short and long-term consequences if she does not receive adequate treatment. Among the short-term ones are hypertensive syndromes, polyhydramnios, urinary infections, pyelonephritis, hypoglycemia, ketoacidosis and candidiasis (REIS et al., 2019). Such conditions increase the chance of the pregnant woman experiencing premature labor, miscarriage and needing a cesarean section, increasing complications, due to the fact that it is a surgery. These complications include hemorrhages and puerperal infections (OLIVEIRA et al., 2016).

Long-term complications include the risk of developing type 2 diabetes mellitus and other cardiovascular diseases due to the altered vasculature (REIS et al., 2019).

According to Oliveira et al. (2016)

> There is a 35% to 60% chance that a woman who has had GDM will develop diabetes in the next 20-20 years.

TREATMENT

Given the various complications that GDM can result in for pregnant women and newborns, after the diagnosis of gestational diabetes mellitus the patient must begin treatment.

There are two treatment modalities for glucose control, non-pharmacological and pharmacological (DURNWALD, 2018). Shortly

after the diagnosis, non-pharmacological treatment begins, which consists of nutritional re-education and the inclusion of physical activity in the pregnant woman's daily life (OLIVEIRA et al., 2020). Dietary guidance aims to achieve metabolic control and weight gain, ranging from 300 to 400 g per week (OLIVEIRA et al., 2016).

On the other hand, pharmacological measures consist of oral hypoglycemic agents and insulin (DURNWALD, 2018). The oral hypoglycemic agent of choice is metformin. However, it is indicated as monotherapy in cases of non-adherence to insulin treatment or as an adjuvant in severe hyperglycemia (PAN AMERICAN HEALTH ORGANIZATION; et al., 2019).

Therefore, insulin is used as the drug of choice for treatment whenever changes in the patient's lifestyle are not sufficient to achieve glycemic control. The most used are Neutral Protamine Hagedorn (NPH) and Regular, which are found in the Unified Health System (PAN AMERICAN HEALTH ORGANIZATION; et al., 2019).

With adequate glycemic control and the estimated fetal weight being less than 4kg, the pregnancy will be terminated at 39 weeks in pregnant women using insulin and at 40 weeks in pregnant women not using insulin. (CARDOZO et al., 2020).

METHODOLOGY

The present study used the integrative literature review method, which aims to gather collections already produced on the proposed topic and summarize them. The integrative literature review is divided into six parts:

STEP 1: Identification of the topic and selection of the hypothesis or research question for the preparation of the integrative review.

The theme was defined and questions were selected that guided the research to answer the question: What are the consequences of GDM for the mother and the newborn?

STEP 2: Establishment of criteria for inclusion and exclusion.

The keywords were established: gestational diabetes, diagnosis, complications, newborn. The search strategies were based on combinations of Portuguese and English and with the Boolean operator AND. The data collection sources were the PubMed, Scielo and Virtual Health Library (VHL) databases dated after 2015.

The inclusion criteria for selecting articles were: articles published in Portuguese and English dated after 2015 that have a defined theme. Exclusion criteria included: articles in other languages, published before 2015 and that did not address the selected topic.

STEP 3: Identification of pre-selected and selected studies

At this stage, among the selected articles, their titles, keywords, abstracts were re-read and evaluated according to the inclusion and exclusion criteria.

STEP 4: Categorization of selected studies

In the analysis and categorization of the selected articles, the synthesis matrix was used as a way of organizing the material obtained.

STEP 5: Interpretation of results

After analyzing the articles, the results were interpreted and presented in the form of a discussion. Therefore, scientific knowledge about maternal-fetal complications of diabetes was observed gestational *mellitus*.

STEP 6: Presentation of the knowledge review/synthesis

As a conclusion to this work, a summary was prepared on the production of results on the proposed topic.

RESULTS AND DISCUSSION

The initial sample consists of 500 articles, 28 of which were found in PubMed, 416 in Scielo and 31 in the VHL. The databases, search strategies and the number of articles found and their respective sources are recorded in table 01.

SOURCES OF INFORMATION	SEARCH STRATEGIES	RESULTS
PubMed	Topics: (gestational diabetes [MeSH Terms]) AND (newborn [MeSH Terms]), (gestational diabetes [MeSH Terms]) AND (diagnosis [MeSH Terms]), (gestational diabetes [MeSH Terms]) AND (complications [MeSH Terms])	28
Scielo	Topics: (gestational diabetes) AND (complications), (gestational diabetes) AND (newborn), (gestational diabetes) AND (diagnosis), (gestational diabetes), (gestational diabetes) AND (complications), (gestational diabetes) AND (newborn), (gestational diabetes) AND (diagnosis)	416
BVS	(gestational diabetes) AND (complications), (gestational diabetes) AND (newborn), (gestational diabetes) AND (diagnosis)	56

Frame 01: Database, strategies and results of articles found.

Among the articles found, an analysis was initially carried out by title and abstract, resulting in the exclusion of 399 articles in Scielo, 7 in PubMed and 51 in the VHL. After reading the full text, a total of 10 articles were obtained as a final sample, recorded in table 02.

SOURCES OF INFORMATION	PRE-SELECTED ARTICLES	SELECTED ARTICLES
PubMed	21	7
Scielo	17	2
BVS	4	1

Table 02: Article selection process.

Once the selection part was completed, a sample of 10 final articles was obtained, categorized in table 03.

Regarding the origin of the publications, we found ten articles in the English language with publication dates between 2018 and 2021. Regarding the methodological design, five review articles, two cross-sectional study articles, one prospective study and two retrospective cohort studies were identified. Such information demonstrates that the theme of this study is a current topic and has been further explored since 2018 and in the form of a review.

Of the total articles selected, 90% addressed the consequences of GDM for the mother and fetus, 1% had the consequences for the mother as the central study. The consequence of GDM for the mother is the increased risk of developing type 2 diabetes mellitus, which appears in 80% of the articles. Cesarean section, neoplasms, ophthalmic, psychiatric, renal diseases, eclampsia and pre-eclampsia, postpartum complications such as hemorrhage were also found as possible maternal outcomes.

Silva et al. (2021), showed that in retrospective studies, women with GDM have a 20% to 60% risk of developing DM2 in the 5 to 10 years after pregnancy. In another study carried out by the same author, he shows that even after pregnancy and the woman has achieved ideal BMI, there is an 8-fold increase in the chances of women with GDM having DM2 in 10 years.

According to Nunes et al. (2020), of the 301 pregnant women who were analyzed in their cohort study, 94% of them had GDM and of these, 10.3% had premature births, with 26% of these women being obese.

Plows et al. (2018), also highlights that with each pregnancy, there is a 3-fold increase in the risk of developing DM2 in women with a history of GDM in previous pregnancies. The

No.	AUTHORS, TITLE	YEAR	PURPOSE	METHODOLOGICAL DESIGN
1	Ornoy, A., Becker, M., Weinstein-Fudim, L., Ergaz, Z. Diabetes during pregnancy: a maternal disease that complicates the course of pregnancy with long-term deleterious effects on the offspring. A clinical review.	2021	Fetal complications related to GDM.	Revision
2	Moodley, S., Arunamata, A., Stauffer, KJ, Nourse, SE, Chen, A., Quirin, A., Selamet Tierney, ES Maternal arterial stiffness and fetal cardiovascular physiology in diabetic pregnancy.	2018	Determine the impact that GDM has on the maternal vasculature associated with fetal cardiovascular physiology.	Prospective study
3	Feghali, MN, Abebe, KZ, Comer, DM, Caritis, S., Catov, JM, Scifres, CM Pregnancy outcomes in women with an early diagnosis of gestational diabetes mellitus.	2018	Analysis of pregnancy outcomes in women with GDM.	Retrospective cohort study analysis
4	Silva, CM, Arnegard, ME, & Maric-Bilkan, C. Dysglycemia in Pregnancy and Maternal/Fetal Outcomes.	2021	Analysis of blood glucose changes and their maternal-fetal results.	Revision
5	Tavares, M., Lopes, É. S., Barros, R., Azulay, R., Faria, M. Profile of Pregnant Women with Gestational Diabetes Mellitus at Increased Risk for Large for Gestational Age Newborns.	2019	It analyzes the profile of pregnant women with GDM who are at greater risk of having an LGA baby.	Cross-sectional study
6	Wahlberg, J., Ekman, B., Arnqvist, H.J. Most Women with Previous Gestational Diabetes Mellitus Have Impaired Glucose Metabolism after a Decade.	2018	Analysis of the long-term consequences of GDM.	Revision
7	Plows, JF, Stanley, JL, Baker, PN, Reynolds, CM, Vickers, MH The Pathophysiology of Gestational Diabetes Mellitus.	2018	Review of the pathophysiology of GDM.	Revision
8	Alejandro, EU, Mamerto, TP, Chung, G., Villavieja, A., Gaus, NL, Morgan, E., Pineda-Cortel, M. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes.	2020	Analysis of data on GDM such as screening, diagnosis and peripartum complications and preclinical models of the disease.	Revision
9	Dias Nunes, R., Eloisa Flôres, M., Seemann, M., Traebert, E., Traebert, J. Two criteria of oral glucose tolerance test to diagnose gestational diabetes mellitus.	2020	Analysis of the consequences of GDM using the chi-square test.	Cross-sectional study
10	Sousa Nunes, J., Ladeiras, R., Machado, L., Coelho, D., Duarte, C., Furtado, JM. The influence of preeclampsia, advanced maternal age and maternal obesity in neonatal outcomes among women with gestational diabetes.	2020	Analyzes adverse fetal and neonatal outcomes of women with GDM.	Retrospective cohort study

Table 03: Categorization of selected articles.

annual risk of GDM becoming DM2 is 2 to 3%. Jeanette et al (2018), in a study with 51 women diagnosed with GDM who underwent follow-up for 12 years, found that 4 of these women developed diabetes mellitus.

Alejandro et al (2020), highlights that hyperglycemia can return to normal after pregnancy, however, insulin resistance and pancreatic beta cell dysfunction can persist and this increases the risk of developing DM2.

Moodley et al (2017), showed in their study that pregnant patients with GDM have stiffer arteries and confirming this, Plow et al (2018), reported that the vasculature of women with a history of GDM is permanently altered and this increases the risk in 63% of having cardiovascular diseases in the future.

Macrosomia was found in 100% of the articles as complications for the fetus. Hyperinsulinemia was found in 70% along with hyperbilirubinemia. In addition to

these consequences, neonatal hypoglycemia, respiratory and cardiovascular morbidity, congenital anomalies, spontaneous abortions, prematurity and neonatal death have been reported.

According to Alejandro et al (2020), glucose crosses the placental barrier because the fetus has limited capacity to produce it. Increased maternal glucose in the fetus will induce hyperinsulinemia, independent of fetal glucose production. Insulin acts as a growth hormone for the fetus, and as a result, cell proliferation and increased nutrient transport occur, which can contribute to the fetus being born with neonatal adiposity and being a macrosomic baby. Excess nutrients result in a macrosomic baby and neonatal adiposity is limited to the abdominal region and fetal shoulders. This increases the risk of shoulder dystocia and birth trauma.

According to Ornoy et al (2021), the probability of fetal macrosomia is 15-25% of newborns born to mothers with GDM and is 3 times higher than in normoglycemic mothers.

Macrosomia is characterized by larger shoulders, decreased head-to-shoulder ratio, greater body fat and thicker skin folds on the extremities due to the accumulation of fat in the abdominal and interscapular region. This complication is associated with higher perinatal mortality due to the risk of Erb's palsy, shoulder dystocia and brachial plexus trauma.

With regard to diagnosis, it was found in 40% of the articles that the investigation is initially carried out with fasting blood glucose levels in the first pregnancy tests. And within 24-28 weeks of gestation with the oral glucose tolerance test (OGTT). The test is negative for GDM if the result is < 92 mg/dl and positive for GDM if it is between 92 mg/dl and 126 mg/dl. Feghali et al (2017), shows that women diagnosed before 24 weeks with GDM had higher glucose values during pregnancy and had a higher risk of macrosomia.

A total of 60% of articles briefly commented on the treatment. 33.3% of the 60% reported that there was no consensus on this topic. The other 26.7% describe treatment with diet, oral antiglycemic drugs and insulin. And 30% do not address this topic. Despite this, it is known that for GDM, in Brazil, insulin treatment is used, which can be NPH or regular.

FINAL CONSIDERATIONS

The diabetes *mellitus* pregnancy is a condition that brings a lot of harm to the mother-fetus binomial, if not diagnosed and treated correctly. Maternal hyperglycemia induces several metabolic changes in the fetus both in utero and after birth. Studies have shown that these changes are associated with a greater risk of gestational complications such as macrosomia, hyperinsulinemia, neonatal jaundice, which were the most cited. Neonatal hypoglycemia, respiratory and cardiovascular morbidity, congenital anomalies, spontaneous abortions, prematurity and neonatal death were also mentioned. For the mother, the increased risk of developing DM2 in the future was the most discussed topic in the articles. However, consequences such as increased need for cesarean section, eclampsia, pre-eclampsia, postpartum complications such as hemorrhage are no less important. A diagnosis made at the right time and treatment correctly adhered to by the pregnant woman is the best way to reduce the consequences caused by GDM.

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