Thromboprophylaxis in women with unexplained consecutive recurrent miscarriages

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ABSTRACT

Objective: To **compare the effect of low dose aspirin and enoxaparin on pregnancy in women with recurrent miscarriage.**

Patients& Methods**: Randomized controlled trail, conducted in Basrah Maternity and Child Hospital during the period from January 2012 till April 2013. Participants were 221 pregnant women aged 18-41 years with history of at least 2 previous miscarriage without apparent causes. They were divided into 2 groups; the first group included 111 were given enoxaparin and the second group involved 108 which were given aspirin.**

Results**: In both groups (75%) of patients had negative serological test for thrombophilia. Enoxaparin group had higher significant incidence of term delivery (86%) with less incidence of preterm delivery (4.5%) and less early pregnancy loss (8%).**

No significant differences in obstetrical complication but higher incidence of abdominal delivery in both groups.

Higher incidence of postpartum hemorrhage in the enoxaparin group in comparison with aspirin group and no significant systemic adverse effect of enoxaparin were noticed on the first group.

Conclusion**: Since postpartum hemorrhage is treatable, low molecular weight heparin is safe and effective for treating, preventing thrombosis and achieving successful pregnancy.**

Key words: Aspirin, Enoxaparin, Miscarriage, Thromboprophylaxis,

موانع تخثر الدم في النساء المصابات بالاجهاض المتكرر غير المفسر

الهدف: دراسة مقارنة بين استعمال الجرع القليلة من دواء الاسبرين ودواء الاينوكساباربن اثناء الحمل للوقاية من الاجهاض المتكرر من الحوامل.

المرضى وطرق العمل: اجريت دراسة سرية عشوائية في مستشفى الولادة والطفل في البصرة خلال الفترة بين كانون الاول 2012 ونيسان 2013. المشاركون221 امرأة حامل ذوات الاعمار 18–41 سنة ويعانون من اسقاطين سابقة بدون وجود اسباب واضحة. تم تقسيمهم الى مجموعتين؛ تشمل المجموعة الاولى 111 مريضة اعطين دواء الاينوكساباربن بينما اعطيت المجموعة الثانية (108 مريضة) دواء الاسبرين.

النتائج: لقد تبين ان 75% من النساء الحوامل لديهن نتائج ايجابية لعدم وجود اضطراب في عمل الصفيحات الدموية وقد لوحظ كذلك ان مجموعة الاينوكساباربن هي الاعلى نسبة في الولادة في الشهر التاسع (86%) والأقل نسبة في فقدان الحمل اثناء الاشهر الاولى (8%). لايوجد فرق في مضاعفات الحمل والولادة بين المجموعتين. سجلت اعلى نسبة في الاصابة بنزف مابعد الولادة أي مجموعة الاينوكساباربن اكثر من مجموعة الاسبرين.

الاستنتاجات: نظراً لامكانية معالجة النزف بعد الولادة ، لذا يعتبر دواء الاينوكساباربن امين في الاستعمال وله تأثير جيد في معالجة ومنع حدوث تخثر الدم وبالتالي المحافظة على الحمل

INTRODUCTION

Miscarriage is defined as termination of pregnancy before 20 weeks gestation with no evidence of life.[1,2] WHO defines miscarriage in 1977 as the expulsion of fetus weighing 500gm or less, corresponding to about 20 to 22 weeks gestation.[3,4] It is well established that overall 15% of all clinically recognized pregnancies are ended with miscarriage.[5,6] these are increased to 31-50%if subclinical pregnancies are included.[7,8] Most pregnancies are lost in early weeks than at any other stage of gestation.

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Three of main categories of early pregnancy loss are spontaneous miscarriage, induce miscarriage and ectopic pregnancy.[1] The term spontaneous miscarriage refers to the loss of a fetus during pregnancy due to naturally occurring events, not elective or therapeutic miscarriage procedure.[8] Spontaneous miscarriage can be classified further as sporadic or recurrent. Spontaneous miscarriage occurs in about 15-20% of all pregnancies[9,10], and the chance for a subsequent pregnancy loss increase with each successive miscarriage.[11] Approximately 80% of all spontaneous miscarriage occur before 12 weeks and called early miscarriage, the rest occur between the thirteen and twenty fourth weeks called late miscarriage. The risk for spontaneous miscarriage is higher in women over age 35 years[12], in women with systemic disease (such as diabetes or thyroid dysfunction), and in women with a history of three or more prior spontaneous miscarriage.[13] Recurrent spontaneous miscarriage is healthcare concern occurring in approximately 7,500 couples each day worldwide.[14] Data delivered from epidemiologic studies indicate that the risk of subsequent pregnancy losses 30% after three and 40% after four consecutive spontaneous miscarriage.[5] The occurrence of three or more spontaneous consecutive pregnancy losses defines recurrent spontaneous miscarriage.[14] It is one of the most distressing problem in obstetric, particularly in those who have no successful pregnancies.[12] It affects 1-2% of women.[15] This definition is being modified to mean two consequent outcome are similar for women having two or three losses.[2] Since women with recurrent pregnancy failure can experience a variety of clinical manifestation it is unlikely to be a single etiology.[17] The aim of the study primarily is to evaluate the efficacy and safety of anticoagulant agents such as aspirin and low molecular weight heparin (LMWH) in women with a history of at least two or more unexplained miscarriage. Secondly is to identify which thromboprophylactic treatment is best to prescribe to women with recurrent miscarriage without known cause or thrombophilia.

PATIENTS AND METHODS

Randomized controlled trail, conducted in Basrah maternity and child hospital. The enrolment was performed from January 2012 till April 2013. The trial was approved by written informed consent which was obtained from all patients prior to randomization. Also, the work has been approved by the Ethical Committee of the College of Medicine, University of Basrah, Iraq.

Types of Participants

Participants were 221 pregnant women aged 18-41 years with history of at least 2 recurrent miscarriages without apparent causes. All patients were interviewed about their medical, obstetrical, history and family history. Exclusion criteria includes presence of polycystic ovarian syndrome which is diagnosed either by history or TV ultrasonography, abnormal uterine cavity and endocrine abnormality such as diabetes, thyroid disorder, cardiac disorder, multiple pregnancies, bleeding tendency, parents karyotyping abnormalities and miscarry due to fetal malformation or result from complication of infection.

All patients were checked out for:

- lupus anticoagulant LAI (6-12) weeks apart
- AnticardiolepinIgG and IgM (16-12) weeks apart
- Antinuclear antibodies 12 week apart before pregnancy.
- Serological screen for Toxoplasmosis, Cytomegalovirus, Herpes simplex.

Baseline complete blood picture, urine routine examination, blood sugar, blood grouping, bleeding time, clotting time, prothrombin time and activated partial thromboplastin time were estimated to all participants. All selected patients were given oral folic acid and iron daily and progesteron orally during antenatal period, whether conceived spontaneously or with

treatment. Patients were divided into 2 groups after a positive HCG urine test and before seven weeks gestation. First group received enoxaparin 2000 by subcutaneous injection daily till 34 weeks (platelets were checked at every visit for heparin-induced thrombocytopenia). The second group received 100 mg aspirin till 35 weeks. At the first visit a physical examination, body mass index (BMI) and blood pressure were performed. Follow up was performed by their own obstetrician at 8, 10, 14, 18, 24, 28, 32 and 36 weeks of gestation. During all visits an ultrasound was done and patients were asked for adverse effect and vaginal bleeding complications. Fetal growth was monitored by fundal height measurement and serial ultrasounds. Doppler umbilical wave flow velocity was studied for fetuses with suspected intrauterine growth retardation. For 2 patients aspirin and enoxaparin were discontinued earlier due to abortion, preterm labor, and intrauterine growth retardation preeclampsia leading to premature delivery. Statistical analysis: Data were collected and analyzed using SPSS version 10. Chi-sequare (X^2) or Fisher tests were used to detect the relations between various variables. P-value < 0.05 was considered as statistically significant.

RESULTS

In the whole group the median number of miscarriage was 3(2-10) no significant difference between the two groups with respect to gestational age, parity and body mass index (Table-1).Two women in the enoxaparin group discontinued taking their medication and excluded from the study.

Table 1. Demographic characteristic of the studied groups.

Characteristic features	Enoxaparin n=111	Aspiringroup n=108	P- Value
Maternal age (Years) mean rang	32.5 ± 4.1 22 - 40	32.0 ± 4.3 22 - 40	NS
Body mass index (kg/m^2) **Range**	23.4 ± 3.7 18 - 36	25.4 ± 5.3 17- 40	NS
Blood pressure (mmhgcystolic / diastolic)	117 ± 11.3 70 ± 9.15	114 ± 11 70 ± 6.08	NS
Previous miscarriage			
Median	3.9 ± 1.4	3.0 ± 1.8	NS
Range	(2 - 10)	(2-7)	NS
First trimester miscarriage	76 (68.4)	76 (65.7)	NS
2nd trimester miscarriage	35 (31.5)	37 (34.21)	NS
Gestational age at time of treatments (days)	35.8 ± 4	36.8 ± 4	NS
Parity			
Zero	59 (53.1)	51 (47.2)	NS
P1	29 (26.1)	25 (23.1)	NS
≥ P2	23 (20.7)	21 (19.4)	NS

Thirty seven patients (18.5%) out of 219 patients anticardiolopin antibodies positive, while 75% were negative for serological tests (Table-2).

Table 2. Serological status of the patients.

Serological tests	No.	%
Anticardiolopin antibodies (positive)	37	18.5
Lupus anticoagulant (positive)	2	1.3
ANA Positive	2	1.3
Antiphospholipid antibodies	18	9.1
Serological (negative)	160	75

Eighty six (86%) of the enoxaparin group had term delivery after 37 weeks and 4.5% had preterm delivery which is significantly higher than the aspirin group (Table-3). Early pregnancy loss is higher in the aspirin group (27.2%) which is significantly higher than that of the enoxaparin group (8.1%) (Table-3).

Table 3. Outcome of pregnancies

Complications	Enoxaparin group N 111	%	Aspirin group N108	%	P value
Early pregnancy loss	9	8.1%	23	27.2%	0.01
Live birth at term (37 weeks)	96	86%	75	69%	0.01
Preterm deliveries 28-36 weeks	6	4.5%	9	8.5%	NS

Abdominal delivery is the higher mode of delivery in both groups, vaginal delivery is significantly higher among enoxaparin group than aspirin group (Table-4).

Table 4. Mode of delivery of both groups.

Mode of delivery	Enoxoprin group N %	Aspirin N %	P value
C. S	61	76	NS
Vaginal delivery	41	19	0.01

Table (5) shows no significant difference in the incidence of complication between the two groups except perinatal death is significant among the aspirin group.

Table 5. Pregnancy complications

Complications	Enoxaparin group N	%	Aspirin group N	%	P value
Preeclampsia	5	4.5	9	8.3	NS
Abruptio placentae	0	0	0	0	NS
Gestational age at time of delivery	38.9 ± 1.9 (32 - 42)		38.6 ± 27-42		NS
Birth weight	345.5 ± 6.4		3345 ± 7		NS
Intrauterine growth restriction	6	5.4	11	16.1	NS
Perinatal death	1	1.1	3	2.7	0.01
Admission to NICU	4	3.6	7	6.4	NS

The adverse effect of treatment includes dminor vaginal bleeding during first, second, third trimester with no significant difference was found between the two groups (Table-6). Four women in the enoxapar in group were needed blood transfusion in comparison to 9 patients of the aspirin group. Minor side effect such as skin reaction at site of injection, bruising, itching and nasal bleeding were reported just in few women.

Table 6. Bleeding complication.

Bleeding	Enoxaparin group N %		Aspirin group N %		P value
First trimester bleeding	5	4.9	6	5.5	NS
Second trimester bleeding	2	1.8	1	0.8	NS
Third trimester bleeding	-	-	1	0.8	0.01
Postpartum hemorrhage	31	27.9	13	12.2	0.01
Blood transfusion	4	3.8	0	0	0.01
Skin reaction	2	1.81	0	0	0.01

DISCUSSION

The study was conducted to identify which thromboprophylactictreatment is best to prescribe for women with recurrent miscarriage without known cause or with thrombophilia. Patients were matched by age and demographic features. Twenty five percent of the studied group were positive for thrombophilia which is higher than that reported by other study where 16% was found for inheritedthrombophilia in their trial.[18] The use of thromboprophylaxis during pregnancy appears to be safe for mother and child as was found in a large systemic review.[19] Our study, however, was found an increase in the risk of post-partum blood loss and more blood transfusion in the enoxaparin group in contrast to other study which was proved that LMWH reduced the risk of bleeding.[20] This is possibly due to the active management for labor. Anyhow, post-partum bleeding can be treated anyway. The observed rate of allergic skin reaction (1.8%) is higher than that reported by Bates *et al*[21] which is observed (0.6%). Other study had reported that allergy skin reactions were significantly more common with the use of delteparin and nadroparin than with enaxoparin.[22] It is known that the risk or heparin thrombocytopenia is lower in LMWH user in comparison to long acting heparin.[22] The effect of LMWH on rate of fetal and neonatal loss and prematurity and rate of term delivery were studied and reported: eighty six (86%) of enoxaparin group had term delivery which is significantly higher than aspirin group (69%). This successful pregnancy rate is in agreement with trial by Brenner *et al*.[23] that used either an injection of enoxaparin 40-80mg subcutaneously once daily or 75mg aspirin daily and achieved 93% live birth rate and 9% respectively but is in contrast with other study.[21] In the present study higher mode of delivery is abdominal delivery in both groups and this can be explained because the pregnancy is precious which is in agreement with Brenner *et al*[23] who observed 72% delivered vaginaly and 28% by cesarean section. In the Department of Obstetrics and Gynecology, University of Sheffield, England, enoxaparin was used as 20mg subcutaneous dose which led to 80% live birth rate, 5 underwent preterm delivery but no perinatal mortality was observed.[24] In conclusion, it has been confirmed that LMWH is safe and effective for treating and preventingthrombosis in pregnancy in order to prevent miscarriage and achieve a successful pregnancy. It is important that clinicians continue to justify the use of LMWH in pregnancy for prevention of adverse pregnancy outcome.

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