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Impact of Gestational Diabetes Mellitus (GDM) on the Platelet Activity and Coagulation System

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Abstract: ***This study aims to identify the effect of gestational diabetes mellitus on platelet indices and the coagulation system. Although the mechanism for GDM is unclear, numerous studies have been conducted to determine the correlation between GDM with different immunological factors. A systematic literature review will be conducted herein to assess the influence of GDM on the immunological factors that result in pregnancy complications and adverse pregnancy outcomes. Results for the survey indicated that GDM is associated with altered coagulation systems that may result in hypercoagulability, resulting in bleeding. The report also showed that GDM is linked to increased platelet and inflammatory indices, which predispose pregnant women to vast pregnancy complications. Therefore, the study concluded that even though the mechanism of GDM is unknown, various factors influence its incidence, including altered coagulation systems and increased platelet indices.***

Keywords: Gestational Diabetes Mellitus, Platelet Indices, insulin, coagulation

1. Introduction

Women experience substantial challenges during pregnancy and fetal development, as the condition alters their immune systems. Primary immunological mediators, including T-cells, natural killer cells, and macrophages, must be kept at equilibrium by the mother's immune system from conception to the time of birth, thus preventing adverse pregnancy complications outcomes. [1] Therefore, these immunological modulators influence the health outcomes of the mother and the fetus. Numerous studies have suggested that pregnancy induces immunosuppression on maternal health, making women susceptibleto a wide array of disorders. [2] Gestational diabetes mellitus (CDM) has been identified among the most common diseases affecting pregnant women. The condition affects about 10% of the global pregnancies and is described as any level of glucose intolerance first recognized during pregnancy.[2] It is a severe obstetric condition characterized by limited insulin response to counter the insulin resistance induced by the pregnancy. Although the disorder's pathophysiologyis unclear, a predominant hypothesis suggests that it results from the aberrant expression of hormones from the placenta, thus resulting in reduced insulin functionality and maternal metabolic dysfunction. Other researchers also suggest that gestational diabetes mellitus results from deviant, abnormal adaptation of the maternal immune system to gestation and the increased flux of circulatory inflammatory cytokines. This adaptation causes immune pathway dysregulation that eventually results in vasculopathy and endothelial dysfunction. [3] The immune dysregulation causes that cause CDM results in multiple complications, including imbalances in the cellular responses that affect the coagulation system and the platelets indices.

2. Background

Insulin resistance during pregnancy has been associated with the increasing frequency of gestational diabetes mellitus. Pregnant women are also more likely to experience hyperglycemia, a condition that reduces the availability of insulin. Therefore, pregnant women need to monitor the disorder closely due to the likelihood of developing adverse pregnancy outcomes associated with coagulation problems. Coagulation represents a dynamic equilibrium that is critical to ensuring safe childbirth. The process of coagulation improves towards the third trimester and is higher in pregnant women than their regular counterparts. [4] Similarly, late pregnancy is associated with alterations in liver metabolism, hormone secretion, and higher coagulation indices. [4] Gestational diabetes mellitus exacerbates hypercoagulability in pregnant women, resulting in pregnancy complications like deep venous thrombosis of the lower extremities, increased risk of birth injuries, preeclampsia, and need for cesarean delivery.

The effect of gestational diabetes mellitus has been documented extensively, and it is clear that the disorder affects the endothelial functions and the coagulation systems. The hyperglycemic state in diabetes mellitus and the hypoglycemic agents-induced hypoglycemia influence the hemostatic activities and factors. [4] Pregnancy is associated with the prothrombotic state caused by the prothrombotic coagulation factors with reduced fibrinolysis and increased activation of platelets. Pregnancy also causes a hypercoagulable condition representing an adoptive and physiological mechanism, which facilitates a homeostatic balance responsible for reduced bleeding during delivery. However, in GDM patients who are pregnant, this physiological mechanism may turn into a pathologic process that might also be accompanied by preeclampsia or eclampsia. The fibrinolytic system and the coagulation cascade include multiple coagulation factors that interact via complex pathways, making it difficult to understand or reveal the exact mechanism surrounding the homeostatic changes in glucose metabolism. [5] It is still challenging to understand this mechanism considering the dynamics involved at the

pathophysiological level and its impact on the coagulation system.

On the other hand, increased lactogen hormone is linked to elevated lipolysis and an increased secretion of free fatty acids, thereby leading to increased insulin resistance. Increased insulin resistance can be detected in pregnant women due to chronic and mild inflammation that forms part of CDM pathogenesis. [6] Immune cells, including platelets, neutrophils, and lymphocytes, are vital in regulating inflammation. Increased leukocyte count, including neutrophils, is recorded in mild and chronic inflammation. [6] A complete blood count helps identify platelet indices, including the mean platelet volume, plateletcrit, mean platelet volume to platelet ratio, platelet distribution width, and overall platelet count. Besides, complete blood counts are effective and inexpensive, explaining why they are used in these estimations. GDM has been associated with changes in some indicators, including platelets and blood cells. [6] However, the contradictory result in the studies posted initially suggested the need to facilitate more research.

Study Question

What is the Impact of Gestational Diabetes Mellitus (GDM) on the Coagulation System and Platelet Indices?

3. Methodology

A systematic review was conducted by searching articles published from 2016 to 2021 from databases and search engines like ScienceDirect, PubMed, SpringerLink, and google scholar. The keywords included in this search were impacts, gestational diabetes mellitus (GDM), coagulation system,and platelet indices. The inclusion criteria included articles that are relevant to the research question and the date of publication. Therefore, only articles that were less than five years old and relevant to the discussion topic were included in the review. The literature search generated 67 sources, although this number was reduced to 23 based on publication date. The number was further reduced to 15 based on their relevance to the study. Only full articles were used in the study, and thus abstract sources were all excluded. The final number of articles used in the review was five due to the inclusion of the key words.

4. Literature Review

Dong and his colleagues conducted a study to assess the relationship between bleeding and coagulative function in GDM. The research, which included 662 subjects, found out that women with GDM experienced increased blood fibrinogen, shortened APTT, and shortened PT even though the platelet parameters remained the same during mid-pregnancy. However, the platelet parameters, including platelet distribution width, mean platelet volume, and thrombocytosis, increased during late pregnancy. This article suggested that GDM is associated with an unspecified level of glucose intolerance that is first diagnosed during pregnancy with no history of diabetes before the pregnancy. According to these authors, GDM causes about 12% of morbidity cases in china, with an increased incidence of about 30% in the last ten years. [7] The authors also suggest that GDM is a common condition globally, with a worldwide prevalence rate of about 0.6% to 15%. [7] The state increases the risk of adverse pregnancy outcomes, including macrosomia, shoulder dystocia, preeclampsia, and increased hemorrhage in both the mother and the child.

Platelet-mediated primary homeostasis and blood coagulation from the anticoagulation systems regulate clotting to maintain the natural equilibrium of physiological conditions. The hemostatic cascade is characterized by activated platelets that convert prothrombin into thrombin and convert fibrinogen into fibrin.[7] Numerous other changes also occur in normal pregnancy, including alterations in various proteins, protein factors, and plasma fibrinogen. Fibrinolysis and activation of platelets also happen in normal pregnancy. The collective effect of these changes results in physiological hypercoagulation that is normal in normal pregnancy and is regarded as a maternal response to delivery. [7] However, the report also suggests that gestational diabetes mellitus increases the risk of hemorrhage three to five times than in normal pregnancy. [7] Therefore, the researchers hypothesized that GDM increases the risk of hypercoagulability, a risk factor for hemorrhage. Nevertheless, this research also suggests that further research is essential to determining the relationship between increased risk of bleeding and coagulation functions.

Gestational diabetes mellitus is a serious problem during pregnancy and causes postpartum diabetes mellitus and severe fetal complications. However, these authors also note that diagnosis of GDM is only possible in the third trimester, even though the antenatal complications are evident even later. [8]Therefore, these researchers conducted qualitative and quantitative analyses on peripheral and cord blood samples of diabetic patients to identify the pathways of molecular events associated with fetopathy and diabetes mellitus. It was determined that faulted lipid metabolism is widely associated with impaired glucose uptake, triglycerides transport, and insulin resistance. Inflammation and Oxidative stress aggravate the likelihood of these outcomes due to their secondary role in altering the matrix architecture. [8]This study identified unequal alterations in the cord and peripheral blood proteomes, thus suggesting that numerous molecular processes influence the incidence of diabetes during gestation. These changes significantly impact the growth and development of the fetus.

Another article published in 2019 also described pregnancy as a hypercoagulable condition characterized by an elevated risk of venous thrombosis. The authors suggested that the risk for thrombosis increases in pregnancy and can be determined through the calibrated automated thrombogram, a test that monitors thrombin generation. [9]Thrombin generation has been linked to the utilization of insulin in pregnant women with gestational diabetes mellitus. However, the risk of thrombosis increases with the increasing duration of

pregnancy. [9]The authors also noted that maternal thromboembolic conditions are common adverse pregnancy outcomes, pregnancy complications and that the most common complication is the prethrombotic state. The prethrombotic condition is associated with an alteration in the anticoagulation protein C system or the endothelial function injury that causes an increased thrombin formation. [9]Elevated thrombin levels consequently result in increased hypercoagulability and increased risk of developing embolism. Although this study intended to study thrombin generation in pregnant Chinese women, it is relevant for the topic as it addressed the relationship between thrombin generation and GDM. The authors stated that the condition increases the risk of developing changes in the coagulation system and causes vascular endothelial injury resulting in a prethrombotic state and hypercoagulability. [9] They further reported an increased risk of thromboembolism resulting from GDM, as evidenced in other studies.

According to Fashami and colleagues, GDM is the most common medical abnormality during pregnancy. However, they also stated that diagnosing GDM early enough could influence the pregnancy outcome. [6] These authors conducted a case-control study that involved two groups of 110 women to identify whether there is a relationship between the risk of GDM and the platelet indices. One group included women with gestational diabetes mellitus, while the other group comprised women with normal pregnancy. The relationship between the research variables was identified through a complete blood count test that estimated the differences in the plateletcrit, mean platelet volume, platelet count, and white blood cell count. This study suggested an association between increased risk of GDM and increased platelet and inflammatory indices. [6] There are several complications associated with GDM, including preeclampsia, prenatal mortality, cesarean section, fetal macrosomia, prenatal mortality, and instrumental labor. Similar to other articles, this article stated that early diagnosis is essential to preventing these problems. This can be made possible since the pathophysiological process of diabetes happens earlier before the diagnosis. Furthermore, the factors relative to the condition can be detected in the blood before diagnosing a patient with GDM. This research also noted that an elevated level of placental lactogen hormone is likely to increase lipolysis, while insulin resistance might be exacerbated by the production of free fatty acids.

A study to understand the correlation between mean platelet volume and insulin resistance in GDM, conducted a correlational study involving 114 subjects with GDM and 76 other subjects with normal pregnancy. [10] This study aimed at comparing the mean platelet volumes of the subjects and assess the relationship between the established values and insulin resistance in women with gestational diabetes mellitus. Results showed that mean platelet volumes (MPV) in women with GDM were relatively higher than in women with normal pregnancy. [10] The researchers also identified a positive correlation between homeostasis model assessment insulin resistance index (HOMA-IR) and MPV.

According to Baldane et al., pregnancy increases insulin resistance, particularly in the last two trimesters. [10] The secretion of numerous hormones, including human placental lactogen, cortisol, leptin, and prolactin,has been associated with increased resistance to insulin during pregnancy. Therefore, for pregnant women to effectively regulate the normal glucose metabolism, they depend on the functional enhancement of beta cells. The inability of these cells to synthesize sufficient amounts of insulin might result in hyperglycemia. Although glucose intolerance is resolved during the postnatal period, patients develop a lifetime risk of cardiovascular disorders and type 2 diabetes. Measuring the volume of platelets is a simple and inexpensive method that is considered a marker of platelet activation and function. Elevated MPV values have been associated with increased insulin resistance and other associated conditions, including hypertension, diabetes mellitus, impaired fasting glucose, obesity, and metabolic syndrome.

5. Findings

Out of the fifteen articles identified, five were chosen for review. All five articles described the molecular effects of GDM on the health of pregnant women. According to these articles, there is a relationship between increased insulin intolerance and GDM. Gestational diabetes mellitus causes increased insulin resistance through increased platelet parameters, thereby increasing the risk of other complications, including hypercoagulability, hemorrhage, type 2 diabetes, hyperglycemia, hypertension, and other heart disorders. Therefore, the inability of the beta cells to produce enough insulin to regulate the blood glucose causes GDM, which in turn is associated with increased platelet indices and an altered coagulation system.

6. Discussion

Although the studies included herein identify a correlation between GDM and increased platelet parameters, the mechanism that results in increased mean platelet values during pregnancy is yet to be understood. Plateletcrit values in the second trimester have been indicated to have the highest correlation to the risk of GDM. [6] However, since the diagnosis of GDM depends on screening tests, the CBC test is critical in determining the platelet and inflammatory indicators of the condition. [9] Early identification of the increased platelet parameters could help doctors prevent the incidence or delay the onset of GDM.

Platelet indicators, which are the activation biomarkers, allow various diagnostic tests based on the identification of the plateletcrit, mean platelet volume,and platelet distribution width using the complete blood count test. Platelets not only take part in thrombosis and homeostasis but are also involved in immunization, inflammatory activity, and intercellular communication. [6] These studies suggest a correlation between GDM and high values of mean platelet value and platelet count. However, the inconsistent findings from these

studies indicatethat the mean platelet volume cannot be used to ascertain the incidence of GDM. Instead, the PCT value directly correlated to the risk of GDM since it indicates the total platelet mass and holds more weight than either MVP or platelet. [6] These studies consistently show that increased values of PCT are ass associated with GDM and can therefore be used as a predictor of GDM during the second trimester.

Cellular processes that result in inflammation during pregnancy could result in GDM. Specific inflammation cytokines, including tumor necrosis factor-alpha, and interleukin six, have been identified in the pathogenesis of GDM. [8] Women with GDM have reported increased values of inflammation cytokines that could explain the incidence of GDM. Activation of coagulation factors and platelets coupled with reduced anticoagulant function results in the prethrombotic state exhibited in GDM patients. [10] Therefore, the molecular and immunological changes that occur during pregnancy increase the platelet indices while increasing hypercoagulability.

7. Conclusion

This study proves a link between GDM and the alteration of the coagulation system and the platelet indices. Although a definitive mechanism that causes GDM is not precise, the research included herein suggests multiple mechanisms that exacerbate the risk of GDM. Nevertheless, the condition has been associated with increased platelet indices and altered coagulation systems, resulting in numerous complications, including hypercoagulability, hemorrhage, type 2 diabetes, hypoglycemia, obesity, hypertension, and other heart conditions. This study also shows that identifying GDM is only possible in the second and third trimesters even though the factors that potentiate the state are available earlier than that time. Still, there is a need for the condition to be identified earlier enough to prevent these complications.

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