

## Prophylactic Measures in Early Recurrent Pregnancy Loss in Women with Polycystic Ovary Syndrome and Hyperhomocysteinemia

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### Abstract

**Background:** The Polycystic Ovary Syndrome (PCOS) is the commonest endocrine disturbance affecting women, several complications of pregnancy in women with Polycystic Ovary Syndrome (PCOS) including recurrent pregnancy loss, the exact mechanisms that may cause RPL in PCOS patients are obscure. Several etiologies have been proposed, hyperhomocysteinemia is a common finding in women with PCOS and was found to be associated with both RPL and PCOS.

**Aim of Study:** Aim of the study is to evaluate prophylactic measures against early recurrent pregnancy loss before 20 weeks of gestation in women with polycystic ovary syndrome and hyperhomocysteinemia by either Low Dose Aspirin (LDA), LMWH or both.

**Patient and Methods:** The present study was carried out on 120 pregnant women in reproductive period, their age ranged between 20 and 35 years. They were classified into three groups, group I treated with Low Dose Aspirin (LDA) (40), group II treated with low molecular weight heparin (40) and group III treated with low dose aspirin and low molecular weight heparin (40).

**Result:** Hyperhomocysteinemia is a common finding in women with PCOS and was found to be associated with both RPL and PCOS. It was shown that combined treatment with aspirin and Low Molecular Weight Heparin (LMWH) in women with hyperhomocysteinemia improved successful pregnancy rates.

**Conclusion:** The use of clexane or Clexane with LDA prevent early recurrent pregnancy loss in patients with PCOS and hyperhomocysteinemia better than LDA alone.

**Key Words:** *Recurrent pregnancy loss – Polycystic ovary syndrome – Hyperhomocysteinemia.*

### Introduction

THE Polycystic Ovary Syndrome (PCOS) is the commonest endocrine disturbance affecting women and comprises a heterogeneous collection of signs

and symptoms that gather together to form a spectrum of a disorder with a mild presentation in some women and a severe disturbance of reproductive, endocrine and metabolic function in others [1].

A higher prevalence of several complications of pregnancy in women with Polycystic Ovary Syndrome (PCOS), compared with healthy mothers with no PCOS, has been described. These include an increased prevalence of spontaneous miscarriage, gestational diabetes, pre-eclamptic toxemia and Pregnancy-Induced Hypertension (PIH) and the birth of Small-for-Gestational-Age (SGA) babies [1].

Homocysteine is thought to exert a toxic effect on the haemostatic system perhaps indirectly by its effects on the endothelium through generation of hydrogen peroxides, depletion of nitric oxide mediated detoxification of homocysteine, and impairing endothelial cell thrombomodulin expression [2]. Increased thrombosis caused by Hhcy resulting micro thrombi formation in the vessel bed of placenta can impair sustained placental function. These micro thrombi may cause multiple placental infarctions and subsequently maternal complications of pregnancy [3].

Hyperhomocysteinemia is a common finding in women with PCOS and was found to be associated with both RPL and PCOS [4]. It was shown that combined treatment with aspirin and Low Molecular Weight Heparin (LMWH) in women with hyperhomocysteinemia improved successful pregnancy rates [5-7].

### Patients and Methods

This is a randomized prospective comparative study was conducted on (120) pregnant women

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have high level of homocystiene <15mmol/L in department of Obstetrics & Gynecology at Tanta University Hospital in a duration of one year from April 2017 to April 2018. All patients were undergoing the standard procedures of protocol. Women included in this study were classified into 3 groups:

*Group I:* Included 40 pregnant women diagnosed as polycystic ovary syndrome with high level of homocystiene <15mmol/L and suffered from recurrent pregnant loss and were treated with Low Dose Aspirin (LDA) 75mg dially.

*Group II:* This group included 40 pregnant women diagnosed as polycystic ovary syndrome with high level of homocystiene <15mmol/L and suffered from recurrent pregnant loss and were treated with low molecular weight heparin (clexane 40mg once dially).

*Group III:* This group included 40 pregnant women diagnosed as polycystic ovary syndrome with high level of homocystiene <15mmol/L and suffered from recurrent pregnant loss and were treated with Low Dose Aspirin (LDA) 75mg dially plus clexane 40mg once dially.

*The inclusion criteria were:*

- Age between 20 and 35 years old.
- Gestational age (till 20 weeks) calculated from the last menstrual period.
- Patients with PCO (PCOS was diagnosed according to the rotterdam criteria if at least two of the following criteria were present: Oligo / amenorrhoea, clinical or biochemical hyperandrogenism and PCO on Ultrasound (US).
- Patients with hyperhomocysteinemia (<15mmol/L).
- Patients with recurrent pregnancy loss (two or more consecutive miscarriages).

*The exclusion criteria were:*

- Women with any systemic disease (hypertension, diabetes mellitus, renal or hepatic diseases) was ruled out by either physical examination or patient history.
- Women have other causes of RPL including chromosomal, uterine abnormalities; anti phospholipid syndrome, inflammatory, autoimmune, and any other condition affecting homeostasis, was ruled out by either physical examination or patient history.
- Smokers and alcohol consumption.

*All patients subjected to the following:*

- An informed consent obtained from all participants in this research.
- Full history taking:
  - *Personal history:* Name, age, occupation, residency and Special habits.
  - *Husband history:* Name, age, occupation, residency, special habits and diseases.
  - *Obestatric history:* Gravidity, parity, gestational age.
  - *Past history:* Medical diseases, abdominal surgeries, drug therapy or allergy.
  - *Menstrual history:* Menarche, regularity, duration, amount and associated pain.
- *General & local clinical examination:* To exclude general diseases, local causes of RPL.
- Measurement of homocysteine by ELISA.
- *Drugs used for treatment:*
  - LDA 75mg once dially used for patients in group I.
  - LMWH 40mg once dially used for patients in group II.
  - LDA 75mg once dially and LMWH 40mg once dially used for patients in group III.
- Follow-up all patients till pregnancy complete 20 weeks gestation to evaluate treatment effect in prophylaxis against early recurrent pregnancy loss in three groups.

## Results

The present study was carried out on 120 pregnant women in reproductive period. They were classified into three groups:

- Group I treated with low dose aspirin (40).
- Group II treated with low molecular weight heparin (40).
- Group III treated with low dose aspirin and low molecular weight heparin (40).

And followed them till the age of 20 weeks of gestation to evaluate the effect of these drugs in prevention of miscarriage.

Patient's age range in all groups between 20-35 years and there were other socio-demographic data which have no significant difference as gravidity, parity and BMI.

Table (1): Age, gravidity, parity, BMI of patient of three groups.

	Group I	Group II	Group III	F.test	p-value
<b>Age:</b>					
Range	20-35	20-34	20.5-35	1.396	0.252
Mean ± SD	28.88±4.85	27.33±3.79	28.48±4.21		
<b>Gravidity:</b>					
Range	4-6	4-6	4-6	0.377	0.687
Mean ± SD	4.73±0.64	4.80±0.61	4.68±0.69		
<b>Parity:</b>					
Range	0-2	0-2	0-2	0.345	0.709
Mean ± SD	0.45±0.68	0.53±0.64	0.58±0.71		
<b>BMI:</b>					
Range	19-32	19-32	19-31	0.439	0.646
Mean ± SD	25.68±3.85	26.23±3.91	25.45±3.65		

There was no significant difference between age, gravidity, parity and BMI of patients of three groups.

Table (2): Homocysteine level of the patients in three groups.

Hemocystien	Group I	Group II	Group III
Range	15-25	15.2-25	15-25
Mean ± SD	20.28±2.09	20.08±3.20	19.43±2.82
F-test		1.051	
p-value		0.353	

The level of homocystiene in the patients of three groups show no significant different.

Table (3): Miscarriages rate in three groups.

Miscarriages	Group I (n=40)	Group II (n=40)	Group III (n=40)
N	22	10	8
%	55%	25%	20%
$\chi^2$		12.901	
p-value		0.002*	
p1	p2		p3
0.006*	0.001*		0.592

p1: Group I & Group II.

p2: Group I & Group III.

p3: Group II & Group III.

• Significant difference between three groups according to miscarriages cases.

• Significant difference between Group I and Group II ( $p=0.006$ ).

• Significant difference between Group I and Group III ( $p=0.001$ ).

• Non significant difference between Group II and Group III ( $p=0.592$ ).

### Discussion

The prevalence of PCO morphology among women with RPL is thought to be as high as 40%, although there are reports about higher prevalence. Using a combination of clinical findings and Ultrasound (US) or biochemical features [8,9].

The exact mechanisms that may cause RPL in PCOS patients are obscure. Several etiologies have been proposed, related to the pathophysiology, endocrinology, and metabolic disturbances in PCOS. Among these are obesity, insulin resistance or hyperinsulinemia, thrombophilia-associated

disorders, elevated LH, and hyperandrogenism [10,11].

Homocysteine is thought to exert a toxic effect on the haemostatic system perhaps indirectly by its effects on the endothelium through generation of hydrogen peroxides, increased thrombosis caused by Hhcy resulting micro thrombi formation in the vessel bed of placenta can impair sustained placental function. These micro thrombi may cause multiple placental infarctions and subsequently maternal complications of pregnancy [12,13]. Hyperhomocysteinemia is a common finding in women with PCOS [14] and was found to be associated with both RPL and PCOS [4]. It was shown that combined treatment with aspirin and Low Molecular Weight Heparin (LMWH) in women with hyperhomocysteinemia improved successful pregnancy rates [5-7].

The present study aimed to detect prophylactic effect of low dose aspirin and low molecular weight heparin against early recurrent pregnancy loss in patients with PCOS and hyperhomocysteinemia.

It was carried out on 120 pregnant women in reproductive period. There were classified into three groups: Group one womens treated with Low Dose Aspirin (LDA) 75mg once dially (40 women). Group two women treated with LMWH 40mg once dially (40 women). Group three womens treated with LDA and LMWH.

This study included women age ranged between 20-35, 20-34 and 20.5-35 years with mean of 28.88 ±4.85, 27.33±3.79 and 28.48±4.21 years for group 1, group 2 and group 3 respectively. Ther was no statistical significant difference between three groups regarding age. The included women in this study were with BMI ranged between 19-32, 19-32 and 19-31 with mean of 25.68 ±3.85, 26.23±3.91 and 25.45±3.65 for group 1, group 2 and group 3 respectively. Ther was no statistical significant difference between three groups regarding BMI.

In the present study serum fasting homocysteine level ranged between 15-25, 15.2-25 and 15-25 Umol/l with mean of 20.28±2.09, 20.08±3.20 and 19.43±2.82 for group 1, group 2 and group 3 respectively. Homocysteine level is high in three groups, there was no statistical significant difference between three groups regarding homocysteine level lastly.

The use of clexan or Clexan with LDA prevent early recurrent pregnancy loss in patients with PCOS and hyperhomocysteinemia are better than LDA alone.

**Conclusion:**

The use of clexane or Clethane with LDA prevent early recurrent pregnancy loss in patients with PCOS and hyperhomocysteinemia better than LDA alone.

**Disclosure:**

We announce that we did not get any funds from whatever individual or establishment. If the patient refused to finish the field, she was taken out and replaced by another one from who are satisfying the inclusion criteria of the survey. We did not classify the patients according to their religious belief or civilization or race or any other unrelated points. The authors declare no conflicts of interest in this study.

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None.

**Conflict of interest:**

Author declares that there is no conflict of interest.

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## الإجراءات الوقائية لحالات تكرار الإجهاض المبكر في السيدات اللاتي يعانين من متلازمة تكيس المبايض مع إرتفاع مستوى الهرموسيستاتين بالدم

يعرف فقدان الحمل المتكرر بأنه تكرار الإجهاض مرتين أو أكثر بصفة متتالية قبل الإسيوع العشرين للحمل ويمثل نسبة من ٢-٤٪ بين الأزواج وتعتبر التشوهات الكروموسومية للأباء ومشاكل السيولة عند الأم والتشوهات الرحمية والأجسام المضادة للفوسفوليبيد ومتلازمة تكيس المبايض من الأسباب المباشرة للإجهاض المتكرر.

متلازمة تكيس المبايض هي واحدة من أشهر الأمراض الهرمونية المرتبطة بالسمنة وعدم إنتظام الطمث ومقاومة الأنسولين وتأخر الإنجاب وتعتبر واحدة من أكبر أسباب تأخر الحمل. المرضى الذين يعانون من متلازمة تكيس المبايض لديهم زيادة في نسبة حدوث إجهاض خلال الثلاث أشهر الأولى للحمل يتراوح ما بين ٢٥ إلى ٧٣٪.

تعتبر مادة الهرموسيستاتين حمض أميني من النوع ألفا. وإرتفاع مستوى مادة الهرموسيستاتين في الدم يجعل الشخص أكثر عرضة لإصابة الخلايا البطانية وإلتهاب في الأوعية الدموية. وقد إرتبط فرط الهرموسيستاتين في الدم مع حدوث جلطات الدم والنوبات القلبية والسكتات الدماغية، وكذلك إرتبط بفقدان الحمل المبكر.

وعلاوة على ذلك فإن إرتفاع نسبة الهرموسيستاتين بالدم قد يؤدي إلى أمراض وعائية مبكرة ومثال على ذلك الإصابة المبكرة للأوعية الدموية للمشيمة والتي تؤدي إلى إختلال بزراع الحمل المبكر. التحاليل المعملية لمادة الهرموسيستاتين تحدد نسبته في مصل الدم بنظام توهج الفحص الآلي ونسبته ١٥ملى مول لكل لتر.

والهدف من هذا البحث هي الوقاية من الإجهاض المتكرر في حالات تكيس المبايض مع إرتفاع الهرموسيستاتين بإستخدام الهيبارين صغير الجزيئات بالحقن تحت الجلد يوميا وإستخدام الأسبرين بجرعات صغيرة يوميا.