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Original article

A NARRATIVE REVIEW ON THE ROLE OF OXIDATIVE STRESS IN GESTATIONAL DIABETES MELLITUS AND PREECLAMPSIA.

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Abstract:

This review examined the role of oxidative stress in hypertensive disorders of pregnancy (HDP) and metabolic illnesses, including gestational diabetes mellitus. Oxidative stress induces hypoxia in the placenta in preeclampsia (PE) and gestational hypertension (GH). This hypoxia usually causes a systemic inflammatory reaction in the mother. In physical education, the disease causes kidney inflammation and proteinuria. Proteinuria is characterised by urine 8-oxoGuo excretion in preeclampsia. Due to increased insulin synthesis during pregnancy, oxidative stress is linked to gestational diabetes mellitus (GDM). Unregulated insulin release generates lipid peroxidation agents, which inhibit antioxidant secretion. Therefore, reactive oxygen species (ROS) grow dramatically in the cellular environment, inhibiting glucose delivery to diverse organs.

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1. Introduction:

Gestational diabetes mellitus (GDM) is the most prevalent metabolic disease in pregnancy, characterised by abnormal blood sugar levels and resulting in a variety of maternal and neonatal complications [1]. Currently, the prevalence of GDM is rising steadily, particularly in Asia. This is associated with a higher risk of metabolic disorders and a more advanced maternal age in recent years [2]. In 2015, the International Diabetes Federation estimated that the prevalence of hyperglycemia during pregnancy was approximately 16.2%, possibly as high as 24.5% in South-East Asia, with 85.1% of cases involving GDM [3]. GDM is clinically significant due to its association with increased adverse pregnancy outcomes, which is correlated with blood glucose levels [4-6], such as gestational hypertension and preeclampsia, foetal macrosomia, shoulder dystocia, and the incidence of caesarean section [5]. In addition, GDM is associated with a 50% chance of developing diabetes mellitus type 2 (DM type 2) 22–28 years after pregnancy [4].

Gestational diabetes mellitus (GDM) and preeclampsia (PE) are common pregnancy complications with comparable risk factors, including obesity, advanced age, and multiple gestation [1, 2]. Moreover, the pathophysiological processes of both GDM and PE include oxidative stress, pro-inflammatory factor release, and vascular endothelial dysfunction [3, 4], which all increase the risk of future maternal diabetes and cardiovascular disease. Thus, a correlation may exist between GDM and PE [5].

Many risk factors have been related to hypertensive disorders during pregnancy. Body mass

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index, anaemia, maternal age, first-time motherhood, multiple pregnancies, previous HDP, gestational diabetes mellitus, preexisting hypertension, type 2 diabetes, urinary tract infection, and family history of hypertension, type 2 diabetes, and poor diet [6]. The cause of hypertensive disorders of pregnancy (HDP) is unknown, but oxidative stress may be a major factor. Multiple studies have linked oxidative stress to hypertension [7]. An imbalance of reactive oxygen species (ROS) in vascular walls causes blood vessel constriction and hypertension [6].

Objective: Oxidative stress is associated to metabolic abnormalities during pregnancy, including gestational diabetes mellitus, as well as hypertensive illnesses. Reactive oxygen species (ROS) inhibit insulin's glucose absorption by cells. Insulin resistance contributes to gestational diabetes. This review aims to examine the role of oxidative stress in preeclampsia, prenatal hypertension, and gestational diabetes mellitus. Preeclampsia is the leading cause of death and morbidity in India.

1.1. Preeclampsia:

The placenta's unhealthy condition preeclampsia (PE) harms both mother and child. This issue affects 6-8% of pregnancies worldwide [8]. Preeclampsia is characterised by the onset of hypertension, as measured at four-hour intervals, and a 24-hour urine test with a protein level of 300 mg/day or higher, occurring after 20 weeks of gestation, or proteinuria≥1+, detected by a visual dipstick. Without proteinuria, hypertension can be identified by thrombocytopenia, renal insufficiency, HELLP syndrome, pulmonary edoema, or cerebral or visual abnormalities [8]. This disease causes global prenatal morbidity and mortality in industrialised and developing nations [9]. Prior studies have shown that preeclampsia kills 50,000 to 60,000 newborns worldwide [8]. Preeclampsia is caused by aberrant spiral arteriole cytotrophoblast invasion, which reduces uteroplacental perfusion [3]. This disease causes HELLP syndrome, a maternal systemic illness with hypertension, abrupt haemolysis, increased liver enzymes, and low platelets [4].

1.2. Factors associated with preeclampsia in GDM women

1.2.1. Age and Ethnicity:

Age, parity, and race also affect pulmonary embolism (PE) in women with gestational diabetes mellitus. Several studies show that older age does not independently predict pulmonary embolism (PE) in women with gestational diabetes mellitus (GDM) [10]. Only a retrospective study identified advanced age as an independent risk factor for pulmonary embolism (PE) in women with gestational diabetes mellitus (GDM) [10]. Nulliparity was independently associated with preeclampsia in women with gestational diabetes mellitus in a randomised controlled trial. This supported another retrospective study [11]. Previous research has shown no link between parity and preeclampsia in women with gestational diabetes [11]. Ethnicity affects gestational diabetes mellitus (GDM) women's PE risk. A randomised controlled trial in New Zealand and Australia enrolled 724 ethnically diverse participants. Polynesian people had twice the risk of pulmonary embolism (PE) as European, Caucasian, or mixed-ethnic people [11]. The US retrospective analysis demonstrated no substantial variation in pulmonary embolism (PE) rates across Mexican American, Caucasian, and African American populations [12]. The retrospective investigation in Fiji found no significant effect of ethnicity on preeclampsia in women with gestational diabetes [13].

1.2.2. Gestational Weight Gain:

Pregnancy issues have been linked to gestational weight gain (GWG), a common nutritional indicator [14]. A Chinese retrospective cohort research investigated 1,606 women with gestational diabetes mellitus (GDM). Considering maternal age, pre-pregnancy BMI, education, in vitro fertilisation, fasting glucose levels, and 2-hour glucose levels, the study found different results. After controlling for these characteristics, the study found a 2.06-fold greater risk of excessive gestational weight gain (GWG) leading to preeclampsia (PE). The risk was 2.28 times higher in the second trimester and 2.17 times higher in the third

[14]. A rise in body weight during early pregnancy may potentially lead to preeclampsia [14]. Given the early ambiguity around gestational diabetes mellitus (GDM) in pregnant women, weight management becomes more important after a diagnosis.

A retrospective cohort study in the US examined how gestational weight gain (GWG) affected pregnancy outcomes after GDM diagnosis. After correcting for race (particularly black ethnicity), pre-pregnancy BMI, and chronic hypertension, GWG after GDM diagnosis did not predict preeclampsia. In the logistic regression model, pregnant women with gestational diabetes mellitus (GDM) had weekly weight gain as a continuous variable. They adjusted for pre-pregnancy BMI, maternal age, and weekly weight gain before diagnosing GDM. The probability of preeclampsia (PE) increased 83% for every 0.45 kg/week weight gain [15].

A meta-analysis of gestational weight gain (GWG) and pregnancy outcomes in women with gestational diabetes mellitus (GDM) found that excessive GWG increases the risk of pregnancy-induced hypertension. GWG and preeclampsia were not particularly examined in the study. This came from [16]. Additional clinical studies are needed to determine whether gestational weight gain (GWG) may cause preeclampsia (PE) in women with gestational diabetes mellitus (GDM), especially after GDM diagnosis. Additionally, the 2009 Institute of Medicine/National Academy of Medicine GWG criteria must be confirmed for women with gestational diabetes mellitus.

Gestational weight gain (GWG) affects the incidence of preeclampsia (PE) in women with gestational diabetes mellitus (GDM) and perinatal outcomes in those who develop PE. While excessive gestational weight gain (GWG) in its entirety reduces the risk of preterm delivery, excessive GWG in the middle trimester increases the risk of a large baby, and excessive GWG in the late trimester increases the risk of severe preeclampsia and a caesarean section [16]. In conclusion, gestational weight gain (GWG) is a changeable factor during pregnancy, but it does not have a greater impact on preeclampsia (PE) than pre-pregnancy BMI.

1.2.3. Pre-pregnancy BMI:

Body Mass Index (BMI) is a common nutritional assessment tool, including during pregnancy. Obesity is a risk factor for GDM and preeclampsia. Obesity increased GDM and PE risk threefold and twofold, respectively, in a meta-analysis of cohort data from Europe, North America, and Australia [16]. PE is independently linked to obesity and gestational diabetes mellitus (GDM) [16]. When these two situations overlap, their combined influence on PE development is greater than each alone [16]. Pre-pregnancy BMI is independently associated with preeclampsia in women with gestational diabetes mellitus (GDM) in most studies [2, 6, 9].

A retrospective cohort study examined the relationship between maternal obesity, early gestational diabetes mellitus (GDM) diagnosis, poor glycemic control, and preeclampsia (PE) in GDM women. The results showed that maternal obesity, early GDM diagnosis, and inadequate glycemic control independently caused PE. Obesity was the most risk factor among the three [17]. Obesity and pulmonary embolism (PE) were evaluated in a prospective observational study, taking blood glucose management and therapy into account. Obesity was only associated with PE in the insulin treatment group with poor blood glucose control, while the diet and insulin treatment groups with good blood glucose control did not [17]. Thus, blood glucose levels and treatment modalities may affect the impact of pre-pregnancy body mass index (BMI) on preeclampsia (PE) in women with gestational diabetes mellitus (GDM).

1.2.4. Blood Glucose:

Blood glucose regulation is an independent risk factor for pulmonary embolism (PE), but oral glucose tolerance test (OGTT) blood glucose lev- els do not [8]. Others have noted that optimis- ing blood glucose management can reduce PE, although it is not an independent cause. However, the oral glucose tolerance test (OGTT) fasting blood glucose level is an independent variable substantially related with PE. In women with severe glucose tolerance impairment, blood glucose

management must be tightened. The association between second-trimester HbA1c levels and preeclampsia (PE) is controversial. A secondary analysis of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial and a retrospective study found a link between oral glucose tolerance testing (OGTT) HbA1c levels and PE [18]. However, two retrospective studies found no link between second-trimester HbA1c and preeclampsia [19].

The risk of pulmonary embolism (PE) and gestational diabetes mellitus (GDM) in women is also affected by blood glucose levels. According to [20], women who don't check their blood glucose are more likely to have preeclampsia. Continuous blood glucose monitoring helps identify postprandial rises and food impacts. Rapid treatment plan adjustments reduce blood glucose swings. Women who monitor their blood glucose have a lower risk of pulmonary embolism (PE). The average amplitude of hyperglycemia excursions is another PE risk factor [21]. Due to oxidative stress, blood glucose variations may increase the risk of pulmonary embolism (PE). However, a small study found no link between glycemic variation in the third trimester of gestational diabetes mellitus (GDM) without insulin reliance and preeclampsia [21].

2. Conclusion:

In most studies of single-foetus pregnancies, gestational diabetes mellitus (GDM) is independently correlated with preeclampsia (PE). PE risk is also linked to pre-pregnancy BMI and blood glucose levels. Thus, optimising gestational diabetes mellitus (GDM) treatment and management may reduce preeclampsia. Oral hypoglycemic drugs like metformin and glibenclamide and insulin did not significantly differ in PE incidence. The effects of gestational weight gain (GWG) on pre-eclampsia (PE), especially after GDM and early-onset GDM, are debated. Thus, further prospective investigations are needed to clarify this issue.

3. List of abbreviations:

HDP- hypertensive disorders of pregnancy
PE- preeclampsia/ pulmonary embolism
GH- gestational hypertension
GDM- gestational diabetes mellitus
ROS- reactive oxygen species
DM- Diabetes Mellitus
GWG- gestational weight gain
OGTT- oral glucose tolerance test
HAPO- Hyperglycemia and Adverse Pregnancy Outcome

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