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Low dose aspirin versus low dose aspirin plus omega 3 versus low molecular weight heparin in treatment of unexplained recurrent miscarriage

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Abstract--Introduction: recurrent miscarriages are the loss of 3 or more consecutive pregnancies before the 20th week of gestation. It is classified into primary and secondary. Objective: to evaluate the effectiveness of low dose aspirin vs. low dose aspirin and omega 3 vs. LMWH in treatment of unexplained recurrent miscarriage. Materials and methods: This comparative prospective research was conducted on 60 1st trimester pregnant female with a history of two or more unexplained spontaneous consecutive abortion aged from 18 to 36 years old with gestational age (5-7 weeks) and single intrauterine pregnancy. Patients were subdivided equally into 3 groups: Group A: received a daily dose of 75mg of aspirin, group B: received a daily dose of 75 mg of aspirin in addition to 300mg of omega -3 fatty acids and group C: received a daily dose of 4000 IU of enoxaparin. Results: There was an insignificant difference in pregnancy outcome among the three groups. 12 (60%) cases in group A, 15 (75%) cases in group B and 14 cases in group C completed 20 weeks of pregnancy. Cost of therapy in group C was significantly higher than group B and group A (p <0.001) and was significantly higher in group B than group A (P <0.001). Conclusions: There were no differences between daily doses

of 75mg of aspirin, 75 mg of aspirin in addition to 300mg of omega -3 fatty acids and 4000 IU of enoxaparin in improving of pregnancy outcome and decreasing abortion rate.

Keywords---Miscarriage, Aspirin, Omega 3, LMWH.

Introduction

Recurrent miscarriages are the loss of three or more consecutive pregnancies before the 20th week of gestation. It is classified into primary (in women without a previous live-born infant) and secondary (in women with at least one previous live-born infant) (El Hachem et al., 2017). Omega-3 fatty acids are a part of all cell membranes and are precursors of locally produced hormones that play essential and multifaceted roles in human reproduction. It is believed that omega3 affect the reproductive process through several mechanisms. It seems that omega3 supplementation can provide a vasodilatory effect by means of modulation of prostaglandins secretion. In particular, it has been reported that omega3 enhance the prostacyclin/thromboxane ratio through the reduction of thromboxane A2 production at the platelet level. Accordingly, different studies suggest that nutritional omega 3 sufficiency is an effective and inexpensive strategy for optimizing pregnancy outcome. In fact, omega3 supplementation has been associated with a reduced risk of pregnancy induced hypertension, preterm delivery, and fetal growth restriction (Coletta, Bell, & Roman, 2010).

Aspirin (acetylsalicylic acid) is classified among the nonsteroidal anti-inflammatory drugs (NSAIDs). These agents reduce the signs and symptoms of inflammation and exhibit a broad range of pharmacologic activities, including analgesic, antipyretic, and antiplatelet properties (Cadavid, 2017). Low dose aspirin (e.g., 75mg/day) are sufficient to irreversibly acetylate serine 530 of COX-1, inhibiting platelet generation of thromboxane-A2, resulting in an antithrombotic effect (Cadavid, 2017).

The clinical usage of low molecular weight heparin (LMWH) has been proposed to enhance placental function by improving blood flow to the implantation site and decreasing the occurrence of thrombotic lesions, LMWH has been utilised in clinical practise to reduce pregnancy problems. Preeclampsia, intrauterine growth retardation (IUGR), and unexplained recurrent pregnancy loss may all be prevented with the use of LMWH (Papadakis et al., 2019).

Because of its low molecular weight, Enoxaparin hinders the conversion of fibrinogen to fibrin and speeds up the production of anti-trypsin three and thrombin. It also causes thrombin to be inactivated. Thrombus-preventative properties, as well as a role in preventing endothelium damage, are provided via binding to antiphospholipid antibodies and gamma interferon antibodies, respectively, in the mother and embryo (Nazari, Ghaffari, & Ebadi, 2015). The aim of this study was to evaluate the effectiveness of low dose aspirin versus low dose aspirin and omega 3 versus low molecular weight heparin in treatment of unexplained recurrent miscarriage.

Materials and Methods

This comparative prospective research was carried out on 60 women with unexplained recurrent miscarriages aged from 18 to 36 years old, first trimester pregnant female with a history of two or more unexplained spontaneous consecutive abortion, gestational age (5-7 weeks) and single intrauterine pregnancy. An informed written consent was obtained from the patient or relatives of the patients. The study was done after approval from the Ethical Committee Tanta University Hospitals.

Exclusion criteria were congenital anomalies of female genital tract (bicornuate uterus) and diseases like endocrinal diseases, renal, cardiac, hepatic infectious diseases or immunological diseases like (anticardiolipin, antinuclear and anti-phospholipids antibodies). Patients were subdivided equally into three groups:

Group A: 20 patients received a daily dose of 75mg of aspirin

Group B: 20 patients received a daily dose of 75 mg of aspirin in addition to 300mg of omega -3 fatty acids

Group C: 20 patients received a daily dose of 4000 IU of enoxaparin.

All patients were subjected to full history taking, full general, abdominal examination and investigations related to recurrent abortion including [routine laboratory investigations (CBC, Rh and complete Urine analysis), immunological investigations (anti cardiolipin, antinuclear and anti-phospholipids antibodies), hormonal investigations (thyroid function test, fasting and postprandial blood sugar, HbA1C, thrombophilia), hysterosalpingography and transvaginal ultrasound to exclude female genital anomalies.

Folic acid (400mg) and progesterone (100mg) were taken twice daily by all three groups. To monitor the health of the foetus, a Samsung ultrasound machine (model H60, uss-H60, uss-H60Nf4K/WR) was used to do foetal ultrasounds at (5-7) weeks and every two weeks afterwards until 20 weeks of gestation (Samsung, Korea with 3.5-MHz convex probes). Until 20 weeks of pregnancy, all patients were required to attend weekly prenatal care clinic appointments.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 25 was used for the statistical analysis (IBM Inc., Chicago, IL, USA). In order to compare the two groups, the F test and post hoc (Tukey) test were used to compare the means, SDs, and ranges of quantitative variables (such as age). The Chi-square test was used to do statistical analysis on categorical variables (such as gender). In the case of the two-tailed P value, significance was defined as being less than 0.05.

Results

There was an insignificant difference in age, BMI, gravidity and parity among the three groups. Table I

There was an insignificant difference in previous abortion, gestational age, outcome (completing 20 weeks) and duration before abortion among the three

groups. 12 (60%) cases in group A, 15 (75%) cases in group B and 14 cases in group C completed 20 weeks of pregnancy. Table II

The cost per day in group A was 0.3 pound, in group B was 3.9 pound, and in group C was 67.5 pound. Cost of therapy in group C was significantly higher than group B and group A ($p < 0.001$) and was significantly higher in group B than group A ($P < 0.001$). Table III

Discussions

Abortion may be caused by a variety of causes. Even though the cause of the majority of recurrent miscarriages (50-60%) is still unknown, these include those caused by genetic abnormalities, anatomical malformations, endocrinological disorders, and immunological disorders such as antiphospholipid antibody syndrome (Ford & Schust, 2009).

This study found that there were no significant differences in the demographics of the two groups in terms of age, BMI, gravidity, parity, past abortion, and gestational age. Elmahashi et al. (Elmahashi, Elbareg, Essadi, Ashur, & Adam, 2014) Age, past miscarriage rates and gestational ages were not significantly different between the two groups at the time of enrollment in the study. Regarding efficacy of study medications, in terms of the research result (completing 20 weeks), there was no statistically significant difference between the study groups, with a P value of 0.583. Sixteen patients (60%) in group A completed their study, while eight patients (40%) did not. Fifteen patients (75%) completed their study, while five patients (25%) did not. Fourteen patients (70%) completed their study, while six (30%) did not.

Similarly, Wojcieszek et al. (Wojcieszek et al., 2018) who found that LDA and LMWH were shown to have no effect on stillbirth, infant mortality or other adverse perinatal outcomes when compared to placebo. Our results were not in line with Grandone et al. (Grandone et al., 2021) who found in women without thrombophilia that LMWH prophylaxis was shown to have a significant and independent effect on the chance of a live birth. Women with inherited or acquired thrombophilia may also have contributed to the disparity in results. There was no statistically significant difference between the three groups when it came to the period leading up to an abortion, according to our findings.

In line with our results, Wojcieszek et al. (Wojcieszek et al., 2018) reported after reviewing nine trials including 1228 women with unexplained recurrent miscarriage, with or without inherited thrombophilia, that evidence of a beneficial effect of anticoagulants on rates of livebirth among this population was lacking. In consistent with our findings, Yuksel et al. (Yuksel et al., 2014) reported that abortion week showed insignificant difference between LMWH group and the control group.

Limitations: COVID 19 pandemic, blinding of researcher wasn't performed, side effects of study medications, relatively small sample size and there was no control group, however recruiting patients with recurrent miscarriage and depriving them from suitable treatment violates the ethical consideration.

Conclusions

In cases of unexplained recurrent miscarriage, there were no differences between daily doses of 75mg of aspirin, 75 mg of aspirin in addition to 300mg of omega -3 fatty acids and 4000 IU of enoxaparin in improving of pregnancy outcome and decreasing abortion rate.

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Tables:

Table (I): age, BMI, gravidity and parity among the three groups

	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	P value
Age (years)	27.7 ± 3.83	29.65 ± 4.36	26.9 ± 3.97	0.097
BMI (kg/m ²)	25.66 ± 5.23	26.27 ± 5.09	26.65 ± 5.22	0.831
Gravidity	4.9 ± 1.97	5.7 ± 1.81	4.55 ± 1.7	0.135
Parity	0.2 ± 0.41	0.4 ± 0.5	0.15 ± 0.37	0.160

Data are presented as mean ± SD, BMI: Body mass index

Table (II): abortion, gestational age at enrolment, outcome and duration before abortion among the three groups

	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	P value
Abortion	3.7 ± 1.78	4.3 ± 1.66	1.4 ± 1.67	0.243
Gestational age at enrollment (w)	5.85 ± 0.81	6.05 ± 0.89	6.25 ± 0.72	0.302
Outcome	Completed 20 weeks	15 (75%)	14 (70%)	0.583
	Didn't complete 20 weeks	5 (25%)	6 (30%)	
Duration before abortion	12.62 ± 3.62	14.6 ± 1.14	13.67 ± 2.5	0.480

Data are presented as mean ± SD or frequency (%)

Table (III): cost of therapy per day and total cost of therapy among the three groups

	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	P value
Cost per day (EGP pound)	Aspirin	0.3	0.3	---
	Omega-3	-	3.6	
	Enoxaparin	-	-	
	Total per day	0.3	3.9	
Total cost of therapy	29.72 ± 1.7	381 ± 24	6497 ± 339	<0.001*
	P1: <0.001*, P2:<0.001*, P3:<0.001*			

Data are presented as mean ± SD or frequency (%)