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Prospective Observational Study Of Hyperhomocysteinemia In Patients With Recurrent Pregnancy Loss In Teaching Hospital

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Abstract:
Background*: Spontaneous pregnancy loss can be physically and emotionally taxing for couples, especially when faced with recurrent losses. Recurrent pregnancy loss (RPL), also referred to as recurrent miscarriage or habitual abortion, is historically defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period . RPL is also defined by two or more failed consecutive pregnancies. It is estimated that fewer than 5% of women will experience two consecutive miscarriages and only 1% experience three or more. At present, there exists a small number of accepted etiologies for RPL. Most of the diagnosed etiologies include endocrine abnormalities, autoimmune disorders, uterine anomalies, and genetic factors. After evaluation for these causes, approximately half of all cases will still remain unexplained. Hence the present study was taken up to investigate the association between hyperhomocysteinemia and recurrent pregnancy loss, evaluating prevalence, potential mechanisms and implications for management.*
Materials and Methods: *The prospective observational study was conducted on 50 patients in the Department of OBG in Dr. B. R. Ambedkar Medical College and Hospital for a period of 18 months. Prior to the initiation of the study, Ethical and Research Committee clearance was obtained from Institutional Ethical Committee.*
Results: *The majority of participants in both groups were aged 35 to 40 years (32.35% in Group A and 37.5% in Group B).Statistically significant differences were observed between the groups regarding hypertensive disorders of pregnancy, co-morbidities, adverse pregnancy outcomes, the nature of abortion (primary vs. secondary), fetal outcomes, APGAR scores at 1 and 5 minutes, neonatal birth weight, and NICU admissions, with p-values of 0.001 across these measures.Group B (with hyperhomocysteinemia) showed higher instances of hypertensive disorders, co-morbidities, adverse pregnancy and fetal outcomes, abnormal APGAR scores at 1 and 5 minutes, lower neonatal birth weight, and NICU admissions.The mean homocysteine levels were 13.28 ± 1.8 µmol/L in Group A and 73.98 ± 5.1 µmol/L in Group B, with a highly significant difference (p: 0.0001).Most subjects in Group B had intermediately severe hyperhomocysteinemia (50%), with 37.5% experiencing moderately severe hyperhomocysteinemia and 12.5% with severe hyperhomocysteinemia. All abortions in Group A were primary, whereas Group B had 60% primary and 40% secondary abortions.*
Conclusion: *Hyperhomocysteinemia is a risk factor for recurrent pregnancy loss. About 1 in 3 patients of RPL have hyperhomocysteinemia and therefore as a routine workup for RPL serum homocysteine measurement should also be included. Treatment of hyperhomocysteinemia with folic acid and vitamin B12 decreases homocysteine levels significantly.*
Keywords: *Recurrent pregnancy loss (RPL)*

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I. Introduction

Recurrent pregnancy loss (RPL), defined as the occurrence of three or more consecutive miscarriages before 20 weeks of gestation, poses a significant emotional and physiological challenge for affected individuals and couples. The causes of RPL are often complex and multifactorial, but recent research has highlighted the potential involvement of hyperhomocysteinemia in pregnancy loss.Hyperhomocysteinemia, characterized by elevated homocysteine levels in the blood, is associated with various adverse health outcomes, including cardiovascular disease, neural tube defects, and pregnancy complications. Emerging evidence suggests that hyperhomocysteinemia may also contribute to the pathophysiology of RPL, although the underlying mechanisms remain unclear.Several studies have observed elevated homocysteine levels in women with recurrent miscarriages, leading to further investigation of the potential connection between hyperhomocysteinemia and RPL. This area of research has gained increasing importance in reproductive medicine, as identifying modifiable risk factors for RPL could guide clinical management strategies and improve outcomes for those affected.

II. Materials And Method

The present study is a prospective observational Study was carried out in the Department of obstetrics and gynaecology in Dr B R Ambedkar Medical College and Hospital. The study is conducted on 50 patients.

Study design: Prospective observational Study.

Study location: This was tertiary care teaching hospital based study done in Dr B R Ambedkar Medical College and Hospital, Bangalore.

Study duration: The study was carried out for a period of 18 months, i.e., from July 2022 to January 2024.

Sample size: 50 patients.

Inclusion criteria:
Patients meeting the following criteria were enrolled into the study.
1. Patients prior to 20 weeks of gestation.
2. Patients with singleton pregnancies.
3. Patients willing to give consent.
4. Patients willing to participate.

Exclusion criteria:
Patients meeting the following criteria were excluded from the study.
1. Patients with anatomical abnormalities.
2. Women with any history of vascular thrombotic events.
3. Patients with infective causes of RPL.
4. Patients with history of vitamin B6 or folic acid supplementation within 6 months of study period.
5. Patients who were not willing to give consent.
6. Patients not willing to participate.

Statistical analysis

The collected data was entered into Microsoft Excel Worksheet-2010 and data was taken into IBM SPSS Statistic for windows, version 24 (IBM Corp., Armonk, N.Y., USA) software for calculation of frequency, percentage, mean, standard deviation and probability value.

Qualitative data was represented in the form of frequency and percentage.
- Association between qualitative variables was assessed by Chi Square test with continuity correction for 2 x 2 tables and
- Fisher's exact test for all 2 x 2 tables, where P value of chi square test was not valid due to small counts.

Quantitative data was represented using mean and standard deviation.
- Analysis of quantitative data within the groups was done using paired t test if data passes 'Normality test'.
- One Way Analysis (ANOVA) was used to compare more than two groups.

* A **'P'** value of <0.05 was considered statistically significant.

III. Results

The present prospective, observational study was conducted on 50 patients in the department of OBG in Dr. B. R. Ambedkar Medical College and Hospital. The patients were divided into two groups based on their homocysteine levels.

GROUP A (N = 34):
34 subjects with normal homocysteine levels.
GROUP B (N = 16):
16 subjects with hyperhomocysteinemia.
The following were the study results:

Table 1: Age wise distribution of subjects.

Age group (years)	Group A N (%)	Group B N (%)	P-Value
20 to 25	6 (17.64 %)	2 (12.5 %)	0.931
26 to 30	7 (20.58 %)	3 (18.75 %)	
31 to 35	10 (29.41 %)	5 (31.25 %)	

35 to 40	11 (32.35 %)	6 (37.5 %)	
Total	**34 (100 %)**	**16 (100 %)**	

In the present study, the subjects were categorized into four age groups. The above table gives data on distribution of study subjects based on their age.

Majority subjects in group **A** were found in the age group of 35 to 40 years, i.e., 11 subjects (32.35 %); followed by 10 subjects (29.41 %) in the age group of 31 to 35 years; 7 subjects (20.58 %) in the age group of 26 to 30 years and finally 6 subjects (17.64 %) in the age group of 20 to 25 years.

Majority subjects in group **B** were found in the age group of 35 to 40 years, i.e., 6 subjects (37.5 %); followed by 5 subjects (31.25 %) in the age group of 31 to 35 years; 3 subjects (18.75 %) in the age group of 26 to 30 years and finally 2 subjects (12.5 %) in the age group of 20 to 25 years.

The p-value calculated was 0.931 indicating no statistical difference between groups in the age wise distribution of subjects.

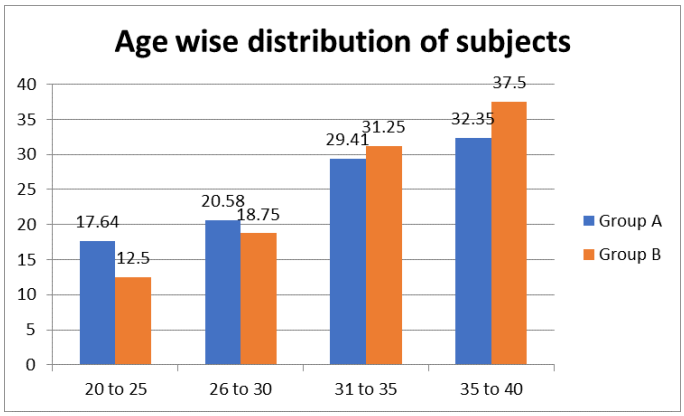

Figure 2: Age wise distribution of subjects.

Table 2: Distribution of subjects based on the presence of hypertensive disorder of pregnancy.

Hypertensive disorder of pregnancy	Group A N (%)	Group B N (%)	P-Value
Yes	5 (14.70 %)	14 (87.5 %)	**0.001**
No	29 (85.29 %)	2 (12.5 %)	
Total	**34 (100 %)**	**16 (100 %)**	

The above table gives data on distribution of study subjects based on the presence of hypertensive disorder of pregnancy.

Majority subjects in group **A** did not have hypertensive disorder of pregnancy, i.e., 29 subjects (85.29 %); followed by 5 subjects (14.70 %) with hypertensive disorder of pregnancy.

Majority subjects in group **B** had hypertensive disorder of pregnancy, i.e., 14 subjects (87.5 %); followed by 2 subjects (12.5 %) without hypertensive disorder of pregnancy.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of presence of hypertensive disorder of pregnancy.

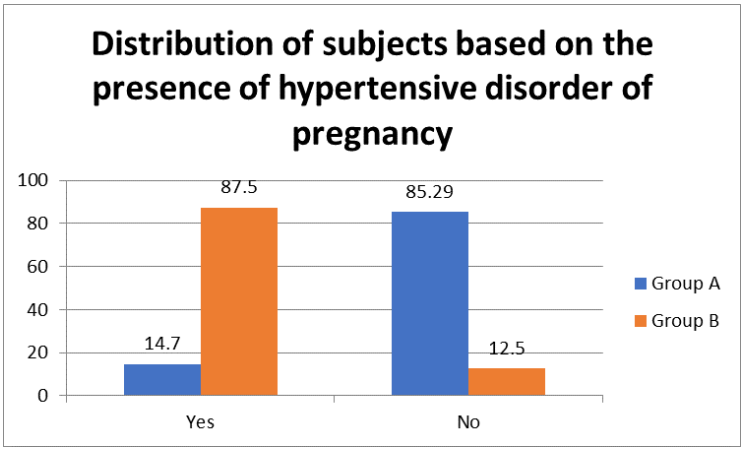

Figure 3: Distribution of subjects based on the presence of hypertensive disorder of pregnancy.

Table 3: Distribution of subjects based on co-morbidities present during pregnancy.

Co-morbidities during pregnancy	Group A N (%)	Group B N (%)	P-Value
Hypertension	5 (14.70 %)	14 (87.5 %)	**0.001**
Gestational diabetes	3 (8.82 %)	8 (50 %)	
Hypothyroidism	6 (17.64 %)	1 (6.25 %)	
Vascular disorders	1 (2.94 %)	6 (37.5 %)	

The above table gives data on distribution of study subjects based on the co-morbidities present during pregnancy.

6 subjects (17.64 %) in group **A** had hypothyroidism; followed by 5 subjects (14.70 %) with pregnancy induced hypertension; 3 subjects (8.82 %) with gestational diabetes; 1 subject (2.94 %) with vascular disorders.

14 subjects (87.5 %) in group **A** had pregnancy induced hypertension; followed by 8 subjects (50 %) with gestational diabetes; 6 subjects (37.5 %) with vascular disorders; 1 subject (6.25 %) with hypothyroidism.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of co-morbidities present during pregnancy.

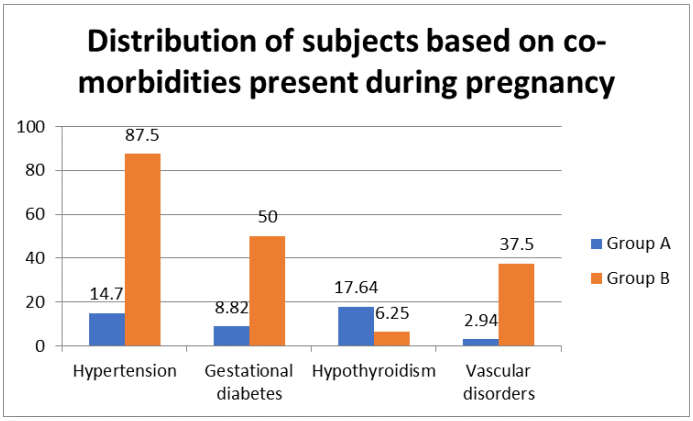

Figure 4: Distribution of subjects based on co-morbidities present during pregnancy.

Table 4: Comparison of mean homocysteine levels between groups.

Parameter	Group A Mean ± SD	Group B Mean ± SD	P-Value
Mean homocysteine levels (micromol/l)	13.28 ± 1.8	73.98 ± 5.1	**0.0001**

The above table gives comparative data on mean homocysteine levels between groups.

The mean homocysteine levels of group **A** subjects was 13.28 ± 1.8 micromol/l and that in group **B** subjects was 73.98 ± 5.1 micromol/l.

The p value calculated was **0.0001** which indicated that there was a highly significant statistical difference between the groups in terms of mean homocysteine levels.

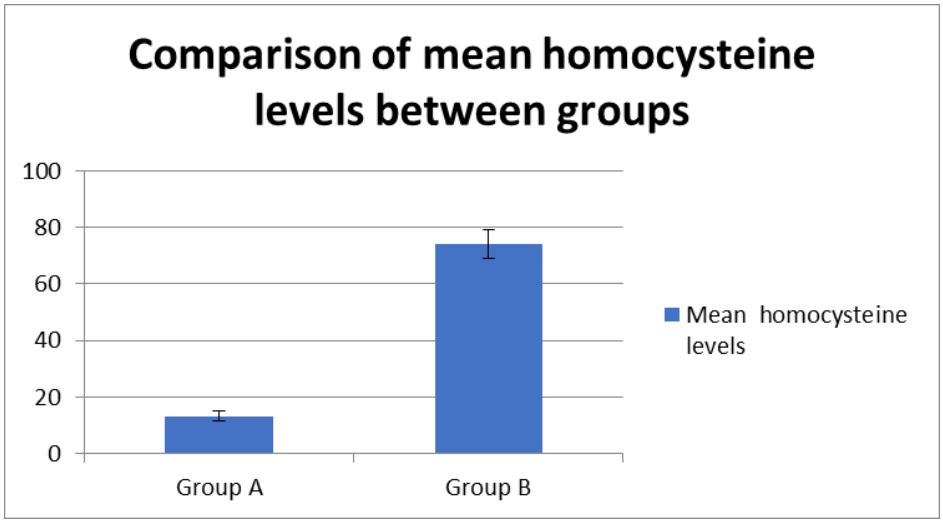

Figure 5: Comparison of mean homocysteine levels between groups.

Table 5: Distribution of subjects with hyperhomocysteinemia based on the severity.

Severity of hyperhomocysteinemia	Number of subjects (N)	Percentage (%)
Moderate	6	37.5
Intermediate	8	50
Severe	2	12.5
Total	**16**	**100**

The above table gives data on distribution of subjects with hyperhomocysteinemia based on the severity.

Majority subjects had intermediately severe hyperhomocysteinemia, i.e., 8 subjects (50 %); followed by 6 subjects (37.5 %) with moderately severe hyperhomocysteinemia and finally 2 subjects (12.5 %) with severe hyperhomocysteinemia.

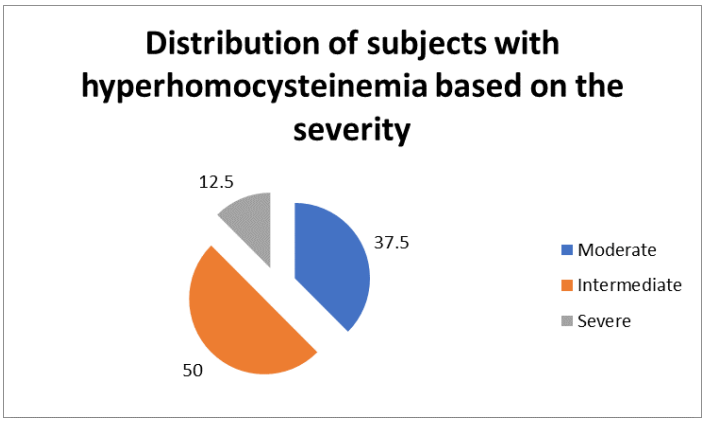

Figure 6: Distribution of subjects with hyperhomocysteinemia based on the severity.

Table 6: Distribution of subjects based on pregnancy outcome.

Pregnancy outcome	Group A N (%)	Group B N (%)	P-Value
Abortions	2 (5.88 %)	10 (62.5 %)	**0.001**
Vaginal delivery	12 (35.29 %)	1 (6.25 %)	
Caesarean section	20 (58.82 %)	5 (31.25 %)	
Total	**34 (100 %)**	**16 (100 %)**	

The above table gives data on distribution of study subjects based on pregnancy outcome.

Majority subjects in group **A** had caesarean sections, i.e., 20 (58.82 %); followed by 12 (35.29 %) with vaginal delivery and finally 2 (5.88 %) with abortions.

Majority subjects in group **B** had abortions, i.e., 10 (62.5 %); followed by 5 (31.25 %) with caesarean sections and finally 1 (6.25 %) with vaginal delivery.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of pregnancy outcome.

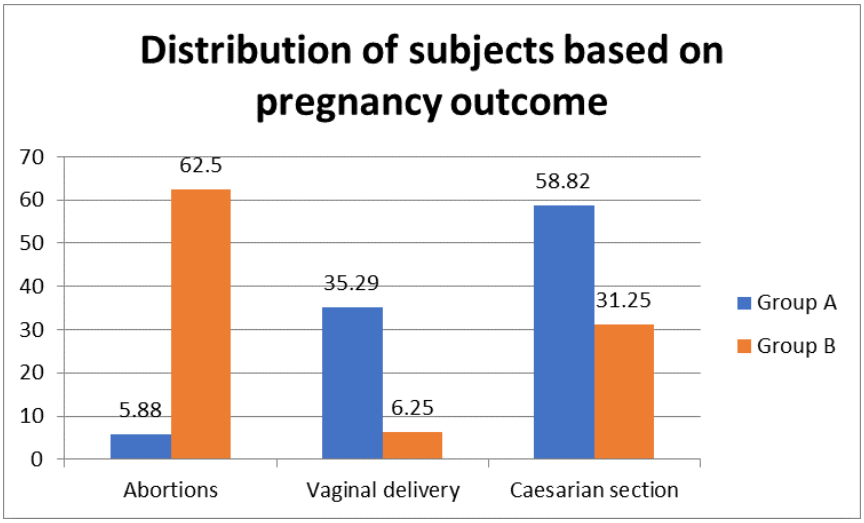

Figure 7: Distribution of subjects based on pregnancy outcome.

Table 7: Distribution of subjects based on the nature of abortion.

Nature of abortion	Group A N (%)	Group B N (%)	P-Value
Primary	2 (100 %)	6 (60 %)	**0.001**
Secondary	0 (0 %)	4 (40 %)	
Total	**2 (100 %)**	**10 (100 %)**	

The above table gives data on distribution of study subjects based on the nature of abortion.
Out of 2 subjects who underwent abortions in group **A**, all (100 %) had primary abortions.

Out of 10 subjects who underwent abortions in group **B**, 6 (60 %) had primary abortions and 4 (40 %) had secondary abortions.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of nature of abortion.

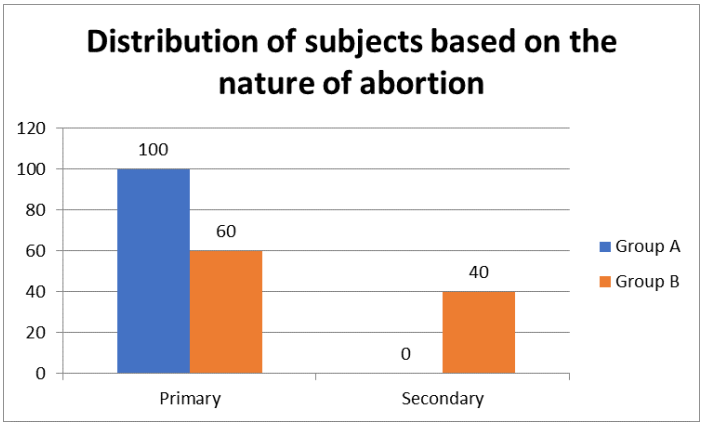

Figure 8: Distribution of subjects based on the nature of abortion.

Table 8: Distribution of subjects based on APGAR score.

APGAR score	Group A N (%)	Group B N (%)	P-Value
Abnormal at 1 minute	11 (34.37 %)	5 (83.33 %)	**0.001**
Abnormal at 5 minutes	5 (15.62 %)	3 (50 %)	

Babies of 11 subjects (34.37 %) in group **A** had abnormal APGAR score at 1 minute and 5 subjects (15.62 %) had abnormal APGAR score at 5 minutes.

Babies of 5 subjects (83.33 %) in group B had abnormal APGAR score at 1 minute and 3 subjects (50 %) had abnormal APGAR score at 5 minutes.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of APGAR score of newborns.

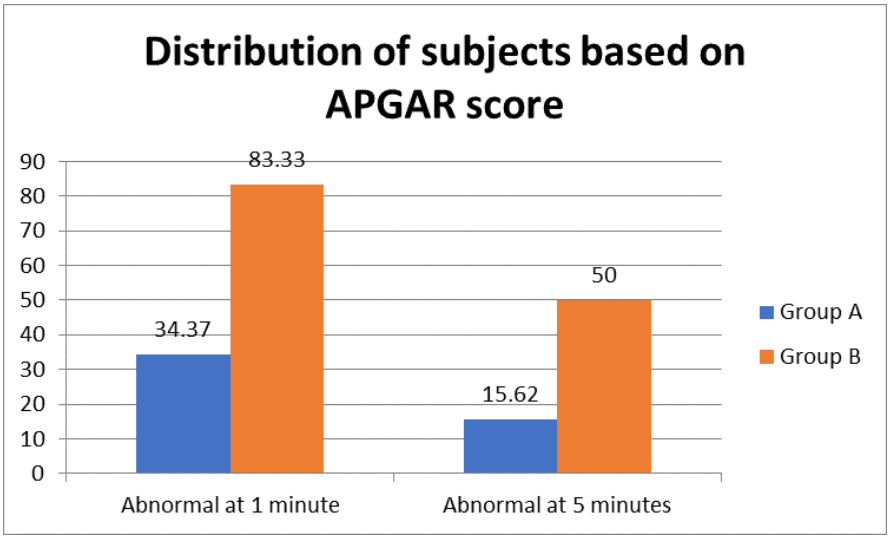

Figure 9: Distribution of subjects based on APGAR score.

Table 9: Distribution of subjects based on neonatal birth weight.

Neonatal birth weight.	Group A N (%)	Group B N (%)	P-Value
Small for gestational age	25 (78.12 %)	5 (83.33 %)	**0.001**
Appropriate for gestational age	6 (18.75 %)	1 (16.67 %)	
Large for gestational age	1 (3.12 %)	0 (0 %)	
Total	**32 (100 %)**	**6 (100 %)**	

The above table gives data on distribution of study subjects based on the neonatal birth weight.

Out of 32 neonates in group **A,** 25 (78.12 %) were small for gestational age;6(18.75 %) were appropriate for gestational age and 1 (3.12 %) was large for gestational age.

Out of 6 neonates in group **B,** 5 (83.33 %) were small for gestational age; 1 (16.67 %) was appropriate for gestational age. The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of neonatal birth weight.

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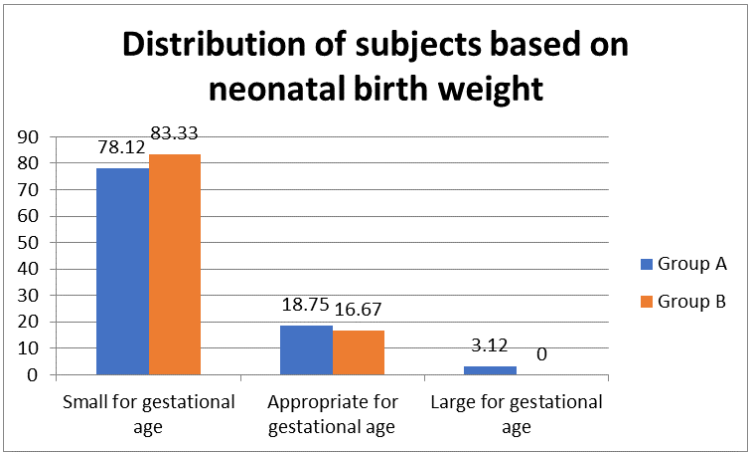

Figure 10: Distribution of subjects based on neonatal birth weight.

Table 10: Distribution of subjects based on the NICU admissions.

NICU admission	Group A N (%)	Group B N (%)	P-Value
Yes	10 (31.25 %)	6 (100 %)	**0.001**
No	22 (68.75 %)	0 (0 %)	
Total	**32 (100 %)**	**6 (100 %)**	

The above table gives data on distribution of study subjects based on the NICU admissions.

Out of 32 neonates in group **A,** 10 (31.25 %) were admitted in NICU and 22 (68.75 %) did not require NICU admission.

Out of 6 neonates in group **B,** all (100 %) were admitted in NICU.

The p value calculated was **0.001** which indicated that there was a statistically significant difference between the groups in terms of NICU admissions.

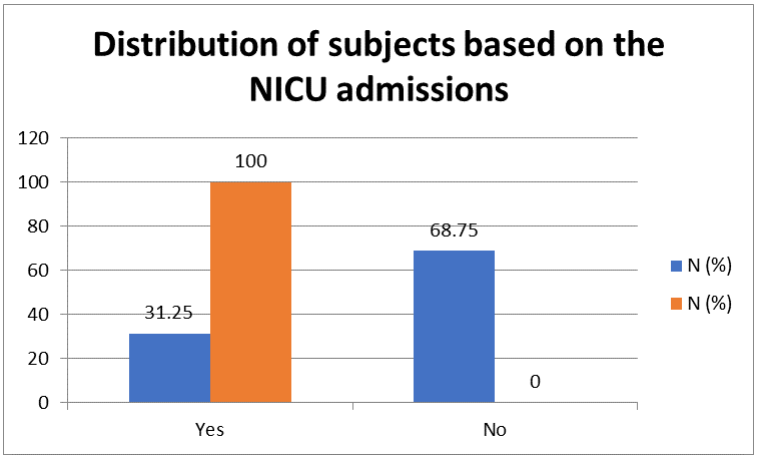

Figure 11: Distribution of subjects based on the NICU admissions.

IV. Discussion

- The majority of participants in both groups were aged 35 to 40 years (32.35% in Group A and 37.5% in Group B).
- Statistically significant differences were observed between the groups regarding hypertensive disorders of pregnancy, co-morbidities, adverse outcome of the nature of abortion (primary vs. secondary), APGAR scores at 1 and 5 minutes, neonatal birth weight, and NICU admissions, with p-values of 0.001 across these measures.
- Group B (with hyperhomocysteinemia) showed higher instances of hypertensive disorders, co-morbidities, adverse pregnancy and fetal outcomes, abnormal APGAR scores at 1 and 5 minutes, lower neonatal birth weight, and NICU admissions.
- The mean homocysteine levels were 13.28 ± 1.8 µmol/L in Group A and 73.98 ± 5.1 µmol/L in Group B, with a highly significant difference (p: 0.0001).
- Most subjects in Group B had intermediately severe hyperhomocysteinemia (50%), with 37.5% experiencing moderately severe hyperhomocysteinemia and 12.5% with severe hyperhomocysteinemia.
- All abortions in Group A were primary, whereas Group B had 60% primary and 40% secondary abortions.

V. Conclusion

Hyperhomocysteinemia is a significant risk factor for recurrent pregnancy loss (RPL). About 1 in 3 patients of RPL have hyperhomocysteinemia and therefore, serum homocysteine levels should be routinely assessed as part of the workup for RPL. Treating hyperhomocysteinemia with folic acid and vitamin B12 has been shown to significantly reduce homocysteine levels.

References

[1] Stirrat GM. Recurrent Miscarriage I: Definition And Epidemiology. Lancet 1990a;336:673-5.
[2] Coulam C Epidemiology Of Recurrent Spontaneous Abortion Am J Reprod Immunol 1991,26 23-7
[3] Warburton D, Fraser FC. Spontaneous Abortion Risks In Man: Data From Reproductive Histories Collected In A Medical Genetics Unit. Am J Hum Genet 1964;16:1-25.
[4] Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PL Early Embryonic Mortality In Women Fertl Stenl 1982,38 447-53
[5] Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence Of Early Loss In Pregnancy. N Engl J Med 1988;319:189-94.
[6] Regan L, Braude PR, Trembath PL Influence Of Past Reproductive Performance On Nsk Of Spontaneous Abortion Br Med J 1989 299 55
[7] Tho PT, Byrd JR, Mcdonough PG. Etiologies And Subsequent Reproductive Performance Of 100 Couples With Recurrent Abortion. Fértil Steril 1979;32:389-95.
[8] Harger JH, Archer DF, Marchese SG, Muracca-Clemens M, Ganzer KL. Etiology Of Recurrent Pregnancy Losses And Outcome Of Subsequent Pregnancies. Obstet Gynecol 1983;62:574-81.
[9] Stray-Pedersen B, Stray-Pedersen S. Etologie Factors And Subsequent Reproductive Performance In 195 Couples With A Prior History Of Habitual Abortion. Am J Obstet Gynecol 1984;148:140-6
[10] Tulppala M, Palosuo T, Ramsay T, Mieffinen A, Salonen R, Ylikorkala O. A Prospective Study Of 63 Couples With A History Of Recurrent Spontaneous Abortion: Contributing Factors And Outcome Of Subsequent Pregnancies. Hum Reprod 1993a;8:764-70.
[11] Simpson JL Incidence And Timing Of Pregnancy Losses Relevance To Evaluating Safety Of Early Prenatal Diagnosis Am J Med Genet 1990,35 165-73