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The Role of Hyperhomocystinemia in Recurrent Pregnancy Loss

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ABSTRACT

Miscarriage is the most common type of pregnancy loss and about 15-25% of recognized pregnancies will end in a miscarriage) and about 5% of women will experience recurrent miscarriage. To assess the prevalence of hyperhomocystinemia in pregnant patients with unexplained recurrent pregnancy loss and to evaluate the association of hyperhomocystinemia with adverse pregnancy outcome as, preterm labour , pre-eclampsia ,placental abruption and intrauterine growth restriction. This was a case- control study conducted in the Obstetrics and Gynecology Department at Al-Diwaniyah Maternity and Pediatrics Teaching Hospital, Iraq, from the period of February 2019 - December 2019 as 37 patients with unexplained recurrent pregnancy loss(RPL) with no live birth were enrolled as a(study group) and 38 patients with Recurrent pregnancy loss with at least one successful pregnancy were enrolled as a (control group). All patients aged 18-40 years with gestational age 10-14 weeks to aiiow abnormal pregnancies to passed spontaneousely ,and fasting plasma homocystin was measured for all patients and they were followed during pregnancy for the development of any adverse pregnancy complications. Fasting serum homocystin level was significantly higher among the study group patients (48.6%) , compared to (26.3%) of the control group patients ($p \leq 0.05$). Fasting homocysytin level mean ∓ SD among the study and control group was(10.08∓ 6.28 µ mol/dL),(6.84∓ 4.89 µ mol/dL), respectively, with a ($p \leq 0.05$).Higher complications rate was among the study group as 18 patients(48.6%) develop adverse pregnancy outcome , while in the control group only 10 patients (26.3%) had developed adverse pregnancy outcome($p \leq 0.05$) as more complications rate as Intra uterine grouth restrictio, Pregnancy induced hyper tention, Pre-eclampsia and spontaneous abortion were among the study group (18.9%, 10.8%, 2.7% and 5.4%) compared to (10.5%, 5.3%, 0.0%, and 5.3%) among the control group, respectively ($p > 0.05$).

Keywords
Hyperhomocystinemia, pregnancy loss , Miscarriage

Introduction

Miscarriage is also known as spontaneous abortion ,it is the natural death of an embryo or fetus before it is able to survive independently, and defined by World Health

Organization (WHO) as the loss of pregnancy before 24 weeks of gestation , and before 20 weeks according to American Collage of Obstetrician and Gynecologists (1), According to the American College of Obstetricians and Gynecologists (ACOG) about 15-25% of recognized pregnancies will end in a miscarriage (2). *Chemical pregnancies* may account for **50-75% of all miscarriages.** This occurs when a pregnancy is lost shortly after implantation, resulting in bleeding that occurs around the time of the patient´s expected period .These pregnancy losses are usually sporadic, often unavoidable and may be due to underlying chromosomal or structural abnormalities (3).

About 80% of miscarriages occur in the first 12 weeks of pregnancy (the first trimester). The underlying cause in about half of cases involves chromosomal abnormalities as half of embryonic miscarriages (25% of all miscarriages) have an aneuploidy (abnormal number of chromosomes).

Common chromosome abnormalities found in miscarriages include an autosomal trisomy (22–32%), monosomy X (5-20%), triploidy (6–8%), tetraploidy (2–4%) and other structural chromosomal abnormalities (2%) . (2)

Risk factors for miscarriage include an older parents, previous miscarriage, smoking, obesity, diabetes, thyroid problems,
autoimmune medical disorders and drugs or alcohol use (4).

Homocystiene level decrease normally during pregnancyHyperhomocysteinemia in recurrent miscarriage:

Hyperhomocysteinmia(HHcy) can result from a variety of genetic and environmental factors. The majority of homocystein is catabolised by the vitamin B6- dependent enzyme Cystathione-b-Synthase (CBS) into cystathionine. A significant proportion of homocystein is regenerated into methionine by methionine synthase. This enzymatic reaction involves methylenetetrahydrofolate reductase (MTHFR) and the cofactor vitamin B12(27).

Patients and methods

This was a case-control study conducted in the Obstetrics and Gynecology Department at Al-Diwaniyah Maternity and Pediatrics Teaching Hospital, Iraq, from the period of February 2019 - December 2019. 37 patients with unexplained recurrent pregnancy loss(RPL) with no live birth were enrolled as a(study group) and 38 patients with RPL with at least one successful pregnancy were enrolled as a (control group). All patients aged 18-40 years with gestational age 10-14 weeks and body mass index (BMI) 19-25 kg/m² .

This study was approved by Iraqi Ethical Committee of Iraqi Board for Medical Specialization and all patients gave informed consent for their participation in the study after explanation for them the aim of the study.

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Results

Out of 80 patients that were enrolled in the study, only 75 patients were enrolled , as 37 patients were followed up as the study group, and 38 patients were enrolled as the control group, i.e. 5 patients were lost to follow up.

Table 1 showed the demographic characteristic of the patients enrolled in the study, as there was no significant statistical differences in the mean age (years) between the control and the study group ($p > 0.05$). No significant statistical differences in the gestation age (weeks) and BMI (kg/m^2) between the control and study groups (10.84∓ 1.10 weeks, 11.43∓ 1.07 weeks) and (19.26∓ 1.13 kg/m^2),(20.05∓ 1.20) kg/m^2 respectively with value($p > 0.05$).

Table 1: Demographic characteristics of women enrolled in this study according to group

Characteristic	Control group *n* = 38	Study group *n* = 37	*P*
Age (years)			
Mean ±SD	**27.13 ±4.71**	**28.38 ±4.63**	**0.252 † NS**
Range	**21 -38**	**20 -34**	
Gestational age (weeks)			
Mean ±SD	**10.84 ±1.10**	**11.43 ±1.07**	**0.107 † NS**
Range	**10 -13**	**10 -14**	
BMI (kg/m^2)			
Mean ±SD	**19.26 ±1.13**	**20.05 ±1.20**	**0.440 † NS**
Range	**18 -21**	**18 -22**	

***n*: number of cases; SD: standard deviation; BMI: body mass index; †: Independent samples t-test; NS: not significant at *P*> 0.05**

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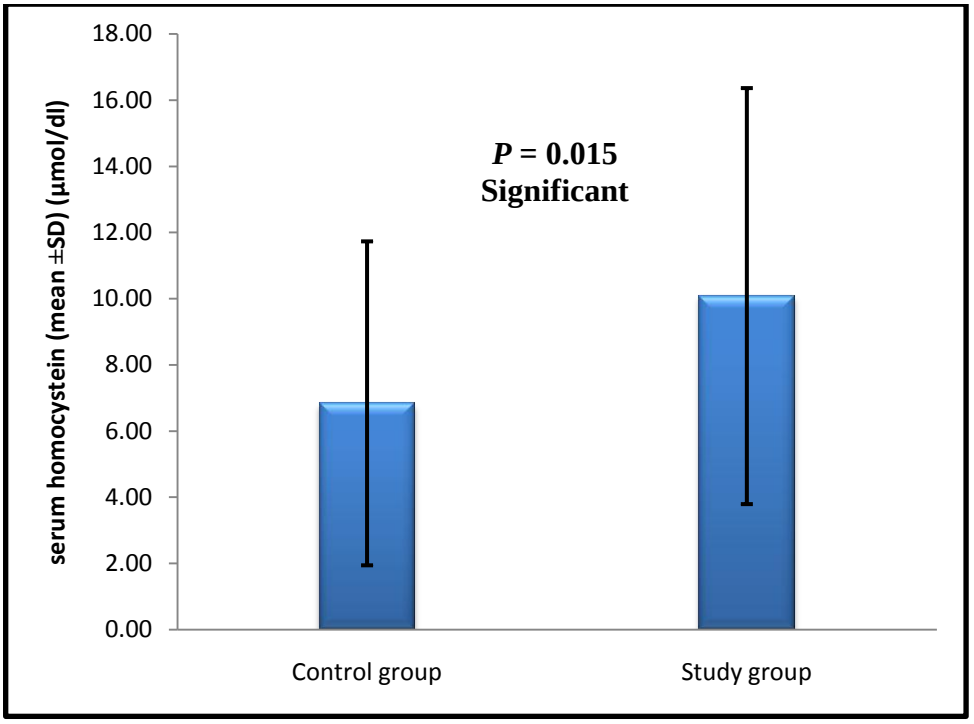

Figure 1: Bar chart showing comparison of mean fasting homocysteine level between control and study groups

Table 2: Fasting serum homocysteine level in control and study group

Fasting Serum homocysteine (µmol/dl)	Control group *n* = 38	Study group *n* = 37	*P*
Hyper (> 10.5), *n* (%)	10 (26.3 %)	18 (48.6 %)	0.046 ¥ S
Normal (< 10.5), *n* (%)	28 (73.7 %)	19 (51.4 %)	
Mean ±SD	6.84 ±4.89	10.08 ±6.28	0.015 † S
Range	2.5 -17.2	2.3 -20	

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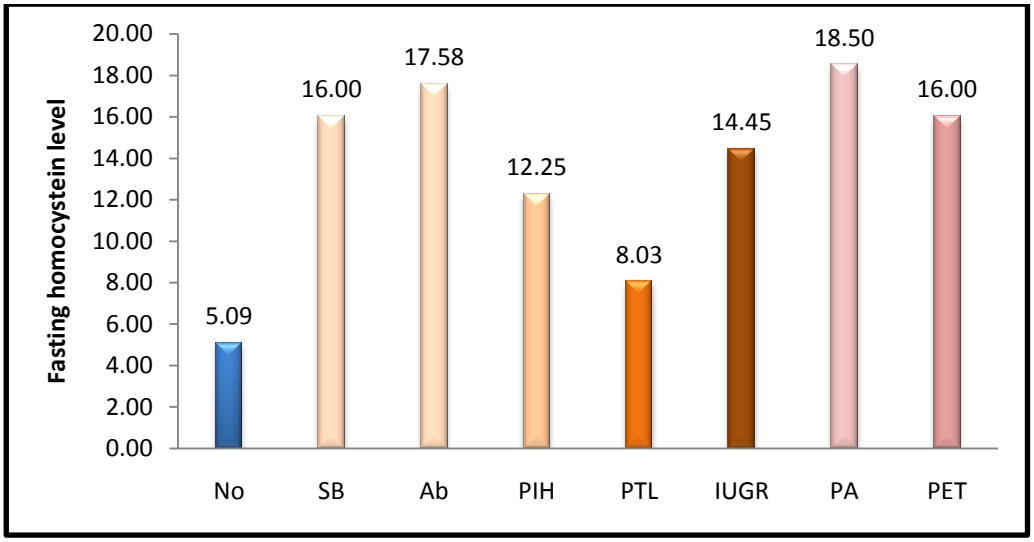

Figure 2:Bar chart showing the level of fasting homocysteine level according to complication in the entire women sample as SB(still birth), Ab(abortion),PIH(pregnancy induced hypertension),PTL (preterm labor), IUGR(intrauterine growth restriction), PA(placental abruption), PET(preeclampsia)

Discussion

Recurrent pregnancy loss has been considered as a public health concern and it is multifactorial in etiology, with considerable heterogenecity in causation with both the known and unknown etiology groups .In this study, there was no significant difference in the mean age (years) between the study group and control group ($p > 0.05$), and no significant statistical difference in the gestational age (weeks) and Body mass index (kg/m^2) between the control and case study.

This result is similar to study by Fatini, et al. (2000) which also showed no significant correlation between age, gestational age and body mass index in recurrent pregnancy loss and hyperhomocysteinemia in patients with RPL with no live birth (p >0.04)(41).

In this study also, there was significantly high level of homocysteine in patients with recurrent pregnancy loss with no live birth compared to patients with recurrent pregnancy loss with at least one live birth (48.6%, 26.3%) respectively, the ($p < 0.05$).(41)

The current study agree with astudy by Nisha B, et al (2017). showed that the mean value of homocysteine levels in the study group was 11.335±5.054µmol/dl whereas in controls it was 7.654±3.477µmol/dl with p≤0.05 and there was no statistically significant association between hyperhomocystenemia with age or body mass index in both study and control groups (42).

While Kumar ,et al (2003). study reported no significant difference in the fasting total homocysteine concentration between women with recurrent miscarriage.

In this study ,higher incidence of obstetrical complications as (IUGR, PIH, PET and spontaneous abortion) were found among the patients with RPL without live birth (18.9%,

10.8%, 2.7% and 5.4%) respectively compared to (10.5% , 5.3%, 0.0% and 5.3%) respectively among patients with RPL with at least one live birth,($p > 0.05$).

In a study by Indrani M ,et al (2017) 15.6% (5 patients) with hyperhomocysteinemia had first trimester pregnancy loss and 22.1% (15 patients) with normal homocysteine values had first trimester pregnancy loss. However, this difference was not statistically significant (46).

A study by Wendy M.White etal,(2014). showed that Hcy level elevated in 4.5% of pregnant patients with RPL without live birth that developed pre-eclampsia and it was about (1.60) folds higher than patients with RPL with at least one live birth and p<0.01(47).

Also Norma C. serrano, et al (20181)study showed that pregnant women with RPL without live birth with pre-eclampsia and pregnancy induced hypertension had higher level of homocystien than in pregnant women with RPL with at least one live birth without pre-eclampsia and pregnancy induced hypertensive disorder (48).

Lindblad B. ,et al (2005) study reported that hyperhomocysteinemia associated with increase in the risk of intrauterine growth restriction in patients with RPL without live birth in comparison to patients with RPL with at least one live birth and(p=0.02 ,OR=0.31, 95% CI 0.10-0.84 (49) .

Kiran Pandy ,et al(2012) study also established a connection between high Hcy level and IUGR and(p=0.0001)(50).

While D Anna R ,et al (2004) study found statistically significant association between elevated Hcy level in patients with RPL and the development of disorders of placental dysfunction as PIH and IUGR (p=0.0003)(51) .

Maayan-Metzger,et al.(2013).found that women with hyperhomocystienemia had high risk of preterm labour P<0.005.(52)

Michle S.Kramer,et al.(2009). Also found that hyperhomocystienemia was risk factor for spontineous pre term labour and odd ratio(OR)=o.5(0.3-0.9)(53).

Stephanie Roberg et al(2018), study showed that was no statistically significance finding between hyperhomocystienemia and subsequent pre term labour P>0.05 ,the same study by Goddijn-Wessel also found that homocystien is significantly elevated in patients who had RPL that subsequently developed placental abruption P<0.05(31%).(54).

Also astudy by O Micle (2012) et al , found that elevated homocystiene level was associated with vasculopathy and placental abruption and odd ratio=25.9,95%.(55).

The difference in these finding may be related to some limitations in number of sample of current study .

Conclusions

This study showed that the mean plasma homocysteine levels in patients with RPL is higher than in patients with good pregnancy outcome, and high homocysteine level is not only a risk factor for pregnancy loss, but also a predicator of complications like preeclampsia and IUGR.

Recommendations

Life style changes and interventions in pre- pregnancy and early pregnancy period with diet rich in fruits and vegetables and nutritional supplements containing high folic acid, vitamin B12 and B6, to ensure a healthy and successful pregnancy outcome.

Attention should be directed toward homocystien screening for women with RPL.

The data should be confirm by further study based on large population.

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