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Case Report

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Role of Hyperhomocysteinemia in Patients with Recurrent Pregnancy Loss and Conception After Treatment: A Retrospective Study

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1. Introduction

Recurrent pregnancy loss (RPL) has been defined as three or more pregnancy losses prior to 20 weeks period of gestation [1]. According to Eshre guideline 2022, presently patients with two or more miscarriages are considered to be RPL and are ideally to be investigated [2].

Recurrent pregnancy loss (RPL) affects about 5% of women and only 1% experience three or more losses. The purpose of this study was to detect the underlying causes of recurrent pregnancy loss (RPL) in addition to the causes like uterine cavity defects, thrombophilia, chromosomal abnormalities, etc. About 15% to 30% of couples are diagnosed with unexplained infertility after their diagnostic workup [3]. In recent years hyperhomocysteinemia (HHcY) is appearing as one of the important cause for RPL. This may be due to rising cases of Polycystic ovarian disease (PCOD) which may be associated with it [4]. Prolonged use of Metformin in treating PCOD may also cause HHcY.

HHcY has been defined as plasma homocysteine levels more than 95th percentile from normal baseline level. The mean fasting level of plasma homocysteine has been found to be higher in women with recurrent pregnancy loss. In pregnant women who have HHcY have been also seen to have deep venous thrombosis, recurrent miscarriage, abruption placentae, pre-eclampsia, neural tube defects and fetal growth restriction [5]. There has been cases where patients with HHcY and recurrent pregnancy loss have conceived after treatment [6].

2. Aim of Study

The primary objective is to estimate the percentage of patients with HHcY who had RPL, conceived after treatment and delivered.

The secondary objective was to identify other causes of RPL, percentage of cases on metformin who had HHcY and their consequent pregnancy outcome.

3. Material and Method

The present study was a multicentric retrospective interventional study conducted at Repose Clinic and Research Centre and Calcutta Fertility Mission over a time period of two years.

3.1 Inclusion criteria

86 patients aged between 20-40 years with history of RPL were divided into two groups,
Group A (n=14) consisting of women with RPL and having high level of homocysteine and Group B (n=72) had women who had other etiology for RPL with normal plasma homocysteine levels. These patients were similar in age, socioeconomic status and essentially had normal karyotyping.

3.2 Exclusion criteria

Patients with history of recurrent pregnancy loss were excluded from study group who could not give clear history of using metformin.

86 patients who had fulfilled the inclusion criteria were included in the first trimester in the study after obtaining informed consent from all the patients. A venous sample of blood was collected by venipuncture for fasting plasma homocysteine. The collected blood sample was assayed within four hours by Chemiluminiscence immunoassay.

These women were given the same standard of care as other antenatal patients with regular antenatal check-ups and iron and folic acid supplements as routinely advised. They were monitored for development of any antenatal complications such as early pregnancy loss, pre-eclampsia or Intrauterine fetal growth restriction and were followed up till delivery.

4. Work Plan

86 pregnant patients with history of RPL were studied from previous records who met the inclusion criteria

↓

Causes of RPL recorded in these patients and documented; patient on metformin were recorded, plasma homocysteine values recorded pre-pregnancy (>15micromol/l)

↓

Patients with HHcY were already on aspirin and folic acid supplements,repeat homocysteine levels were checked at 16 weeks period of gestation and the values were normal (<6mmol/l), so not repeated further

↓

14 patients were diagnosed to have HHcY pre-pregnancy and had conceived after treatment, other causes of RPL diagnosed in other patients

↓

Pregnancy outcome studied and documented

5. Ethical Consideration

The Ethical Committee has given clearance for the retrospective study of a prospective database. (code: CFM/2023/039).Informed consent has been obtained in written from all the women who participated in the study.

6. Statistical Analysis

Categorical variables are expressed in number and percentage of patients and compared across groups using Pearson's Chi-Square test for independence of attributes/ Fisher's test. The statistical software SPSS version 25 has been used for analysis. AN alpha level 5%has been taken, any value p value<0.05 has been considered significant.

7. Results

Age (yrs)	Group A	Group B	Total	p-value
20-25	4	24	28	0.850
26-30	6	26	32	
31-35	3	16	19	
36-40	1	6	7	
	14	72	86	

Data presented as n; Pearson's Chi-Square test; age of the patients have no statistical significance (p value – 0.850)

Table 1: Age of women in groups

Obstetric score	Group A	Group B	Total	p-value
P(0+2)	5	32	37	0.535
P(0+3)	4	28	32	0.440
P(0+4)	4	8	12	0.167
P(1+2)	1	4	5	0.830
	14	72	86	

Data presented as n; Pearson's Chi-Square test; obstetric score of the patients have no statistical significance

Table 2: Obstetric score in groups

Factors	Group A	Group B	Total	p-value
Latent genital tuberculosis (LGTB)	0	52	52	0.000
Hyperhomocysteinemia	14	0	14	0.000
Uterine anomaly	0	4	4	0.040
Hypothyroidism	0	7	7	0.005
Type 2 Diabetes Mellitus	0	6	6	0.011
APLA syndrome	0	3	3	0.077

Data presented as n; Pearson's Chi-Square test; LGTB and HHcY appear as statistically significant factors in these cohort of women

Table 3: Etiology of RPL

Pregnancy outcome	Group A	Group B	Total	p-value
Term delivery	12	40	52	0.006
Preterm delivery	2	11	13	0.923
Intrauterine growth restriction	6	12	18	0.060
Hypertension	6	14	20	0.095

Data presented as n; Pearson's Chi-Square test; outcome of pregnancy of the patients have no statistical significance

Table 4: Pregnancy outcome

8. Discussion

Recurrent pregnancy loss affects the physical and mental health of a woman in her reproductive age and is disgraceful. It is still quite difficult to form a work-up plan to pinpoint the cause of RPL, as continuation of pregnancy involves multiple factors.

These factors may be genetic factors, uterine cavity defects, hormonal causes, or miscellaneous like infections and immunological factors. Routine tests which involve factors mentioned previously have been performed in all patients and relatively newer tests like screening for genital tuberculosis or HHcY as causative factor of RPL [7].

In the present study patients were 20-40years of aged with bad obstetric history of two or more recurrent miscarriage. Both age of the patient or the obstetric history did not have ant statistical significance as per the analysis (Table 1 and 2). The patients included in Group A and Group B were screened with the known causes of RPL (uterine anomalies, type 2 DM, hypothyroidism, APLA syndrome) and these were excluded in Group A (Table 3) [3]. 52 patients in Group B were detected to haveonly latent genital tuberculosis as the cause of RPL similar to the study by Bagchi et.al, where 34.4% of patients were screened positive [8].

14 patients (16.3%) who suffered from RPL were diagnosed to have HHcY and after treatment the pregnancy outcome has been analysed. It has been observed in the study that quite a lot of patients with RPL are affected with HHcY as a sole or strongly associated factor for the development of such an unfortunate condition.
HHcY was higher among patients with RPL, 36% as compared to controls, 17%, the difference being statistically significant ($p<0.003$) [9].

As mentioned by Maristella et.al. and Govindaiah V et.al, the median fasting total plasma homocysteine level was 19.2micromol/l in RPL patients, as compared to 7.85micromol/l in that of study group and that it is more in women with RPL [10,11].

In the present study latent genital tuberculosis and HHcY appear to be statistically significant factors for causing RPL in this cohort of patients. HHcY is becoming risk factor for recurrent pregnancy loss. About 1 in 3 patients of RPL have HHcY and therefore as a routine workup for RPL serum homocysteine measurement should also be included. Treatment of HHcY with folic acid and vitamin B12 decreases homocysteine levels significantly [12,13].

As the pregnancy outcome has been analyzed in the current study 85.7% patients who have been treated for HHcY were seen to have delivery at term gestation (>37 weeks). Delivery of babies at term gestation in both the groups was statistically significant.2 patients in Group A and 11 in Group B had preterm delivery. 42.8% had low birth weight babies. The other complications like Intrauterine growth restriction and maternal hypertension (71%) had developed in few patients in both groups.

9. Conclusion

In our study hyperhomocysteinemia involved a major number of cases in patients with RPL (16.3%) who conceived following treatment. Metformin usage was present in 57% of those cases who were managed with folic acid and vitB12 supplementation. Hence in this part of the world screening for HHcY in cases of RPL may be a good option in screening of RPL and could be the game-changer for the couples who lose hope with repeated miscarriages.

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