Research Article

Treatment of hyperhomocysteinemia and pregnancy outcome in patients with recurrent miscarriage

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Abstract

Background; Developmental dysplasia of the hip (DDH) means femoral head subluxation or dislocation and/or acetabular dysplasia. Management of neglected (DDH) in children after the walking age is challenging to the **Back ground:** During pregnancy hyperhomocysteinemia, can cause damage to the vascular system that support the placental function , and this damage might lead to miscarriage and other adverse pregnancy outcome.
Objective: To investigate whether lowering homocysteine level in women with recurrent pregnancy loss and hyperhomocysteinemia can improve pregnancy outcome
Patients and Method; this study ,initially include 80 women with history of three or more consecutive miscarriage between 8-20 weeks gestation Those with homocystein level >12µmol/l were include in this study (65women) ,they received folic acid 5mg per oral daily ,vitamin B6 40 mg per oral daily , vitamin B12 1000 µg per oral daily for two 2-3 months . After normalization of homocysteine 55 women completed the treatment course and same treatment was continued during pregnancy, 48 women get pregnancy and involved in this study .All participants were followed during pregnancy for any complications that might develop.
Result: out of 80 women 48 women participated in this study, their age ranged from 18-42 years.Pregnancy outcome (alive birth) was significantly improved after normalization of homocysteine level and P value is 0.001. Despite that high incidence of complications still developed the most significantly frequent complications include : 16 patients delivered small for gestational age , 14 pregnancies complicated by pregnancy induced hypertension and preeclampsia, ,8 pregnancies ended with preterm labor ,placental abruption complicated around 6 pregnancies and no congenital abnormality neither still birth were reported in this study.
Conclusion: Lowering homocysteine level would significantly improve pregnancy outcome (alive birth) in women with recurrent pregnancy loss.

Key words: Hyperhomocysteinemia, recurrent pregnancy loss, thrombophilia.

INTRODUCTION

Recurrent pregnancy loss (RPL): defined as three or more consecutive pregnancy loss prior to 20 weeks gestation [1] it affect around 1-2% of pregnant women [2]. Chromosomal anomaly of the parents, anatomical abnormality of the uterus and antiphosphlipid antibody syndrome (APS) in addition to uncontrolled diabetes and hypothyroidism [1], have been directly contributed to RPL. All other factors are considered as possible etiology , immunological abnormality and environmental factors and infection further more thrombophilia both acquired and inherited ,considered as an important causes ,which have been identified , however the exact pathophysiological mechanism of miscarriage remain unrecognized in around 50% of remaining RPL cases [2] .Thrombophilia are common disordered, more than 15% of white population carrying an inherited thrombophilic mutation [1].Thrombophilia defects that may correlated with recurrent pregnancy

loss include :hyperhomocysteinemia, activated protein c resistance associated with factor v leiden mutations ,protein s and c deficiencies and antithrombin mutation, for acquired defect hyperhomocysteinemia ,activated protein c resistance have been linked to RPL[1,3].Methionine which is an essential amino acid cannot be synthesized in the body but obtained from the diet and transport to the liver and demethylated to homocysteine for storage in the liver and utilized when needed [3,4] ,homocysteine in the liver either remethylated back to methionine, this pathway is folate and vitamin B12 dependent , other pathway is transsulfurated of homocysteine to cysteine which is vitamin B6 dependent reaction ,any deficiency in these nutrient may lead to accumulation of homocysteine in the circulation and development of hyperhomocystienemia [5] .Hyperhomocysteinemia is diagnosed when fasting total homocysteine level >12µmol /L [6] .

Scince these micronutrient (folate , vitamin B12 and B6) are essential for the methylation and transsulfuration cycle so their deficiency result in hyper homocysteinemia [7] .

Hyperhomocysteinemia has been suggested to augment hypercoagulable state of pregnancy [8,9] ,and thrombosis in maternal and fetal circulations, this considered as important mechanism of disease during pregnancy [10] ,it lead to abnormality of placental vasculature and disturbances in homeostasis and inadequate fetal circulation and linked with adverse pregnancy outcome like [8,9,10]recurrent pregnancy loss (RPL) ,preeclampsia (PE), preterm labor(PTL), abruption placenta ,intrauterine growth retardation(IUGR) [7] .

Since vitamin B6, B12 and folate are essential homocysteine metabolism ,they consistently lower homocysteine levels in research trials ,several studies have used 400-1000 µg of folic acid daily ,10-50 mg of vitamin B6 daily and50-300 µg of vitaminB12 daily for 2-3 months[11] .

Aim of the study:

To investigate whether lowering homocysteine level in women recurrent pregnancy loss and hyperhomocysteinemia can improve pregnancy outcomeage

PATIENTS AND METHODS

This study was conducted at AL-Yarmouk Teaching Hospital and extended over a period of one year, it was approved by Iraqi Board For Medical Specialization verbal consent was obtained from all patients in this study.

Our study include 80 women from outpatient clinic ,all with history of three or more consecutive miscarriage between 8-20 weeks gestation, their age was ranged between 18-42 years. Full history , clinical examination with vital signs measurement and measurement of height and weight , estimation of body mass index at time of 1st interview ,then all participant were subjected to the following investigation :Thrombophilia screen which include :serum levels protein S, antithrombin 3,activated protein C resistance due to factor v leiden mutation and homocystein level .These parameters were measured after an overnight fasting Five milliliters of Venus blood using ELISA(Abcam company .USA)with normal range (5_12µmol /L). Other investigation include antiphoshpolid antibodies (lupus anticoagulant anti cardiolepin antibody),indirect comb s test ,thyroid function test ,oral glucose tolerance test (OGTT) ,ultrasound and or hysterosalpingography when indicated

Exclusion criteria: women with positive indirect coombs test ,abnormal thyroid function test ,or thyroid antibody , uncontrolled DM or abnormal oral glucose tolerance test ,hyperprolactinemia, women with antiphosphlipid syndrome ,women with known uterine anomaly ,women with polycystic ovarian syndrome

Inclusion criteria : only 65 women with elevated fasting serum level of homocysteine > 12mmol/l ,fit the inclusion criteria were included in this study, they received folic acid 5mg per oral daily ,vitamin B6 40 mg per oral daily , vitamin B12 1000 µg per oral daily for two 2-3 months and then the homocysteine level measured again at the end of treatment period .Those whose homocysteine level was normalized were completed the study (55women)and pregnancy was achieved subsequently within 2-3 months in 48 of them .

After normalization of homocysteine same treatment was continued during pregnancy All participants were followed during pregnancy at regular intervals every 2-4 weeks or even shorter interval when indicated according to clinical situation .During each antenatal visit history was taken regarding any vaginal bleeding ,abdominal pain ,headache , measurement of their vital sign, send them for ultrasound for confirmation of viability and accurate estimation of gestational age ,assessment of fetal growth and detection of fetal abnormality .All patients sent for blood group and Rh antibody titer, complete blood picture ,coagulation profile ,liver function test ,renal function test ,OGTT according to patient situation their pregnancies were observed for any complications that might developed : pregnancy induced hypertension,preeclampsia ,Hellp syndrome , placental abruption, ,intrauterine

growthretardation ,patients were followed till time of delivery for fetal outcome whether pregnancy ended with miscarriage or preterm labor,if alive or dead fetus , any congenital abnormality and estimation of weight .

Statistical analysis: Statistical Package for Social Sciences (SPSS) version 20 for Windows 7 was used for entering coding and statistical analysis of the data. The categorical data were presented as frequency and percentages. The continuous variables were presented as mean, and standard deviations. Pearson's chi-square was used to assess the association between the categorical data of the included cases. McNemar test was used for assessing the success of treatment.

The Paired t-test was used for comparing between the homocysteine level of the study sample before and after the treatment. The level of significance in this study was of p – value less than 0.05.

RESULT

This study include 48 patients, their age was ranged from 18-42 years with mean± SD (25.2±5.7) years. Their mean body mass index ± SD (27.8±3.2 Kg/m^2) ,their parity was ranged from 0-8 ,patients gave history of miscarriage which ranged from 0-7 as show in the table 1.

Table 1: Mean of age, BMI, parity and miscarriages of the included sample, n=48.

Parameters	Mean	SD	Range
Age (years)	25.2	5.7	18-42
BMI (kg/m^2)	27.8	3.2	23.9-36.4
Parity	0.9	0.8	0-8
Miscarriage	3.5	1.2	0-7

As shown in figure 1 below ; 42 out of 48 patients had successful pregnancy outcome which is significantly higher than those with unsuccessful outcome(6 pregnancies ended with miscarriage)p<0.001.

The mean ±SD fasting homocysteine level before treatment was 19.5± 1.2µmol/l and was significantly decreased after 8 weeks of treatment mean± SD 9.6 ± (2.5) and p value was P<0.001 as shown in table 2.

Table 2: Comparison of Homocysteine level before and after the treatment, n=48

Homocysteine (µmol/L)		Paired t-test	p-value
Before treatment Mean ± (SD)	**After treatment Mean ± (SD)**		
19.5 ± (1.2)	9.6 ± (2.5)	26.621	<0.001*
***Significant at alpha <0.05**			

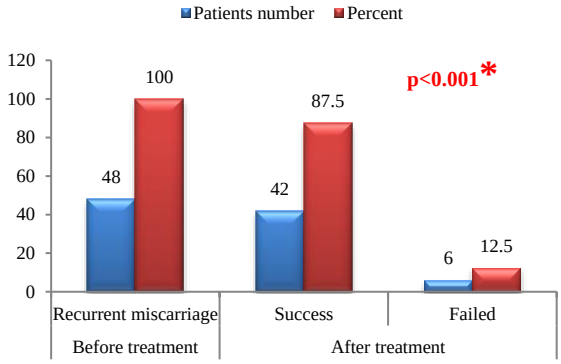

Figure 1: Included cases in the treatment and its sequels, n=48. (McNemar test= 40.02, P < 0.001)

Although 42 pregnancies ended with a live birth ,still high incidence of complications were reported as follows : sixteen patients (38.1%) delivered small for their gestational age fetuses, this represent the most significant complications reported in the treated group p0.039 ,fourteen patients out of 42 developed hypertension(preeclampsia (PE)and pregnancy induced hypertension(PIH)) , pregnancy ended with preterm labor in eight patients and six patients developed placental abruption and no congenital abnormality neither still birth were reported in this study as shown in the table 3, figure2 below.

Table 3: Comparison of complications among patients successfully treated for recurrent miscrriage, n=42.

Complications	Present No. (%)	Absent No. (%)
Low birth weight (Small for gestational age)	16 (38.1)	26 (61.9)
Hypertension(PE and PIH)	14 (33.3)	28 (66.7)
Preterm labor	8(19)	34(81)
Placental abruption	6 (14.3)	36 (85.7)
χ^2= 8.375, p-value= 0.039 (Significant at alpha <0.05)		

PE:preeclampsia, PIH:pregnancy induced hypertension

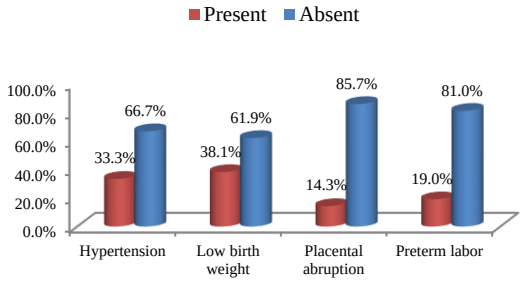

Figure 2: Comparison of complications among patients successfully treated for recurrent miscrriage, n=42.

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DISCUSSION

The mean serum level of homocysteine for patients with recurrent pregnancy loss involved in this study was 19.5±1.2µmol/l, the result of this study was in agreement with Del Bianco etal

(12), who found that the mean serum level for patients with recurrent pregnancy loss was 21±6µmol/l lower levels were reported by Hunber et al (13) 8.3µmol/l ,however this level was significantly higher than control group7.1µmol/l and P <0.093, such variation in the homocysteine level might be due to different type of food ingested i.e. large amount of methionine containing food increased homocysteine level ,and diet high in fruit ,vegetable ,vitamin c whole grain will lower homocysteine level(14,15,16).

In our study the mean fasting homocysteine level was significantly decreased after 8 weeks of treatment P<0.001 ,same result was achieved by Kiran Pandey etal(7)and Leeda etal(16)

Elevated homocysteine level considered as a risk factor for vascular disease (17),and associated with adverse neonatal outcome and pregnancy complications,so lowering homocysteine level result in significant improvement in pregnancy

outcome (18) .

As homocysteine level decreases with treatment this mean treatment has definitive role in lowering plasma homocysteine level.

In this study 87.5% of patients involved in this study continue their viable pregnancy beyond 20 weeks of gestation,this result comparable with the result of a study conducted by American society of reproductive medicine were 90.9% of their patients continued their pregnancies beyond 16 weeks gestation (6).Kiran Panday etal (7)and Leeda etal (16) and others investigators get the same result as homocysteine level lowered with treatment .

Despite this still pregnancy complications happened in our patients with previously elevated homocysteine level the most significant complication is IUGR in comparison with other complications as our study showed,

38.1% of pregnancy in the current study complicated by small for gestational age, higher percentage was reported by other study (8).

In agreement with our study Steegers-Theunissen et al (19) study reported that hyperhomocysteinemia cause 2 to 3 fold increase in the risk of intrauterine growth restriction.

Others investigators discovered a positive correlation between homocysteine level and and IUGR and this relation more evident in younger age women when compared with older age (20).

On the other hand lower percentage 10% has been reported by American society of reproductive medicine (5).

Such variation in the incidence of IUGR might explain by the effect of local factors, hereditary, food consumption that directly affects the homocysteine level.

Regarding pregnancy induced hypertension (PIH) and preeclampsia (PE), 14.3% of pregnancies in this study were complicated PE and PIH.

A positive correlate ion was found by Singh Umila etal (4)between homocysteine level and severity of PE this relation can be explained by the effect of elevated homocysteine in vascular endothelial injury ,such mechanism also involved in the pathogenesis of PE.

Others investigators found no correlation between elevated blood pressure and homocysteine concentration in the maternal blood and cord blood (21).

As in our study many authors found that increase in the homocysteine level can result in increased risk of placental abruption and infarction ,possible mechanism is the increase vascular damage and thrombosis caused by increased in homocysteine level (3) .

Toos A.W.Goddijn Wessel et al (3) who study the serum level of homocysteine in pregnancies complicated by placental abruption and infarction, he found high prevalence of hyper homocysteine in those patients.

High concentration of homocysteine has been associated with reduced nitric oxide concentration and glutathione peroxidase activity and this effect can result in preterm labour(22) other explanation by direct effect of homocysteine on the uterine muscle result in increased the frequency of spontaneous contractions of myomertium (21).

In this study 19% of pregnancies ended with preterm labor(PTL),in agreement with others(5) ,but disagree with Baumert Malgorzata etal (21) ,as they observe that the higher level of homcysteine concentration in term newborn versus preterm newborn but this differences was not found in maternal blood of term and preterm infant.

No cases of congenital malformation were reported in this study in agreement with Guere Iet al

(5),Stein Emill Vollset etal found weak non significant association between all malformation combined and hyperhomocysteinemia(17) .

Conclusion: Lowering homocysteine level would significantly improve pregnancy outcome (alive birth) in women with recurrent pregnancy loss, still pregnant women suffering from complications , the most significant complications hypertension and low birth weight.

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