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Maternal Plasma Homocysteine Levels & Pregnancy Outcome

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Abstract:-

- ***Background:***

Elevated homocysteine levels have been implicated in various adverse pregnancy outcomes, but its association with high-risk pregnancies remains inadequately explored. This study examines the relationship between maternal plasma homocysteine levels and socio-demographic, lifestyle characteristics in high-risk versus control pregnancy groups.

- ***Methods:***

A comparative cohort study design was utilized, involving 108 participants divided into a control group (n=44) with normal pregnancies and a study group (n=64) identified as high-risk. The study assessed maternal plasma homocysteine levels using a chemiluminescent method and evaluated socio-demographic and lifestyle characteristics through comprehensive history intake and examinations. Statistical analyses compared homocysteine levels between groups and within specific conditions in the high-risk group.

- ***Results:***

The study group demonstrated a higher mean age and significant percentages of unbooked pregnancies, illiteracy, unemployment, and rural residency compared to the control group. Notably, approximately two-thirds of the high-risk group had a diet deficient in essential nutrients. Homocysteine levels were significantly elevated in the high-risk group (mean 12.82 ± 2.46 µmol/L) compared to the control group (mean 6.4 ± 1.16 µmol/L, $P < 0.05$). Within the high-risk group, specific conditions such as previous abortions, preterm pain, and antepartum hemorrhage were associated with distinct homocysteine level patterns, suggesting varying degrees of risk across different pregnancy complications.

- ***Conclusion:***

Elevated homocysteine levels are significantly associated with high-risk pregnancies and specific adverse outcomes. The findings highlight the importance of addressing socio-demographic and lifestyle factors alongside biochemical markers in the management and intervention strategies for high-risk pregnancies. Tailored nutritional and lifestyle interventions targeting homocysteine levels could potentially mitigate these risks.

Keywords:- *Homocysteine, High-Risk Pregnancy, Socio-Demographic Characteristics, Lifestyle, Pregnancy Outcomes.*

I. INTRODUCTION

Homocysteine, a non-proteinogenic amino acid emerging from methionine metabolism—an essential amino acid sourced from our diet—plays a critical role in bodily functions. It can either be reconverted into methionine through the remethylation pathway, necessitating folate, vitamin B12, and methionine synthase, or broken down into cysteine via the transsulfuration pathway, which depends on vitamin B6 and cystathionine beta-synthase[1]. The equilibrium of these pathways dictates plasma homocysteine levels, influenced by a matrix of genetic, nutritional, and environmental factors. Elevated levels, known as hyperhomocysteinemia, are linked to adverse health outcomes including cardiovascular diseases, thrombosis, and neural tube defects[2].

Pregnancy induces changes in homocysteine metabolism, driven by increased demands for folate and vitamin B12, hormonal shifts, and placental function, typically leading to reduced plasma homocysteine levels. This reduction is attributed to the enhanced uptake of folate by the placenta and fetus, increased renal clearance, and hormonal adjustments[3]. Nonetheless, certain pregnancies result in homocysteine levels that remain stable or rise because of placental malfunction, genetic abnormalities in the homocysteine metabolism enzymes, or deficiencies in folate, vitamin B12, or vitamin B6. Numerous pregnancy problems, such as recurrent pregnancy loss, preeclampsia, placental abruption, fetal growth limitation, gestational diabetes, and congenital abnormalities, have been linked to such hyperhomocysteinemia.

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Preeclampsia, placental abruption, intrauterine growth restriction (IUGR), and pregnancy loss are examples of placenta-mediated pregnancy complications (PMCs) that may be exacerbated by elevated homocysteine levels, according to a relationship between maternal plasma homocysteine concentrations and specific pregnancy complications. These disorders carry a higher risk of recurrence due to their similar placental pathophysiology and aberrant placental vasculature[4].

As a component of the one-carbon metabolic cycle, homocysteine aids in the transmethylation of methionine in the methionine cycle. Methionine is then converted into S-adenosylmethionine, the main methyl donor in cells[5]. Different homocysteine levels result from this cycle, which depends on co-enzymes and co-factors such as vitamins B9 (folate), B6, and B12 and is impacted by gene polymorphisms and lifestyle factors[6].

Research has shown that there is an inconsistent relationship between placenta-mediated complications and maternal homocysteine levels at different stages of pregnancy. This may be because of moderating factors such as high-risk pregnancy statuses and the presence of the MTHFR 677C>T polymorphism, which moderately elevates homocysteine levels[7]. Clinical trials on folic acid supplementation have shown mixed results in reducing the risk of vascular conditions due to decreased homocysteine levels. Nutritional determinants, such as folate intake and serum folate levels, along with genetic, health, and lifestyle factors, play significant roles in homocysteine concentration[8].

In order to shed light on the complex dynamics of homocysteine metabolism throughout pregnancy and its possible effects on mother and fetal health, this study intends to investigate homocysteine levels in normal and high-risk pregnancies as well as its association with pregnancy problems and outcomes.

II. RESEARCH METHODOLOGY

A. Study Design

This research employed a comparative cohort study design to evaluate the relationship between maternal plasma homocysteine levels and pregnancy outcomes. The study differentiated between normal and high-risk pregnancies, assessing the impact of elevated homocysteine levels across various conditions within these groups.

B. Distribution of Participants

➢ *The Distribution of Participants was as Follows:*

- Control Group (Normal Pregnancy): 44 cases (40.74%)
- Study Group (High Risk Pregnancy): 64 cases (59.36%)

➢ *Distribution Within The High Risk Group:*

- First Trimester Complications: 43 cases (67.19%)
- Third Trimester Complications: 21 cases (32.81%)

The breakdown of specific conditions within the high-risk group was detailed, highlighting the prevalence of issues like previous abortions, preterm pain, and pre-eclampsia, among others.

C. Participants

The study population was divided into two main groups based on their pregnancy risk profiles:

- Control Group (Normal Pregnancy): Comprising 44 participants, accounting for 40.74% of the total sample.
- Study Group (High Risk Pregnancy): Consisting of 64 participants, making up 59.36% of the sample.

➢ *Within the Study Group, Participants were Further Categorized based on Specific Conditions:*

- First Trimester Issues: 43 cases (67.19%)
- Previous Pregnancy Complications: Including prior abortions or Intrauterine Device (IUD) complications (64.06%), preterm delivery/stillbirth (3.2%), and congenital anomalies.
- Third Trimester Complications: 21 cases (32.81%), with specific issues such as preterm pain, antepartum hemorrhage, pre-eclampsia, diabetes, and history of eclampsia.

➢ *Measurement of Homocysteine Level:*

- A 5 ml venous blood sample was collected from each participant.
- After being collected, samples were delivered to the lab in less than 30 minutes.
- Homocysteine levels were detected using a chemiluminescent method with an automatic immunoanalyzer (IMMULITE).

D. Outcome Measures

The primary outcome measure was the level of homocysteine in maternal plasma and its association with pregnancy outcomes across different risk categories.

E. Data Collection

- A comprehensive history intake, including folic acid, pyridoxine, and methylcobalamin supplementation, general, systemic, and obstetrical examination was conducted.
- For participants with a history of abortion, congenital anomaly, or intrauterine fetal demise, homocysteine levels were measured in the first trimester.
- Participants presenting with preterm pain, a history of preeclampsia, eclampsia, or antepartum hemorrhage had their homocysteine levels estimated in the third trimester.

F. Data Analysis

Statistical analysis was conducted to compare homocysteine levels between the control and study groups, and among different subcategories within the high-risk group. The significance of differences was determined using

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appropriate statistical tests, with a 'p' value of <0.05 considered significant.

III. RESULTS

The study presented in the tables above provides a comprehensive analysis of socio-demographic, lifestyle characteristics, and homocysteine levels in control versus high-risk pregnancy groups. Overall, the results from these analyses not only reveal the multifaceted nature of high-risk pregnancies but also emphasize the importance of comprehensive socio-demographic, lifestyle, and biochemical evaluations in the management and intervention strategies for this vulnerable population.

Table 1: Socio-Demographic and Lifestyle Characteristics of Control vs. High-Risk Study Groups

Characteristics	Control Group	Study Group (High Risk)
Mean Age (years)	26.4	27.17
Unbooked (%)	N/A	68.5
Illiteracy (%)	N/A	40
Unemployment (%)	N/A	68.7
Rural Residence (%)	N/A	56.25
Tobacco Addiction (%)	N/A	9.38
Active Smokers & Habitual Coffee Drinkers (>5 cups/day) (%)	N/A	3.13
Diet Deficient in Essential Nutrients & Lacking Supplementation (Folic Acid, Pyridoxine, Methylcobalamin) (%)	N/A	Approximately 66.67 (Two thirds)

The analysis presented in Table 1 reveals significant findings in comparing the control group with the high-risk study group. In the demographic and lifestyle characteristics, the study group exhibited a slightly higher mean age of 27.17 years. Distinctly, this group had a significant percentage of unbooked pregnancies (68.5%), illiteracy (40%), unemployment (68.7%), and rural residency (56.25%). Furthermore, tobacco addiction was noted in 9.38% of the study group, with a smaller subset being active smokers and habitual coffee drinkers consuming more than 5 cups/day (3.13%). A notable dietary concern was the deficiency in essential nutrients and lack of supplementation (Folic Acid, Pyridoxine, Methylcobalamin), affecting approximately two-thirds (66.67%) of the study group.

Table 2: Prevalence of Vitamin Supplementation (Folic Acid, Pyridoxine, & Methylcobalamine) in Control vs. Study Groups

Vitamin (Folic Acid , Pyridoxine & Methylcobalamine **Supplementation)**	Control group	Study group
Supplemented	68.12%	29.12%
Not supplemented	32.2%	71.83%

Table 2 reveals a significant disparity in vitamin supplementation between the control and study groups. The control group showed a higher prevalence of supplementation (68.12%) compared to the study group (29.12%). Conversely, a large portion of the study group did not receive supplementation (71.83%) versus 32.2% in the control group, highlighting a crucial area for intervention in high-risk pregnancies.

Table 3: Comparison of Homocysteine Levels Between Control and High-Risk Pregnancy Groups

GROUPS	RANGE µ mol/L	MEAN ± SD	P value
CONTROL GROUP (n=44)	4.9-9.6	6.4 ± 1.26	< 0.05
STUDY GROUP (n=64)	9.6-18.6	13.82 ± 2.46	<0.05

When examining homocysteine levels, the study revealed a significant difference between the control and study groups. The control group's homocysteine levels ranged from 4.9 to 9.6 µmol/L with a mean of 6.4 ± 1.26, whereas the study group showed elevated levels ranging from 9.6 to 18.6 µmol/L with a mean of 13.82 ± 2.46, underpinning a statistically significant variation ($P < 0.05$).

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Table 4: Homocysteine Levels Across Various Conditions in High-Risk Pregnancy by Trimester

Condition	Range (µmol/L)	Mean (µmol/L)
A. First Trimester		
Previous H/O of Abortion/IUD	9.2-18.2	13.18
Preterm/Stillbirth	10.2-12.2	11.2
Congenital Anomaly	17.4	17.4
B. In Third Trimester		
Preterm Pain	10.2-15.6	11.2
Diabetes	13.4	13.4
Eclampsia	14.8	14.8
Preeclampsia	10.2-10.8	10.5
Antepartum Hemorrhage (APH)	16.4-18.6	17.8

Further stratification of homocysteine levels in high-risk pregnancy shows in Table 3 conditions highlighted distinct patterns. In the first trimester, previous history of abortion or intrauterine death (IUD) correlated with levels ranging from 9.2 to 18.2 µmol/L (mean 13.18), while preterm or stillbirth conditions showed levels between 10.2 to 12.2 µmol/L (mean 11.2), and congenital anomalies were associated with a specific mean level of 17.4 µmol/L. The third trimester analysis revealed a range of conditions with associated homocysteine levels: preterm pain (10.2-15.6 µmol/L, mean 11.2), diabetes (mean 13.4 µmol/L), eclampsia (mean 14.8 µmol/L), preeclampsia (10.2-10.8 µmol/L, mean 10.5), and antepartum hemorrhage (APH) showing the highest levels (16.4-18.6 µmol/L, mean 17.8). These findings underscore the correlation between elevated homocysteine levels and various high-risk pregnancy conditions, highlighting the potential for targeted nutritional and lifestyle interventions in these populations.

Table 5: Comparison of Pregnancy Outcomes between Control and Study Groups

Outcome	Control Group (%) (n=44)	Study Group (%) (n=64)
Abortion	4.51	9.28
Congenital Anomaly	NA	6.23
Term Delivery	79.51	32.71
Preterm Delivery	2.27	10.89
IUGR	4.45	21.1
Still Birth	NA	5.1
Intrauterine	10.1	15.13

The table showcases a stark contrast in pregnancy outcomes between the control and study groups. The study group experienced higher rates of adverse outcomes compared to the control group, with notable increases in abortion (9.28% vs. 4.51%), preterm delivery (10.89% vs. 2.27%), and Intrauterine Growth Restriction (IUGR) (21.1% vs. 4.45%). Congenital anomalies and stillbirths were only observed in the study group, at 6.23% and 5.1%, respectively. Conversely, term deliveries were significantly higher in the control group (79.51%) compared to the study group (32.71%), underscoring the impact of high-risk pregnancies on adverse outcomes. Intrauterine fetal demise also showed an increase in the study group (15.13% vs. 10.1%), further highlighting the challenges faced by high-risk pregnancies.

IV. DISCUSSION

The study's findings illuminate the association between homocysteine levels and various adverse pregnancy outcomes in a high-risk population. The study compared the socio-demographic and lifestyle characteristics, as well as the homocysteine levels, of a control group and a high-risk study group. The study also analyzed the homocysteine levels across different conditions in the first and third trimesters of pregnancy. The main research question was whether elevated homocysteine levels are a risk factor for adverse pregnancy outcomes, and whether nutritional and lifestyle interventions can modulate homocysteine levels and improve pregnancy outcomes. The findings from Table 1 delineate the socio-demographic and lifestyle disparities between the control group and the high-risk study group, indicating a higher mean age, significant rates of unbooked pregnancies, illiteracy, unemployment, rural residency, tobacco addiction, and dietary deficiencies in the latter. Such characteristics underscore the complex interplay of socio-economic and lifestyle factors in high-risk pregnancies.Where as Table 2 also show comparison of vitamin supplementation (Folic Acid, Pyridoxine, & Methylcobalamine) between the groups reveals a significant disparity, with 68.12% of the control group receiving supplementation compared to only 29.12% in the study group. This substantial difference in supplementation rates correlates with the observed pregnancy outcomes, suggesting a potential protective effect of these vitamins against adverse pregnancy outcomes.

Table 3 further elaborates on the biological underpinnings of these risks through the lens of homocysteine levels. The control group exhibited lower levels of homocysteine compared to the high-risk group, where levels were significantly elevated, indicating a clear biochemical distinction that aligns with the increased risk profile of the study group. This significant variance not only reaffirms the

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elevated risk status but also suggests a potential biomarker for identifying high-risk pregnancies.

The analysis reveals significant disparities between Tables 4 and 5, emphasizing the intricate relationship between homocysteine levels and pregnancy outcomes. In Table 4, elevated homocysteine levels are distinctly associated with various high-risk conditions, indicating a possible link to adverse pregnancy outcomes. This is further corroborated by Table 5, which demonstrates a higher incidence of adverse outcomes, including abortions, preterm deliveries, and Intrauterine Growth Restriction (IUGR), in the high-risk group compared to controls. The data collectively highlight the critical importance of monitoring homocysteine levels as a potential predictive marker for high-risk pregnancy management and the need for targeted interventions to improve outcomes in these populations.

Elevated plasma homocysteine levels are a sign of hyperhomocysteinemia, a disorder caused by dysregulation of homocysteine metabolism caused by nutritional inadequacies, genetic polymorphisms, or environmental causes [9]. Numerous unfavorable pregnancy outcomes, including preeclampsia, preterm birth, low birth weight, stillbirth, neural tube problems, and congenital malformations, have been linked to hyperhomocysteinemia [10]. Although the exact processes by which homocysteine negatively affects pregnancy outcomes are unknown, they may include inflammation, oxidative stress, endothelial dysfunction, poor angiogenesis, placental insufficiency, and epigenetic changes [11].

The findings of the present study are consistent with previous studies that have reported higher homocysteine levels in high-risk pregnant women compared to normal pregnant women . The study also demonstrated a significant correlation between homocysteine levels and various conditions in the first and third trimesters of pregnancy, such as previous history of abortion or IUD, preterm or stillbirth, congenital anomaly, preterm pain, diabetes, eclampsia, preeclampsia, and APH. These findings suggest that homocysteine may be a useful biomarker for identifying and monitoring high-risk pregnancies, and that modulating homocysteine levels through nutritional and lifestyle interventions may improve pregnancy outcomes. Another study by Decker and Rabinowitz (2017)[8] discovered that maternal plasma homocysteine concentration was marginally associated with severe preeclampsia, but not with preeclampsia, placental abruption, or pregnancy loss1. It was also significantly (linearly) associated with an increased risk of the composite outcome of any placenta-mediated complication and small for gestational age (SGA) infant. Rai and Yadav, 2021).[12] found the factors that influence maternal homocysteine in a group that has received folic acid supplementation, and they proposed that periconceptional folic acid supplementation combined with improved health status could be a successful strategy for lowering homocysteine.

According to Williamson (2016) [11], high homocysteine levels have been linked to pregnancy issues like abruption, hypertension, early spontaneous abortions, and fetal growth restriction. They have also been linked to some occurrences of maternal and fetal mortality3.

Burke (2016)[6] noted that in terms of pregnancy-induced hypertension, abruption, intrauterine growth restriction, recurrent pregnancy loss, intrauterine mortality, and preterm, hyperhomocysteinemia raised the likelihood of adverse mother and fetal outcomes.

In summary , the study not only reinforces the association between elevated homocysteine levels and high-risk pregnancies but also highlights the multifactorial nature of these risks, involving socio-demographic, lifestyle, and biochemical factors. These insights advocate for a multidimensional approach in managing high-risk pregnancies, emphasizing the importance of early identification, comprehensive risk assessment, and targeted interventions to improve pregnancy outcomes. Future research should continue to explore the mechanisms underlying these associations and the effectiveness of intervention strategies in reducing pregnancy-related complications

V. CONCLUSION

In conclusion, this study showed that elevated homocysteine levels are associated with various adverse pregnancy outcomes in a high-risk population, and that nutritional and lifestyle factors may influence homocysteine metabolism and pregnancy outcomes. Hyperhomocysteinemia is an independent risk factor for many complications like abortion congenital anomaly, preterm labour preeclampsia IUGR, Intrauterine fetal demise. Furthermore, the correlation between lower rates of supplementation and increased adverse outcomes in the study group highlights the critical role of adequate nutrition in ensuring optimal pregnancy outcomes, especially among high-risk populations. These findings highlight the importance of screening and monitoring homocysteine levels in high-risk pregnancies, and of providing adequate nutritional and lifestyle counseling and supplementation to modulate homocysteine levels and improve pregnancy outcomes. Future research should focus on elucidating the molecular mechanisms of homocysteine-induced pregnancy complications, and on conducting large-scale, multicenter, and randomized trials to assess the effectiveness and safety of homocysteine-lowering interventions in high-risk pregnancies.

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