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Study on the Association of Mitochondrial DNA Copy Number with Early-Onset and Late-Onset Preeclampsia

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Abstract
Background: *Preeclampsia (PE) remains a significant cause of maternal and perinatal morbidity and mortality worldwide. There is emerging evidence on mitochondrial dysfunction in the pathophysiology of PE, but the association of mitochondrial DNA copy number (mtDNA-CN) with PE subtypes is unclear. This study analyzed the association of mtDNA-CN with early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE).*
Methods: *51 preeclampsia cases (EOPE and LOPE) and 51 normotensive controls were recruited in this case-control study. Peripheral blood samples were collected, and mtDNA-CN was measured by quantitative PCR based on the ratio of mitochondrial-encoded NADH dehydrogenase-1 (ND-1) to the nuclear gene hemoglobin subunit β (HGB). Statistical analysis included chi-square tests, unpaired t-tests, ANOVA, and ROC curve analysis for determining optimal mtDNA-CN cutoff values for preeclampsia risk prediction.*
Results: *There were noticeable differences in mtDNA-CN in the three groups (p=0.001) with the highest values seen in EOPE cases (97.42±15.30), followed by LOPE (63.40±16.07), and normotensive controls (44.67±3.56). The optimum mtDNA-CN cut-off level was >45, with 68.6% sensitivity and 58.8% specificity. Participants with mtDNA-CN >45 had approximately three times higher odds of developing preeclampsia (OR 3.1, 95% CI 1.4-7.0, p=0.005). Overall diagnostic accuracy was 63.7% (95% CI 53.6%-73.0%).*
Conclusion: *The gradient effect of mtDNA-CN between EOPE, LOPE, and controls is in favor of the hypothesis that these disorders are distinct pathophysiological processes. Elevated mtDNA-CN may reflect mitochondrial dysfunction secondary to placental hypoxia and oxidative stress, particularly in EOPE. While mtDNA-CN is of moderate value as a single biomarker, it may be of value when included in a multi-marker panel in risk stratification and classification of preeclampsia.*
Keywords: *Mitochondrial DNA, Preeclampsia, ND-1, HGB, q-PCR.*

I. Introduction

Preeclampsia (PE) continues to be a major cause of maternal and perinatal morbidity and mortality globally, occurring in 2-8% of pregnancies worldwide [1]. It is pregnancy-induced hypertension defined by the presence of recently acquired hypertension (≥140/90 mmHg) post-20 weeks of gestation, along with proteinuria or clinical evidence of maternal organ dysfunction [2]. Notably, PE is not a uniform disorder but does present with characteristic clinical phenotypes, most particularly when distinguished based on gestational age of onset. Early-onset preeclampsia (EOPE) as before 34 weeks gestation, and late-onset preeclampsia (LOPE), which appears at or later than 34 weeks, are two different disease entities with potentially distinct pathophysiologic pathways [3]. EOPE is commonly associated with placental development impairment, intrauterine growth restriction, and greater maternal complications, whereas LOPE typically presents with less severe maternal symptoms and normal fetal growth [4]. Although there has been intense investigation, the precise etiology and pathogenesis of these subtypes of PE are not well clarified, hampering the advancement of effective prophylactic strategies and targeted therapeutic interventions. Recent studies indicate that mitochondrial dysfunction may play a central role in PE pathophysiology [5]. Mitochondria are crucial organelles that are involved in cellular energy metabolism, regulation of calcium homeostasis, and oxidative stress control. Each cell contains multiple mitochondria, and each mitochondrion contains its own circular DNA (mtDNA), which encodes proteins necessary for oxidative phosphorylation. Mitochondrial DNA copy number (mtDNA-CN) is a mitochondrial content and function marker, and alterations could be reflective of cellular stress and bioenergetic requirements [6]. Numerous studies have

documented alterations in mtDNA-CN during pregnancy pathology, including PE [7, 8]. However, results were inconsistent, with some identifying higher mtDNA-CN in PE placentas [9] and others indicating decreased levels [10]. Contributing to some of these discrepancies is viewing PE as a uniform condition without differentiating between EOPE and LOPE, both of which will probably present various mitochondrial patterns consistent with their distinct pathophysiological mechanisms. There is new evidence favoring the role of mitochondrial dysfunction in PE pathogenesis through various mechanisms. Placental ischemia and hypoxia, signature characteristics of PE pathophysiology, lead to enhanced oxidative stress and mitochondrial damage [11]. Dysfunctional mitochondria can discharge mitochondrial DNA into the maternal circulation, which may function as damage-associated molecular patterns (DAMPs) to initiate systemic inflammation and endothelial dysfunction characteristic of PE [12]. Besides, pathological mitochondrial biogenesis and function could also be responsible for trophoblast cell apoptosis and abnormal placentation in PE, particularly EOPE [13]. Our study aims to investigate the association between mtDNA-CN and PE subtypes, particularly comparing EOPE and LOPE. Through the examination of mtDNA-CN in maternal blood EOPE, LOPE, and normal pregnancies (healthy control), we aim to identify potential variations in mitochondrial profiles that may reflect variations in pathophysiological mechanisms. Having an understanding of these variations may provide important information on the etiology of PE subtypes and could lead to better diagnostic strategies, risk assessment, and targeted therapeutic strategies.

II. Methods

This is a case-control study where we investigated the association of mitochondrial DNA copy number (mtDNA-CN) with preeclampsia at Bangabandhu Sheikh Mujib Medical University for one year. 51 cases of early onset and late onset Preeclampsia and 51 normotensive controls were enrolled by purposive sampling from Feto-Maternal Medicine and Obstetrics and Gynecology units. Inclusion criteria for cases were blood pressure ≥140/90 mmHg, proteinuria or organ involvement, and gestational age 20-40 weeks, whereas controls were blood pressure <140/90 mmHg without proteinuria. Pregnant women with multiple gestations, chronic hypertension, renal disease, diabetes, autoimmune diseases, or other complications were excluded from the study. Socio-demographic data, obstetric history, and physical examination findings were recorded after obtaining IRB approval by a structured data collection sheet. Three milliliters of peripheral blood were collected from all the study participants and left on ice at -20°C. Leukocytes were used to prepare genomic DNA, while mtDNA-CN was measured by quantitative PCR based on the proportion of mitochondrial-encoded NADH dehydrogenase-1 (ND-1) concerning nuclear gene hemoglobin subunit β (HGB). SYBR Green PCR Master Mix was used with duplicate sample assays, while the scholars were blinded to clinical data. Statistics were analyzed using SPSS version 26, comparing categorical data with chi-square tests and continuous data by unpaired t-tests. Optimal mtDNA-CN cutoff values for preeclampsia risk were calculated using ROC curves, odds ratios, and 95% confidence intervals were computed, and $p<0.05$ was considered statistically significant.

III. Results

Table 1: Socio-demographic the participants (n=102)

Characteristics	**Case N (%)**	**Control N (%)**	**p-value**
Age (years)			
≤20	3 (5.9%)	5 (9.8%)	0.744[a]
21-30	25 (49%)	25 (49%)	
>30	23 (45.1%)	31 (41%)	
Mean±SD	30.0±4.3	28.5±4.8	
Educational Qualification			
Illiterate	4 (7.8%)	3 (5.9%)	0.063[a]
Primary	6 (11.8%)	8 (15.7%)	
SSC	6 (11.8%)	17 (33.3%)	
HSC	35 (68.6%)	23 (45.1%)	
Monthly family income (BDT)			
<10,000	2 (3.9%)	3 (5.9%)	0.281[a]
10,000-25,000	17 (33.3%)	24 (47.1)	
>25,000	32 (67.7%)	24 (47.1%)	
Total	**51 (100%)**	**51 (100%)**	

[a]p-value obtained from chi-square test

Table 1 depicts a comprehensive socio-demographic breakdown of early-onset and late-onset Preeclampsia cases (n=51) and normotensive controls (n=51). The distribution of age is such that the largest proportion of participants in each group with 25 respondents (49%) fell within the 21-30 years category. The case group was 1.5 years older in mean age, i.e., 30.0±4.3 years, compared with the control group whose mean age

was 28.5±4.8 years. In exploring age groups, 9.8% of the controls and 5.9% of the cases were ≤20 years of age, while 41.2% of the controls and 45.1% of the cases were >30 years of age. According to educational level, a difference between groups did not exist that reached the level of statistical significance (p=0.063). There was a higher percentage of HSC in the case group at 68.6% compared to 45.1% for the control group. More control group patients had lower education levels with 33.3% having SSC compared to the case group where 11.8% of the patients were SSC. The proportion of cases (11.8%) and controls (15.7%) with primary education was equal, and the illiteracy rates were equal at 7.8% in cases and 5.9% in controls. Monthly family income distribution revealed that the majority of the cases (67.7%) had more than 25,000 BDT income, whereas 47.1% of the controls fell in this category. More controls (47.1%) had incomes between 10,000 and 25,000 BDT compared to the cases (33.3%). Low-income subjects (<10,000 BDT) accounted for 3.9% of the cases and 5.9% of the controls. Though the income distribution was not the same between the groups, there was no statistically significant difference based on the chi-square test (p=0.281).

Table 2: Obstetrics characteristics of the participants (n=102)

Characteristics	**Case** N (%)	**Control** N (%)	**p-value**
Gravida			
Primigravida	14 (27.5%)	16 (31.4%)	0.664[a]
Multigravida	37 (72.5%)	35 (68.6%)	
Gestational age (weeks)			
20-25	0 (0%)	1 (2%)	0.333[a]
26-30	4 (7.8%)	9 (17.6%)	
31-36	37 (72.5%)	32 (62.7%)	
>36	10 (19.6%)	9 (17.6%)	
Total	**51 (100%)**	**51 (100%)**	

[a]p-value obtained from chi-square test

Table 2 provides comprehensive details about obstetric features among the study cases. Gravidity distribution demonstrates that 72.5% of cases and 68.6% of controls were multigravida, while 27.5% of cases and 31.4% of controls were primigravida. A chi-square test did not observe any statistical variability in gravidity between groups (p=0.664). The gestational age distribution indicates that the largest proportion of both the case (72.5%) and control (62.7%) groups were between 31-36 weeks of gestation. In cases, 19.6% had gestational age >36 weeks compared to 17.6% of controls. Less common were the early gestational ages with 7.8% of cases and 17.6% of controls between 26-30 weeks. Precisely, none of the cases were 20-25 weeks pregnant, whereas 2.0% of the controls were so. Despite these differences, the chi-square test did not reveal a statistically significant difference in gestational age distribution between the groups (p=0.333).

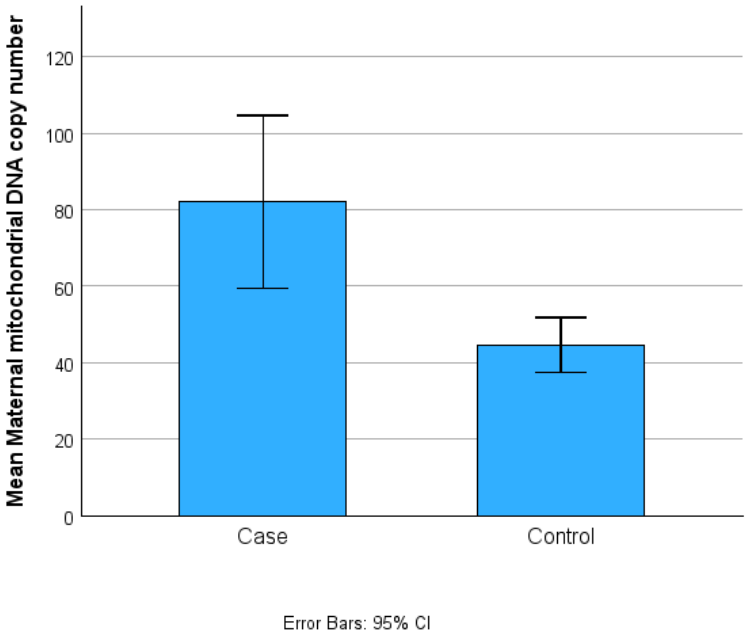

Figure 1: Mean mitochondrial DNA copy number among the participants

Figure 1 demonstrates a graphical illustration of the range of mitochondrial DNA copy number (mtDNA-CN) across the study participants. As indicated in the bar chart, the high range of mtDNA-CN is observed in distinguishing the preeclampsia patients from normotensive controls. The y-axis is employed to describe the mtDNA-CN, while the x-axis divides the study groups. The figure shows a sudden spike in mtDNA-CN in early-onset and late-onset Preeclampsia cases compared to controls. The graphic depiction emphasizes how immense the difference is, with the bar for cases sitting very far above that for controls. Error bars indicate the standard error of the mean, providing a measure of variation within each group. The higher level of the case bar above the control bar visually confirms the statistically significant group difference, suggesting a potential role of mitochondrial dysfunction in preeclampsia pathophysiology.

Table 3: Comparison of Mitochondrial DNA copy number between onset of PE and control

Early onset Mean ± SE	**Late-onset Mean ± SE**	**Control Mean ± SE**	**P value**
97.42±15.30	63.40±16.07	44.67±3.56	0.001[c]

[c]p-value obtained from ANOVA F-test

Table 3 presents a thorough three-way comparison of mtDNA-CN between early-onset preeclampsia, late-onset preeclampsia, and normotensive controls. The data are presented as mean ± standard error (SE) per group to facilitate proper evaluation of differences among these clinically distinct entities. The results indicate a clear gradient trend of mtDNA-CN in the three groups. The highest mtDNA-CN (97.42±15.30) was observed in the early-onset preeclampsia patients, which was significantly higher compared to late-onset preeclampsia (63.40±16.07) and controls (44.67±3.56). The observation that late-onset preeclampsia cases are intermediate between early-onset cases and controls suggests an apparent dose-response relationship between mtDNA-CN and the severity of preeclampsia. Statistical comparison with the ANOVA F-test established that such differences were strongly significant (p=0.001), suggesting that the gradient in mtDNA-CN observed between the three groups was very unlikely due to chance.

Table 4: Sensitivity and specificity of maternal mitochondrial DNA copy number in different cut-off values

Cut-off value	**Sensitivity**	**Specificity**	**Youden Index (Sensitivity+Specificity-1)**
>20	0.96	0.14	0.10
>25	0.94	0.24	0.18
>30	0.92	0.31	0.24
>35	0.84	0.39	0.24
>40	0.77	0.49	0.26
>45	**0.69**	**0.61**	**0.29**
>50	0.59	0.65	0.24
>55	0.45	0.80	0.26
>60	0.37	0.82	0.20
>65	0.33	0.86	0.20
>70	0.33	0.90	0.24

Table 4 provides the information compulsory to pick the best cut-off for clinical application by comparing the diagnostic performance characteristics of mtDNA-CN at multiple possible threshold values. For each potential cut-off, the table provides the resultant sensitivity (ratio of true preeclampsia cases correctly classified), specificity (ratio of true non-preeclampsia cases correctly classified), and Youden Index (sensitivity + specificity - 1), which is an index of the overall discriminatory ability at that cut-off. There is an increasing trade-off between sensitivity and specificity as the cut-off increases. For lower thresholds (e.g., >20), sensitivity is extremely high (0.96) but so is the false-positive rate (0.14), so virtually all instances of preeclampsia would be detected but with an overwhelming number of false positives. Increasing the threshold reduces sensitivity but increases specificity. With the Youden Index, which considers these two opposing factors, an optimal cut-off value of >45 was determined with sensitivity of 0.69 and specificity of 0.61, with the highest Youden Index of 0.29.

Table 5: Association between maternal mitochondrial DNA copy number and preeclampsia (n=102)

Mitochondrial DNA copy number	**Case N (%)**	**Control N (%)**	**P-value**	**OR (95% CI)**
>45	35 (68.6%)	21 (41.2%)	0.005[a]	3.1 (1.4-7.0)
≤45	16 (31.4%)	30 (58.8%)		
Total	**51 (100%)**	**51 (100%)**		

- [a]p-value obtained from chi-square test

Table 5 assigns a quantitative value to the strength of the relationship between raised mtDNA-CN and preeclampsia with the generally accepted optimum cut-off value of >45. The values illustrate that more than two-thirds of women with preeclampsia (68.6%) had values above this cut-point, compared to only 41.2% of controls. The proportion difference was statistically significant (p=0.005), providing conclusive proof of association. The odds ratio (OR) of 3.1, with a 95% confidence interval of 1.4-7.0, offers a quantitation of this association, and from it, one can observe that women with mtDNA-CN >45 had approximately three times higher odds of getting preeclampsia than with less than these values.

Table 6: Diagnostic accuracy of serum mtDNA-CN level to identify preeclampsia

Statistics	Value	95% CI
Sensitivity	35/51=68.6%	54.1% to 80.9%
Specificity	30/51=58.8%	44.2% to 72.4%
PPV	35/56=62.5%	53.3% to 70.8%
NPV	30/46=65.2%	54.1% to 74.9%
Accuracy	(35+30)/102=63.7%	53.6 to 73.0%

Table 6 represents an overall appraisal of the diagnostic precision of mtDNA-CN with a cut-off of >45 as established. This 68.6% sensitivity (95% CI 54.1%-80.9%) implies that this cut-off would recognize roughly two for every three preeclampsia women but miss roughly a third (false negatives). With the specificity being 58.8% (95% CI 44.2%-72.4%), this would imply that roughly 60% of non-preeclampsia women would correctly be diagnosed negative and roughly 40% of them would mistakenly be reported positive. The positive predictive value (PPV) of 62.5% (95% CI 53.3%-70.8%) is that 63% of women with mtDNA-CN >45 would have preeclampsia. The negative predictive value (NPV) of 65.2% (95% CI 54.1%-74.9%) is that among women with mtDNA-CN ≤45, 65% would not have preeclampsia. The overall accuracy of 63.7% (95% CI 53.6%-73.0%) is the proportion of all women (both with and without preeclampsia) who would be correctly classified by using this threshold.

IV. Discussion

This case-control study examined the association between mitochondrial DNA copy number (mtDNA-CN) and preeclampsia (PE), with special focus on distinguishing between early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE). Our results showed significantly increased mtDNA-CN levels in PE cases versus normotensive controls, with EOPE having higher values than LOPE. This confirms the hypothesis that mitochondrial dysfunction is involved in PE pathophysiology [25]. The gradient pattern observed between the three groups (EOPE > LOPE > controls) suggests that alterations in mtDNA-CN could be indicative of disease severity and could be reflective of various mechanisms of pathophysiology. EOPE is usually defined by impaired placentation, increased oxidative stress, and increased maternal complications [26]. This knowledge is evident in our finding, where EOPE cases had the highest mtDNA-CN values. This increase in mtDNA-CN may be a protective response against placental hypoxia and oxidative stress, which are well-documented to stimulate mitochondrial biogenesis through activated mitochondrial replication [27]. Oxidative stress in PE has been convincingly demonstrated, particularly in early-onset disease [28]. Under conditions of hypoxia characteristic of PE, mitochondria can over-numeric in response, producing the elevated mtDNA-CN observed in our study. These findings agree with previous study by Marschalek et al. [29], who demonstrated increased levels of maternal serum mtDNA in PE. However, our results contradict those of Lattuada et al. [30], who demonstrated decreased content of mtDNA in intrauterine growth restriction placentas. The discrepancy may be due to differences in tissue samples analyzed (maternal blood vs. placental tissue) and technical variations. Clinical utility of mtDNA-CN as a biomarker was established through ROC curve analysis, which demonstrated an optimal cut-off value of >45 with moderate sensitivity (68.6%) and specificity (58.8%). While these values indicate low diagnostic accuracy as a stand-alone biomarker, they suggest that mtDNA-CN would be valuable in a multi-marker panel for PE risk stratification. The odds ratio of 3.1 (95% CI: 1.4-7.0) indicates that individuals with mtDNA-CN >45 have approximately three times higher odds of having PE, indicating its prognostic value. Socio-demographic comparison detected no difference between cases and controls for age, education, and income, diminishing the risk of confounding effects. Similarly, obstetric characteristics like gravidity and gestational age were comparable in both groups, contributing to the reliability of our findings. Mitochondrial impairment in PE can lead to systemic inflammation and endothelial dysfunction through various mechanisms [31]. Defective mitochondria can release mtDNA into maternal circulation, where it acts as damage-associated molecular patterns (DAMPs), eliciting inflammatory processes [32]. Mitochondrial impairment also leads to increased generation of reactive oxygen species, augmenting oxidative stress and endothelial damage characteristic of PE [33]. The distinctive mtDNA-CN profiles observed between EOPE and LOPE support the notion that these are different entities with divergent pathophysiological mechanisms. EOPE is predominantly associated with placental insufficiency, while LOPE is more frequently associated with maternal constitutional factors and underlying conditions [34]. The gradient of

mtDNA-CN values across these populations provides molecular evidence for this clinical distinction. Our results disclose the potential contribution of mitochondrial impairment to PE pathogenesis and highlight mtDNA-CN as a putative biomarker for disease stratification. However, longitudinal studies will be required to ascertain whether changes of mtDNA-CN are pre-PE or a consequence of the disease process.

Limitations of the Study

The study is restricted by its fairly small sample size, which may affect the ability to generalize the findings. Cross-sectional design also does not enable causality of mtDNA-CN alterations and the development of preeclampsia to be determined. Additional studies with larger prospective cohorts need to be performed to validate these results.

V. Conclusion

Our study demonstrates a high correlation between elevated mitochondrial DNA copy number and preeclampsia with a distinct pattern of gradient variation among early-onset preeclampsia, late-onset preeclampsia, and normotensive controls. The findings provide molecular evidence for preeclampsia subtypes as distinct pathophysiologic disorders. Although mtDNA-CN offers moderate diagnostic validity as an isolated biomarker, it holds the potential for inclusion in multi-marker panels to screen for preeclampsia risk. Further longitudinal studies are required to establish the temporal relationship of mtDNA-CN alterations with the onset of preeclampsia and to explore the potential for therapeutic intervention aimed at mitochondrial function.

VI. Recommendation

Longitudinal pregnancy studies of mtDNA-CN changes would be required to determine its utility as an early-onset preeclampsia predictive biomarker and to develop targeted interventions to improve mitochondrial function.

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