

Analyzing the Link: Hyperhomocysteinemia, Recurrent Pregnancy Loss, and the Impact of Folic Acid and Vitamin B12 SupplementationAnkita Kashyap¹, Aritra Maji², Chandni Sehgal³¹Junior Resident cum PGT, Department of Obstetrics and Gynaecology, MGM Medical College & LSK Hospital, Kishanganj, Bihar, India²Associate Professor, Department of Obstetrics and Gynaecology, MGM Medical College & LSK Hospital, Kishanganj, Bihar, India³Assistant Professor, Department of Obstetrics and Gynaecology, MGM Medical College & LSK Hospital, Kishanganj, Bihar, India

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Abstract:**Introduction:** Hyperhomocysteinemia is connected to RPL, which affects 5% of women. This illness can be caused by genetic defects, folic acid, vitamin B6, and B12 deficiencies, hypothyroidism, medicines, aging, and renal issues. This study investigates hyperhomocysteinemia and obstetric outcomes.This qualitative, cross-sectional study investigated women with RPL for their homocysteine levels. Hyperhomocysteinemia was defined as ≥ 15 $\mu\text{mol/L}$. High-level patients received folic acid and vitamin B12 before reassessing their homocysteine levels.**Finding:** 46 (76.67%) of 60 individuals have elevated homocysteine. Folate and vitamin B12 treatment reduced hyperhomocysteinemia to 32 (53.33%), showing a significant drop in homocysteine levels.**Conclusion:** Hyperhomocysteinemia is linked to RPL, especially in the initial and early second trimesters. Folic acid and vitamin B12 supplements are essential for homocysteine reduction.**Keywords:** Folic acid, Hyperhomocysteinemia, Recurrent pregnancy loss, Vitamin B12, Poor obstetric history (BOH)This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Recurrent pregnancy loss (RPL) is characterized by multiple unsuccessful clinical pregnancies, confirmed through ultrasound or histopathology, or by a series of three consecutive pregnancy losses, which may not all occur within the uterus. Excessive accumulation of homocysteine (Hct), a byproduct of methionine metabolism and a necessary amino acid obtained from our diet, can occur in individuals with hyperhomocysteinemia (HHct). This condition arises from a variety of sources, including genetic mutations in certain genes and environmental factors like deficiencies in certain vitamins, hypothyroidism, medication, aging, and renal dysfunction. Elevated Hct levels can contribute to the development of various cardiovascular conditions, including vascular diseases, coronary artery diseases, atherosclerotic changes, and embolic conditions. During pregnancy, Hct levels typically decrease compared to levels in women who are not pregnant. HHct has been associated with RPL, PE, premature birth, placental abruption, FGR, and gestational diabetes in several studies.

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Methodology

Our study, utilizing cross-sectional observational analysis, was carried out at MGM Medical College & LSK Hospital from July 2022 to December

2023. The study aimed to investigate the correlation between homocysteine levels and recurrent pregnancy loss (RPL), as well as the influence of folic acid and vitamin B12 supplementation on homocysteine levels. A total of sixty patients who had experienced recurrent pregnancy losses and met the requirements were included in the study after obtaining their informed consent. To be eligible for the study, participants were required to have experienced the unfortunate event of two consecutive fetal losses before reaching the 20-week gestation mark, with no identifiable cause. Individuals who had identifiable factors contributing to recurrent pregnancy loss, as well as individuals with ongoing health conditions like diabetes, hypertension, cardiac issues, thyroid disorders, or kidney diseases, or those who were carrying multiple pregnancies, were not included in the study according to specific criteria. We performed measurements to assess the levels of homocysteine, where a threshold of $\geq 15 \mu\text{mol/L}$ indicates the presence of hyperhomocysteinemia. The recommended treatment consisted of taking 5 mg of folic acid orally every day and receiving a 1 mg injection of vitamin B12 once a week for a duration of 12 weeks. Following this time frame, it was necessary to reevaluate the levels of homocysteine. The data was carefully analyzed using suitable statistical methods, and any p-value below 0.05 was deemed significant.

Result

We conducted a study that assessed 60 patients from the Obstetrics and Gynaecology Outpatient Treatment Department (OBG OPD) who had experienced recurrent pregnancy loss. The age distribution of the participants can be found in Table 1: a total of 18 patients in the 18-24 years category, 26 patients in the 25-30 years age bracket, 12 patients in the 31-35 years range, and 4 patients over the age of 35. Among the 60 patients who experienced recurrent pregnancy loss, it was discovered that 14 individuals (23.33%) had homocysteine levels that fell within the normal range, while 46 individuals (76.67%) had higher than normal levels. Following a 12-week regimen of folic acid and vitamin B12 treatment, there was an increase in the number of patients with homocysteine levels within the normal range. Specifically, 28 individuals (46.67%) achieved this improvement, while 32 patients (53.33%) still displayed elevated homocysteine levels. This significant shift in levels is documented in Table 2. For the group of 60 patients who had a history of recurrent pregnancy loss, the average homocysteine level was found to be $14.66 \pm 5.12 \mu\text{mol/L}$. Following the administration of a mixture of folic acid and vitamin B12 supplements, the average level experienced a decrease to $11.28 \pm 4.62 \mu\text{mol/L}$. Table 3 presents evidence of a significant decrease in homocysteine levels.

Table 1

Age	No. of Patients
18-24	18
25-30	26
31-35	12
>35	4
Total	60

Table 2

Homocysteine level	No. of Patients		P value
	Pre-T/t	Post T/t	
<15	14	28	0.02 Significant
>15	46	32	

Table 3

Homocysteine level	Pre T/t	Post T/t	P value
		$14.66 + 5.12$	$11.28 + 4.62$

Discussion

This study was carried out as an 18-month cross-sectional observational analysis to explore the relationship between elevated levels of homocysteine and recurrent pregnancy loss (RPL), as well as to assess the influence of folic acid and vitamin B12 supplementation on homocysteine levels.

We selected a group of 60 pregnant patients who had suffered from multiple consecutive pregnancy losses without any known causes for the recurrent losses, such as diabetes or hypothyroidism. We ensured that those who have experienced three or more losses underwent APLA screening and standard parental karyotyping to eliminate any possible concerns. As part of the initial antenatal appointments, the medical team conducted tests to measure serum homocysteine levels. If the levels

were determined to exceed 15 micromol/L, a daily oral folic acid (5 mg) regimen was recommended until delivery. In addition, a weekly injection of vitamin B12 (1 mg) was given intramuscularly for 12 weeks.

The efficacy of this treatment was assessed by retesting homocysteine levels six weeks after the last vitamin B12 injection. In our sample, most pregnant women with a history of recurrent pregnancy loss were younger than 30 years old. Among the 60 women in this group, 44 were within the specified age range, while the rest were over 30 years old. In previous cases of RPL, the majority of instances (68%) consisted of two occurrences, while a notable portion (30%) had three episodes. A small percentage (2%) had the unfortunate occurrence of enduring four episodes.

Around 20% of the patients who had elevated homocysteine levels experienced first-trimester losses, while 25% of those with normal levels also experienced such losses. Nevertheless, it should be emphasised that this difference holds no statistical significance. Following the administration of vitamin treatment, a significant proportion of the participants who originally exhibited high homocysteine levels experienced a return to normal levels. However, it is worth noting that the majority of individuals still displayed elevated levels. There was a significant reduction in average homocysteine levels, with a decrease from $14.66 \pm 5.12 \mu\text{mol/L}$ before treatment to $11.28 \pm 4.62 \mu\text{mol/L}$ after treatment. There has been a noteworthy decrease of 37.41% ($p < 0.0002$).

Conclusions

Research has found that high levels of homocysteine may increase the risk of recurrent loss of pregnancy (RPL), as around one-third of RPL patients have been found to have elevated homocysteine levels. Therefore, it is advisable to incorporate serum homocysteine testing as a routine part of the diagnostic process for RPL. Ensuring patients receive folic acid and vitamin B12 supplements is of utmost importance, as they play a vital role in lowering serum homocysteine levels.

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