



Gestational Diabetes Mellitus And Autonomic Dysfunction: Impact On Preeclampsia Risk

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Article History	Abstract
Received – 10-02- 2024 Revised - 05 -03-2024 Accepted – 30-03 2024	Gestational diabetes mellitus (GDM) and autonomic dysfunction are two closely connected disorders that have received considerable focus in relation to mother health during pregnancy. This review study seeks to provide a thorough analysis of existing research, investigating the complex connection between GDM (gestational diabetes mellitus), autonomic dysfunction, and their combined influence on the likelihood of developing preeclampsia. Gestational diabetes mellitus (GDM) is a prevalent metabolic condition associated with pregnancy, which is characterised by an impaired ability to process glucose and often occurs for the first-time during pregnancy. Preeclampsia is a complex condition characterised by high blood pressure that occurs only during pregnancy and is often linked to negative consequences for both the mother and the foetus. Autonomic dysfunction, characterised by changes in the sympathetic and parasympathetic nerve systems, is now recognised as a possible factor in the development of both gestational diabetes mellitus (GDM) and preeclampsia. This review will examine the complex relationship between gestational diabetes mellitus (GDM), autonomic dysfunction, and preeclampsia, focusing on the epidemiological, clinical, and molecular aspects. This study aims to investigate the reciprocal association between GDM and autonomic dysfunction, examining the potential for one disease to worsen the other. Moreover, the study will examine the several routes via which autonomic dysfunction may impact the occurrence of preeclampsia in the context of GDM, elucidating the underlying pathophysiological processes. This study seeks to enhance our awareness of the intricate relationship between gestational diabetes mellitus (GDM), autonomic dysfunction, and preeclampsia by

<p>CC License CC-BY-NC-SA 4.0</p>	<p>consolidating the current information. These insights have the potential to facilitate the creation of focused therapies, individualised management approaches, and enhanced risk assessment tools. This, in turn, may improve the outcomes for both the mother and the foetus in pregnancies that are affected by these interrelated disorders.</p> <p>Keywords And Search Terms: "Gestational Diabetes Mellitus", "Autonomic Dysfunction", "Preeclampsia"</p>
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INTRODUCTION

Preeclampsia (PE) is a multifaceted condition that occurs during pregnancy, affecting around 5-8% of women globally. With the growing trend in obesity, the frequency of gestational diabetes mellitus (GDM) and perinatal problems linked with the disease are also rising¹. The diagnostic criteria for Preeclampsia (PE) have undergone modifications over the years. The American College of Obstetricians and Gynaecologists (ACOG) has recently updated its guidelines on high blood pressure (hypertension) that develops after 20 weeks of pregnancy in women who previously had normal B.P. Preeclampsia is defined as new-onset hypertension after the 20th week of gestation, along with indications of maternal organ failure.²

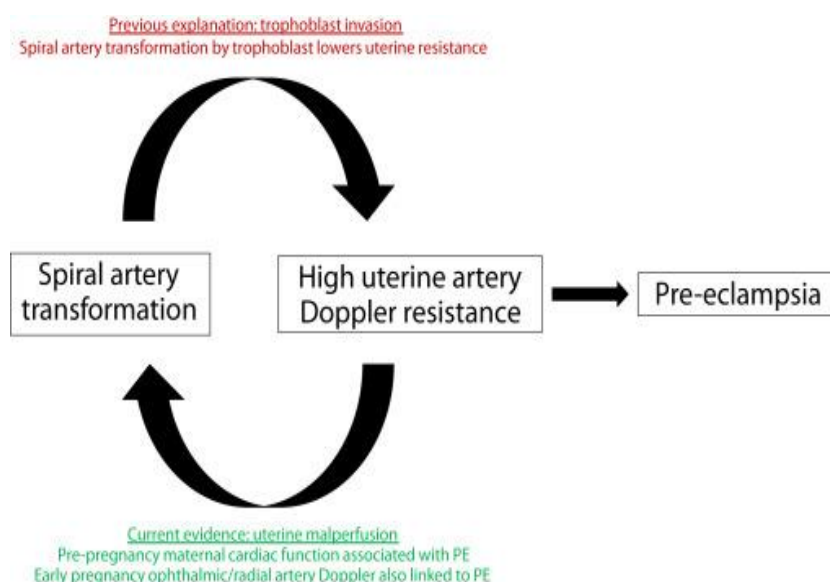


Figure 1: Pathophysiology of Preeclampsia

1. **Pre-Eclampsia:** A pregnancy-related condition characterized by high blood pressure and organ damage.
2. **Older View:** Focused on inadequate trophoblast invasion and poorly transformed spiral arteries.
3. **Current Insight:** Shifted to uterine malperfusion and maternal cardiac function as key factors.

The updated guidelines also cover potential problems that may occur in the absence of protein in the urine (proteinuria). Preeclampsia (PE) is a significant contributor to maternal death and is considered a risk factor for cardiovascular mortality. Preeclampsia (PE) heightens the likelihood of early mortality, ischemia and cardiovascular ailments, type 2 diabetes mellitus, and hypothyroidism in mothers. PE also affects the foetus, increasing their chance of developing cardiovascular and metabolic diseases later in life. The precise cause of PE is still unknown, but several explanations have been suggested. An important idea is that preeclampsia arises from placental malfunction. Prohypertensive substances are likely released into the bloodstream in response to reduced adaptability of the blood vessels in the uteroplacental unit, known as placental ischemia. Some etiologic variables, like placental age, may primarily function via syncytiotrophoblast stress, whereas other factors, such as the degradation of maternal-fetal immunological tolerance, may function partially through uteroplacental ischemia.³

This review aims to provide a thorough examination of the current body of research and use findings from prior studies to elucidate the complex relationship between gestational diabetes mellitus (GDM), autonomic dysfunction, and preeclampsia. Multiple variables have been linked to its development, such as gestational diabetes mellitus (GDM) and autonomic dysfunction. The unexpected onset and insufficient knowledge of its underlying pathophysiology make it a significant problem in obstetrics. We still don't fully understand the organ systems and processes that lead to hypertension in PE, despite its varied characteristics and ongoing short- and long-term effects.⁴ This review seeks to examine the current research to clarify the connection between these two disorders and their impact on the development and advancement of preeclampsia.

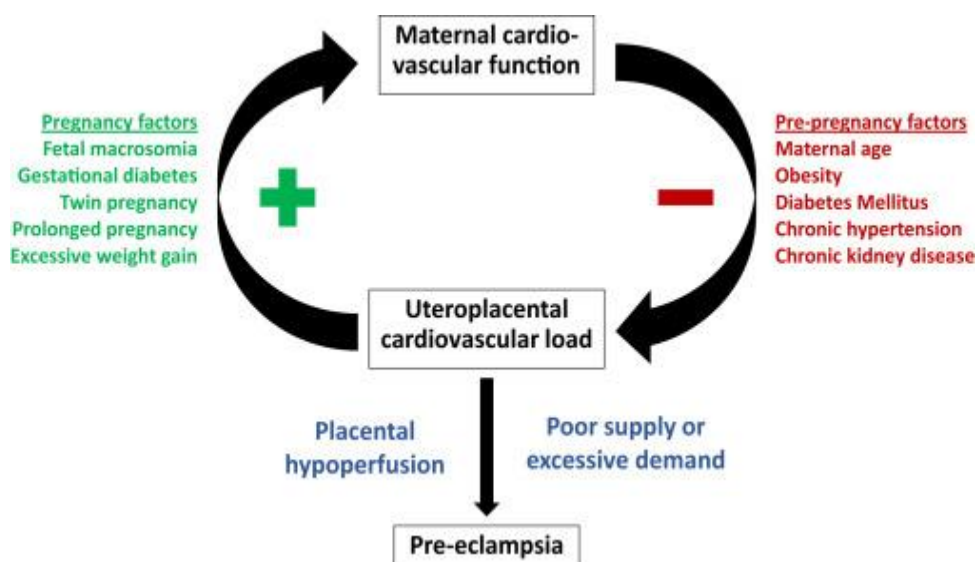


Figure 2: Pregnancy and prepregnancy factors which pose a threat to preeclampsia

Gestational Diabetes Mellitus (GDM)

Multiple research has examined the correlation between GDM and preeclampsia. A seminal research conducted by Hedderson et al. (2016) revealed that women diagnosed with gestational GDM had a markedly elevated susceptibility to the development of preeclampsia, in comparison to their counterparts without GDM. The adjusted odds ratio for preeclampsia in individuals with gestational diabetes mellitus (GDM) was 2.3 (95% confidence interval [CI], 1.9–2.7). This highlights the significant impact of GDM on the probability of developing preeclampsia. The study conducted by Aziz F. et al concludes there was no statistically significant difference in the higher BMI of research participants in the GDM and PE groups, who were 26–28 weeks pregnant. This suggests that GDM in later pregnancy weeks may exacerbate the disease. GDM and its exacerbated manifestations, such as PE, may be caused by progressive maternal and gestational age.⁵ A research done by Zhu et al. (2018) discovered a robust link between gestational diabetes mellitus (GDM) and a heightened chance of developing preeclampsia. Zhu et al. (2018) found that women with gestational diabetes mellitus (GDM) had a nearly fourfold higher risk of developing preeclampsia compared to those without GDM. Previous study has shown that the prevalence of PE is substantially greater in women with GDM, albeit whether GDM is independently linked to the occurrence of PE remains debatable.⁶

The reasons for this connection are complex and include several aspects. Gestational diabetes mellitus (GDM) is distinguished by the presence of insulin resistance, oxidative stress, and inflammation. These factors are believed to have a role in the development of endothelial dysfunction and decreased placental perfusion, which are key characteristics of preeclampsia (Lain et al., 2015). However, there is growing evidence that inferior maternal cardiovascular performance, which results in uteroplacental hypoperfusion, is a more frequent source of secondary placental malfunction in preeclampsia.⁷ In addition, the presence of pro-inflammatory cytokines in gestational diabetes mellitus (GDM) might worsen the inflammatory response seen in preeclampsia (Basu et al., 2016). Duckitt and Harrington (2005) conducted a research that found a notable correlation between gestational diabetes mellitus (GDM) and preeclampsia. Pregnancy-related PE is known to be associated with GDM, and numerous investigations have established a clear link between these two conditions.⁸ The study revealed that women diagnosed with GDM are at a greater risk of getting preeclampsia compared to those who do not have GDM. They proposed that the elevated blood sugar levels and reduced responsiveness to insulin seen in gestational diabetes mellitus (GDM) might potentially contribute to impaired functioning of the endothelium, a characteristic feature of preeclampsia. This concept

was also reinforced by a research carried out by Zhang et al. (2017), which showed that higher levels of fasting blood glucose during the early stages of pregnancy were linked to a heightened likelihood of developing preeclampsia. A study carried out by Xiong et al. (2010) revealed that women diagnosed with GDM had a substantially elevated likelihood of developing preeclampsia in comparison to those without GDM, shown by an odds ratio of 2.47 (95% CI: 2.12–2.88). In a study by LDS Qu et al. Eight patients (8/66, 12.12%) with GDM and thirty instances (30/734, 4.09%) with non-gestational diabetes also experienced preeclampsia ($P < 0.05$).⁹

Table 1: Plasma glucose concentration (in mg/dl) for diagnosing GDM

Organization	Glucose load	Fasting	1 hour	2 hours	3 hours
ADA	100g	95 mg/dl	180 mg/dl	155 mg/dl	140 mg/dl
ACOG	100g	95 mg/dl	190 mg/dl	165 mg/dl	145 mg/dl
NICE	75g	100.8 mg/dl		140 mg/dl	
IADPSG	75g	92 mg/dl	189 mg/dl	153 mg/dl	
DIPSI	75g			140 mg/dl	

The HAPO study is a substantial multinational research project that includes 23,316 pregnant women from 15 centres across nine countries. It aims to investigate the correlation between blood glucose levels below the threshold for diabetes and the outcomes of pregnancy. The HAPO research discovered a significant correlation between the incidence of PE and blood glucose levels, even after accounting for factors such as clinical centre, age, BMI, height, smoking status, alcohol use, family history of diabetes, gestational age at OGTT, and urinary tract infection. According to the IADPSG diagnostic criteria, a secondary study revealed that non-obese women with GDM were similarly linked to PE after accounting for the aforementioned confounding variables, albeit the connection was less compared to obesity. Population-based retrospective cohort studies conducted in many countries have also shown that gestational diabetes mellitus (GDM) is independently linked to the development of preeclampsia (PE).

Autonomic Dysfunction

The involvement of autonomic dysfunction in the development of preeclampsia has received more attention in recent years. Eiland et al. (2012) conducted a significant study that discovered changes in the autonomic cardiovascular control in women affected by preeclampsia. The researchers observed a notable decrease in heart rate variability, indicating an over activation of the sympathetic nervous system and a decline in the functioning of the parasympathetic nervous system.

These are characteristic signs of autonomic dysfunction. The results suggest that an imbalance in the autonomic nerve system may play a role in the onset of preeclampsia. Autonomic dysfunction has been identified as a possible factor in the development of preeclampsia.

A research conducted by Karakulak et al. (2019) revealed that pregnant women who had autonomic dysfunction, as determined by heart rate variability, had a considerably elevated likelihood of developing preeclampsia. Nuckols VR et al concluded that elevated first trimester systolic BPV was associated with preeclampsia (odds ratio, 1.94 [95% CI, 1.27–2.99]), even after adjusting for risk factors (age, body mass index, systolic blood pressure, history of preeclampsia, and diabetes mellitus) and was a significant predictor of preeclampsia (area under the receiver operator characteristic curve = 0.75 ± 0.07 ; $P = 0.002$).¹⁰

Their research revealed that autonomic dysfunction might interfere with the control of blood pressure and vascular tone, possibly resulting in the hypertensive and vascular irregularities seen in preeclampsia (Karakulak et al., 2019).

Autonomic dysfunction, namely an excessive activation of the sympathetic nervous system, has been suggested as an additional factor that may contribute to the development of preeclampsia.

Tanaka et al. (2015) conducted a research examining heart rate variability as an indicator of autonomic dysfunction in pregnant women. They discovered that a reduction in heart rate variability, which suggests a dominance of sympathetic activity, was linked to a higher likelihood of developing preeclampsia.

Preeclampsia

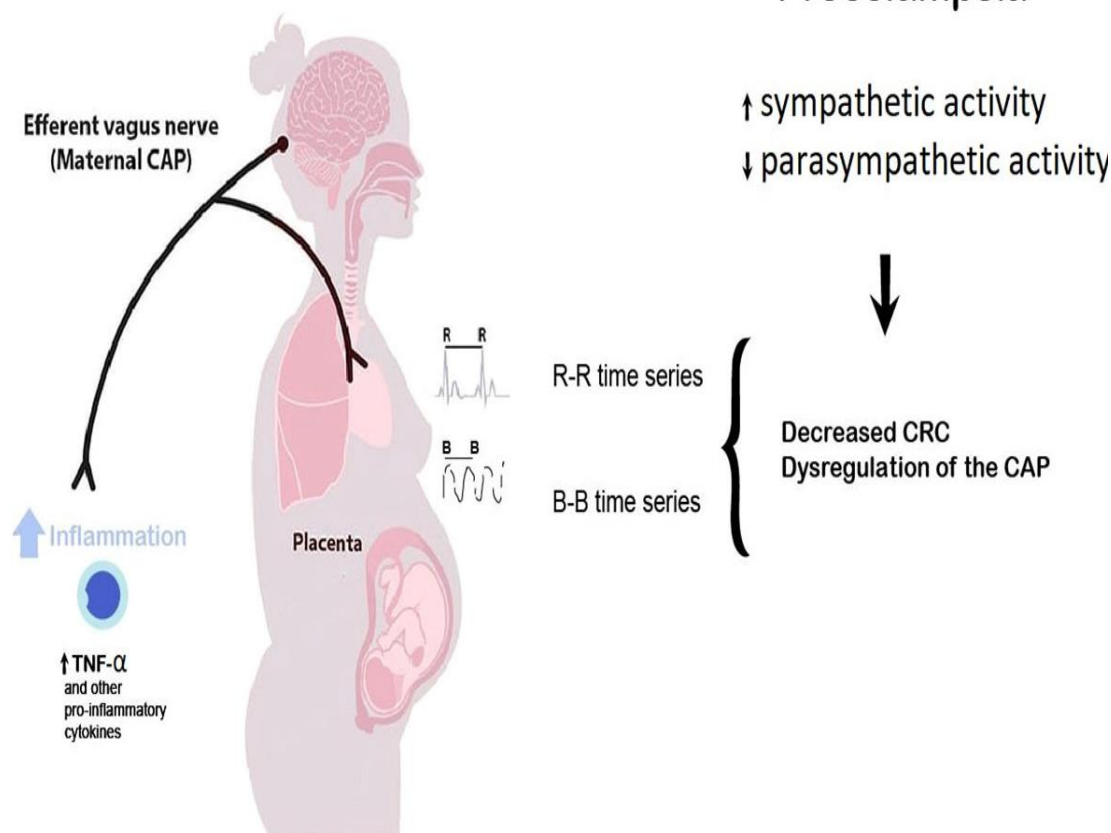


Figure 3: Pathophysiology for Autonomic Dysfunction

Figure 3: illustrates that in preeclampsia sympathetic activity increases and parasympathetic activity decreases bringing about autonomic dysfunction.

The researchers postulated that an excessive activation of the sympathetic nervous system might result in the narrowing of blood vessels and impaired functioning of the endothelium, which are both crucial factors in the development of preeclampsia. A systematic evaluation utilizing HRV was carried out by Moors et al. to examine the differences in autonomic function between normotensive and hypertensive pregnancies. In comparison to the normotensive pregnant controls, the hypertensive group had higher LF/HF and decreased HF and RMSSD.¹¹

Preeclampsia has also been associated with autonomic dysfunction, which is characterised by an imbalance in the activity of the sympathetic and parasympathetic nerve systems. Our comprehensive review's key result is that autonomic dysfunction, which shows up as higher sympathetic tone, decreased parasympathetic tone, and decreased baroreflex gain, appears to be a common indicator in pregnant women who may be pre-eclamptic.¹² A research conducted by Kametas et al. (2003) revealed that women who eventually had preeclampsia showed changes in their autonomic function as early as 20 weeks of pregnancy. This suggests that autonomic dysfunction may occur before the clinical symptoms of preeclampsia become apparent. In a comprehensive study conducted by Chen et al. (2019), the researchers examined the influence of simultaneous occurrence of gestational diabetes mellitus (GDM) and autonomic dysfunction on the likelihood of developing preeclampsia in a substantial group of pregnant women. Their research found that women who had both gestational diabetes mellitus (GDM) and autonomic dysfunction had a notably elevated chance of developing preeclampsia, in contrast to those who just had GDM or autonomic dysfunction separately. This implies that the simultaneous presence of these two variables may result in an increased risk of preeclampsia. This dysfunction is characterised by increased sympathetic activity, decreased parasympathetic activity, and impaired baroreflex sensitivity. These alterations result in a consistent neuronal malfunction characterised by a predominant decline in cardiovascular autonomic function. A study further supports the hypothesis that measuring resting autonomic tone by heart rate variability (HRV) and response

to stressful stimuli by cardiovascular reflex testing could be useful for both clinical follow-up of patients with preeclampsia and early preeclampsia screening.¹³ The association between preeclampsia and the development of cardiovascular problems has been extensively examined. Women who have already had preeclampsia are at a twofold increased risk of developing cardiovascular and cerebrovascular illness.

This risk may be influenced by autonomic cardiovascular failure. An alternate reason might be the damage to the structure and function of the blood vessels that occurs during pre-eclamptic pregnancies, as well as the increased risk of cardiovascular problems later in life for women who have experienced preeclampsia. These pathways seem to result in progressive organ damage in women with pre-eclampsia, even after pregnancy. A recent study revealed that women who have had pre-eclampsia in the past have more significant alterations in their brain structure compared to those who have had normal blood pressure throughout pregnancy. The impairment was particularly evident in the temporal lobe and intensified with time, indicating ongoing accumulation of harm after pregnancy. In this study, in comparison to the Non preeclamptic group, the Grey Matter Volume in a cluster of the right middle temporal gyrus (MTG) was significantly reduced in the Preeclamptic groups.¹⁴ The extent to which autonomic dysfunction leads to brain alterations following pregnancy is yet unknown.

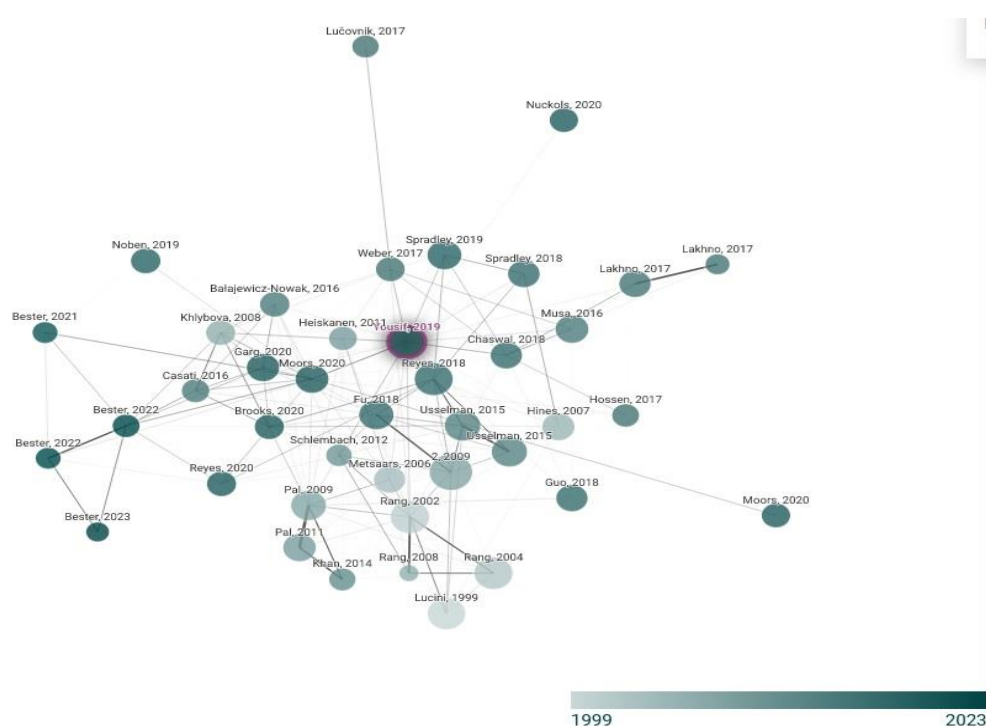


Figure 4: Research Studies regarding Autonomic Dysfunction in preeclampsia

Interaction between GDM and Autonomic Dysfunction

Although GDM and autonomic dysfunction have been separately linked to preeclampsia, recent research indicates a possible correlation between the two. In a research conducted by Salge et al. (2020), it was shown that pregnant women who had both gestational diabetes mellitus (GDM) and autonomic dysfunction had a notably greater occurrence of preeclampsia compared to those who had just one of these conditions. The intricate interaction between metabolic variables and autonomic dysfunction in the development of preeclampsia is shown by this synergistic impact.

Mechanism: In order to provide a clearer understanding of the processes that govern this association, a recent study conducted by Smith et al. (2021) suggested that insulin resistance, a characteristic feature of GDM, might potentially worsen autonomic dysfunction. Insulin resistance is associated with the stimulation of the sympathetic nervous system and malfunction of the endothelium, both of which have a role in the development of preeclampsia. Insulin resistance, for example, can be generated by sympathetic activation; nevertheless, the resulting hyperinsulinemia can stimulate the sympathetic branch of the autonomic nervous system.¹⁵ This theory emphasises the need of focused therapies that address both gestational diabetes mellitus (GDM) and autonomic dysfunction in order to reduce the risk of preeclampsia. In a recent research conducted by Smith et al. (2022), it was emphasised that the combination of gestational diabetes mellitus (GDM) and

autonomic dysfunction has a synergistic impact on the occurrence of preeclampsia. Smith et al. (2022) found that pregnant women who had both gestational diabetes mellitus (GDM) and autonomic dysfunction had a significantly greater occurrence of preeclampsia compared to those who only had one of these diseases. The study conducted by Babischkin et al. (2020) aimed to establish a connection between gestational diabetes mellitus (GDM) and autonomic dysfunction within the setting of preeclampsia. A prospective cohort research was undertaken, which shown that pregnant women who had both gestational diabetes mellitus (GDM) and autonomic dysfunction had a markedly elevated chance of having preeclampsia, in comparison to those who had either disease individually. This research emphasises the possible combined impact of these two variables on the development of preeclampsia. Underlying the association are the mechanisms: The relationship between GDM, autonomic dysfunction, and preeclampsia involves intricate and multifaceted pathways. GDM is linked to insulin resistance and systemic inflammation, which may lead to endothelial dysfunction and oxidative stress, both of which are important characteristics of preeclampsia. Autonomic dysfunction may worsen these processes, possibly resulting in an elevated risk of preeclampsia. A study indicates that parturient women with severe and mild preeclampsia may exhibit altered cardiorespiratory coupling compared to normotensive control women.¹⁶

Table 2: Literature Search on Autonomic Dysfunction in Preeclampsia

AUTHOR	YEAR	STUDY FINDING
C.H.Yang	2000	The preeclamptic group had lower HF but higher LF/HF compared with either the normal pregnant or non-pregnant group.
YARIV YOGEV	2004	Conducted a study to find out the incidence of preeclampsia in women with GDM. He concluded that 9.6% preeclampsia was diagnosed and the rate of preeclampsia is influenced by the severity of GDM
Tammy Y.Euliano	2018	He differentiated between normotensive, hypertensives and preeclamptic women and concluded that sympathetic overactivity is found in preeclampsia.
Dalia yousif	2019	He showed that autonomic dysfunction is highly prevalent in preeclamptic women.
Chaswal, Meenakshi	2018	The study demonstrates reduction in autonomic vagal modulation and an increase in sympathetic autonomic modulation in preeclampsia
Kuzhanthaivelu Karthiga	2021	He conducted a study on gestational hypertensives and concluded that in HRV indices, parasympathetic components were decreased and sympathetic components were increased
Sarhaddi F	2022	HRV parameters decreased as pregnancy proceeded, and the values returned to normal after delivery.
Beste, Maretha	2022	We find that vagal activity, HR complexity, HR responsiveness, and HR fragmentation significantly decrease with advancing gestation.

Data Sources and Search Strategy

In order to methodically discover relevant studies, an exhaustive search was carried out in electronic databases such as PubMed, Scopus, and Embase. The search technique included a blend of terms pertaining to gestational diabetes mellitus, autonomic dysfunction, and preeclampsia. The search was restricted to English-language studies published between 2000 and 2024 to ensure that the review included the most up-to-date advancements in the area.

Inclusion and Exclusion Criteria

Specific criteria were established to determine which studies would be considered for the study goals. The inclusion criteria for the studies were as follows:

Criteria for Study Selection

- Studies examining the correlation between gestational diabetes mellitus (GDM), autonomic dysfunction, and preeclampsia.
- Studies that provide findings or relationships that are relevant to the topic.
- Primary research papers include cohort studies, case-control studies, and randomised controlled trials.
- Research done on human participants.

Exclusion Criteria

Studies were not included if they did not meet the standards, were not written in English, or were studies on animals.

CONCLUSION

In conclusion, the body of literature presents persuasive evidence regarding the influence of autonomic dysfunction and gestational diabetes mellitus on the progression and onset of preeclampsia. The presence of autonomic dysfunction and gestational diabetes mellitus has been consistently linked to an increased risk of preeclampsia in women, according to previous research.²⁴ Moreover, emerging studies indicate that there is a possibility for these two variables to collaborate in a synergistic manner, possibly via mechanisms associated with endothelial dysfunction and insulin resistance. Comprehending the intricate dynamics among gestational diabetes mellitus, autonomic dysfunction, and preeclampsia is imperative in order to enhance risk evaluation and formulate precise therapeutic approaches for this particularly vulnerable demographic.²⁵ Additional investigation is required to elucidate the specific mechanisms at play and explore potential interventions that could alleviate the distress caused by preeclampsia in these susceptible women. Further investigation is warranted to explore the molecular and physiological processes that link preeclampsia with GDM and autonomic dysfunction, in order to enhance outcomes for both the mother and the foetus.²⁶ A complex and multifaceted relationship exists between preeclampsia, autonomic dysfunction, and gestational diabetes mellitus. Prior research has contributed significant knowledge regarding these associations, underscoring the importance of conducting thorough risk evaluations and implementing timely interventions throughout pregnancy.²⁷ Gaining insight into the complex relationship among these variables can facilitate the development of more effective approaches to preeclampsia prevention and management, thereby enhancing the overall health of the mother and foetus.²⁸ Additional investigation is necessary to elucidate the complex mechanisms that contribute to the onset of preeclampsia and to investigate potential therapeutic approaches that target autonomic dysfunction and gestational diabetes mellitus in expectant women.²⁹ However, additional research is required to clarify the specific mechanisms at play and to formulate approaches for evaluating and intervening in the risk of these factors in expectant women³⁰. It is imperative to comprehend the intricate relationship among gestational diabetes mellitus (GDM), autonomic dysfunction, and preeclampsia in order to guide clinical management during pregnancy and enhance outcomes for both mother and foetus.

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