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Research Article

Second Trimeter Recurrent Pregnancy Loss in Women with History of PCOS

Abstract

Recurrent pregnancy loss (RPL) is one of the most frustrating and difficult areas in reproductive medicine because the etiology is often unknown. Hyperinsulinemia ascribed to PCOS and insulin resistance (IR) seem to be a contributing factor to RPL.

The aim of this study was to assess the relationship between serum homocysteine level and insulin resistance in PCOS women with a history of send trimester recurrent pregnancy loss.

The present study was carried out on 100 non-pregnant women in the reproductive period; their age ranged from 20 to 35 years. They were classified under two groups: Group 1: women having a history of second trimester recurrent pregnancy loss with PCOs (60 women). Group 2: women having a history of second trimester recurrent pregnancy loss and non-PCOs (40 women).

We assessed plasma insulin and homocysteine (Hcy) levels in all cases. In addition, insulin resistance was determined using homeostasis model assessment (HOMA2-IR).

The results: We found that homocysteine and insulin resistance are higher in PCOS women with recurrent pregnancy loss than non PCOS women.

Conclusion: We conclude that that women with PCOS having a history of recurrent pregnancy loss had a higher serum level of homocysteine and a higher score of HOMA2-IR women without PCOS.

Introduction

Recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before the 20th week of pregnancy [1]. Among the undetermined causes, genetic predisposition to venous thrombosis caused by heritable thrombophilic defects causing elevation in total homocysteine (tHcy) levels (hyperhomocysteinemia; HHcy) or / have been described as playing a role in the pathogenesis of RPL Moreover, HHcy may lead to premature vascular disease, i.e., early damage to decide or chorionic vessels that may cause disturbed implantation of the conceptus [2].

The relationship between PCOS and recurrent miscarriage remains uncertain due to its wide variation in different studies [3]. The high prevalence of hypersecretion of LH and obesity in the syndrome contributes to the risk factor for spontaneous abortion. Hyperinsulinemia has been proposed as the pathway for the effect of obesity on some reproductive abnormalities, probably through its effect on androgen production. Some authors described insulin resistance (IR), as an integral pathogenetic feature behind the link between PCOS/obesity and the risk of RPL [4].

Furthermore, a number of studies document a possible association between IR and HHcy [5], with the incidence of the latter being increasingly a frequent finding in PCOS women [6], Thus, PCOS involves several confounding factors that may contribute, individually or in combination to RPL, the association of IR, HHcy and obesity in individuals with increased miscarriage rates has already been established [7].

RPL is found in 1–5% of couples desiring pregnancy. Despite various efforts to find an etiologic factor for RPL, 50% of these cases remain unexplained. A plethora of factors has been addressed that are associated with the pathophysiology of RPL in PCOS. The common metabolic derailments of the syndrome like obesity and IR have been implicated as individual risk factors for RPL [8].

The mechanism linking IR with RPL may be complicated. Hyperinsulinemia adversely affects the pre-implantation environment by decreasing the expression of glycodelin and IGF-binding protein-1 [9]. Which may play a role in inhibiting the endometrial immune response of the embryo, and seems to facilitate adhesion processes at the feto-maternal interface? Elevated PAI-I (an endogenous inhibitor of fibrinolysis) levels have an independent association ship with recurrent miscarriages in women in this respect [10].

Aim of the work

The aim of this work is to study the relationship between serum homocysteine level and insulin resistance in PCOS women with a history of recurrent pregnancy loss in the second trimester.

Patients and Methods

An informed consent was obtained from all participants in this research after full explanation of the study protocol. Privacy of participant and confidentiality of the data is preserved. The names of the patients were removed from the file and replaced by code numbers.

Inclusion criteria

- Diagnosis of PCOS according to Rotterdam criteria [11].
- History of recurrent pregnancy loss.

Exclusion criteria

- Ultrasonography documented uterine anatomical anomalies.
- Chromosomal defects as evaluated by peripheral blood karyotyping of both partners.
- Hypothyroidism, diabetes mellitus and positive tests for lupus anticoagulant, anticardiolipin antibodies, or other systemic disease.
- Infections: including Toxoplasma gondii, herpes simplex virus, and cytomegalovirus.
- All patients included in the study were counseled thoroughly about the procedure, including its value and hazards, and the aim of the study. After this, a written consent was obtained and signed by the patient. We did not classify the patients according to their religion or culture or race or any other unrelated points.
- The patients subjected to this study were selected from women, who attended the department of obstetrics and gynecology, Tanta University Hospital. This study extended from August 2014 to August 2015. One hundred subjects were included in this study, and they were divided into two groups:
- Sixty women having a history of send trimester recurrent pregnancy loss with PCOS.
- Forty women having a history of second trimester recurrent pregnancy loss and non-PCOs.
- All patients were subjected to the following methods: Complete history taking, clinical examination, Trans abdominal and transvaginal ultrasound of the uterus, ovaries & cervix. Blood samples were collected between 2nd and 4th days after a spontaneous bleeding episode after an overnight fast for assessment of plasma insulin and homocysteine (Hcy) and determining insulin resistance (IR) using homeostasis model assessment (HOMA2-IR) using the Oxford Diabetes Trials Unit calculator (HOMA2-IR: (fasting insulin × fasting glucose) /22.5). Patients with HOMA2-IR greater than 2.1 were classified as IR [8].

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation and UN paired t test by SPSS V.16.

Results

The results of the current investigations are summarized in three tables. Table 1 shows the comparison between the two groups regarding Age and BMI. It shows no significant difference between the PCOs patients and non-PCOs patients concerning age as ($p>0.05$). However, there is a significant difference between the PCOs patients and non-PCOs patients as related to BMI ($p<0.05$). BMI is higher in PCOs patients than non-PCOs patients. Table 2 depict the mean values of both Non-PCO and PCO groups concerning Homocysteine were 12.97± 5.17 and 26.66± 18.70 for both groups respectively which indicated significance difference ($p<0.05$). Table 3 illustrates the mean values of both Non-PCO and PCO groups concerning HOMA2-IR. It was 1.77± 0.76 and 3.51± 1.91 for Non-PCO and PCO groups, respectively, which indicated significance difference ($p<0.05$).

Discussion

Increased thrombosis caused by HHcy resulting microthrombi formation in the vessel bed of the placenta can impair sustained placental function. This micro thrombi may cause multiple placental infarctions and subsequently maternal complications of pregnancy. Apart from the thrombogenic effect of elevated Hcy on pregnancy in women with PCOS, a few recent studies have also implicated the adverse effect of high serum or follicular fluid Hcy levels on defect in folliculogenesis, embryo quality, oocyte numbers and oocyte maturation, that may have future bearings on the establishment and maintenance of pregnancy [12,13].

The present study aimed to assess the relationship between serum homocysteine level and insulin resistance in PCOS women with a history of recurrent pregnancy loss.

The current investigation shows that the serum fasting homocysteine level ranged between 5.9–47 Umol/l and 6.3 – 17 Umol/l with the mean of 26.66 ± 18.70 and 12.97±5.17 for group 1 and group 2 respectively. Homocysteine is higher in the PCO group than the non-PCO group, there was a statistically significant difference between two groups (p value <0.05).

This is in agreement with the study of Chakraborty et al. [14].

Table 1: The age and BMI of the two studied groups.

	Age		BMI	
	PCO	Non PCO	PCO	Non PCO
Mean ±SD	28.83±3.47	27.65±3.67	28.98±3.74	25.88±4.86
p-value	0.254		0.014	
Significance	NS		S	

*t-value was significant at 0.05significance level.
SD: Standard Deviation p-value: Probability value S: Significant NS: NOT Significant.

Table 2: Mean values of Homocysteine scores of PCO and Non-PCO groups.

	PCO group	Non PCO group
Mean ±SD	26.66± 18.70	12.97± 5.17
p-value	0.0025	
Significance	S	

*t-value was significant at 0.05significance level.
SD: Standard Deviation p-value: Probability value S: Significant.

Table 3: Mean values of HOMA2-IR scores of PCO and Non-PCO groups.

	PCO group	Non PCO group
Mean ±SD	3.51± 1.91	1.77± 0.76
p-value	0.0004	
Significance	S	

*t-value was significant at 0.05significance level.
SD: Standard Deviation p-value: Probability value S: Significant.

Who worked with 126 PCO women and 117 non PCO women as a control group and found that homocysteine level was significantly higher in PCO women than non PCO women (p value <0.0001) with the mean value of 13.14±.061 in PCO group and 8.39±2.22 in the non-PCO group.

Also, Mohammed et al. [15], found that the mean value of serum homocysteine among the studied group was 16.62±6.22 compared with the mean value of serum homocysteine among the non-PCO group (10.75±.039), with statistically significant difference.

Our results also agree with those of several studies that have shown elevated levels of homocysteine in a high proportion of women experiencing recurrent early pregnancy loss [16-20].

In a study of Wouters et al. [16], 21 of 100 cases with recurrent early pregnancy loss were found to have hyperhomocysteinemia. In a retrospective study by Quere and Bombard [17], 12 of 100 cases with recurrent early pregnancy loss were found to have hyperhomocysteinemia. In another study by Nelen et al. [18], found 33 of 122 cases with recurrent early pregnancy loss were found to have hyperhomocysteinemia. In a study by Kumar et al. [19], elevated homocysteine level was identified in 16.7% of women experiencing recurrent early pregnancy loss and in none of the control groups. In a study of Del Bianco et al. [20], 25% of 40 cases with recurrent early pregnancy loss were found to have hyperhomocysteinemia.

On the contrary, Khong and Hangue, 2002 [21], did not find a significant association between homocysteine and spontaneous abortion risk, they suggested that their failure to detect a significant effect of elevated homocysteine might have to be due to the relative small number of abortion patients, also it may be related to the fact that their patients were experiencing their first occurrence of spontaneous abortion.

In the concurrent study HOMA–IR level ranged between 0.682 to 6.23 in group 1 (PCO) with the mean of 3.51±1.91 while it ranged between 0.91 to 3.87 in group 2 (non PCO) with the mean of 1.77±0.76, there was a significant difference between both groups (p - value < 0.05).

This came to the agreement with the study of Chakraborty et al. [14]. Who worked with 126 PCO women and 117 non-PCO women as a control group and found that HOMA–IR level was significantly higher in PCO women than non-PCO women (p value < 0.0001) with the mean value of 2.39±0.91 in PCO group and 1.51±1.34 in the non-PCO group?

This also came to the agreement with the study of Li Tian et al. [22]. Who studied 107 women who received assisted reproductive treatment and found that IR may be a risk factor for spontaneous miscarriage?

Celik et al. [23], who studied sixty for women, with the unexplained etiology of RPL and at least two consecutive miscarriages were enrolled in the study group and were matched with 64 women who were included in the control group, statistical significance was found, so more patients had IR in the RPL group when compared with the control group.

The prevalence of IR was investigated among women with RPL in a study by Craig et al. [24], who compared 74 women with RPL to 74 normal parous female controls and studied IR in all subjects. They found significantly more women with RPL had high IR compared with controls.

While in another study, Diejomaoh et al. [25], compared IR in 35 women with RPL of unknown etiology with 30 controls and reported that IR was more prevalent in the study than in the control group, but the difference between the two groups failed to reach statistical significance.

Khattab et al. [26], examined 120 women who became pregnant while taking metformin and continued metformin use during pregnancy (experimental group) and 80 women who discontinued metformin use at the time of conception or during pregnancy (control group). Rates of miscarriage during early stages of pregnancy were 11.6 and 36.3 % in the experimental and control groups respectively.

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