Enoxaparin and aspirin versus aspirin alone therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS)

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Abstract

Recurrent pregnancy loss (RPL) or habitual miscarriage is the loss of three or more consecutive pregnancies before or during the 20th week of gestation. The most important association between gestational loss and autoimmune phenomena is the presence of antiphospholipid antibodies (APA) represented by the lupus anticoagulants and or anticardiolipin antibodies (Antiphospholipid Antibody Syndrom). The antiphospholipid syndrome (APS) is an acquired autoimmune . The clinical features are thrombosis (venous, arterial and microvascular) and/or pregnancy complications; the most prominent of which is recurrent abortion. It is important to recognize the syndrome and to institute appropriate therapy to reduce the risk of recurrent pregnancy loss. Many treatment regimens introduced. Today anticoagulants and aspirin treatment is emerging as the treatment of choice for the APA syndrome associated with recurrent pregnancy loss.

Aim of the study

To investigate the efficacy of combined aspirin and low molecular heparin therapy as opposed to aspirin alone in the management of immunological recurrent abortion

Patients and methods

This is a prospective study of 70 female patients presented with recurrent pregnancy loss (RPL) or habitual miscarriage (loss of three or more consecutive pregnancies before the 20th week of gestation) and repeatedly positive test results for anticardiolipin and or lupus anticoagulant. The duration of the study was 3 years (February 2013-February 2016); the cases were presented both to the

private clinic and the hospital (Al-Batool teaching hospital). The patients were randomly put in two groups. In both groups the patients started receiving treatment as soon as they had a positive result on a pregnancy test. Group A (47 patients), the women given both low molecular weight heparin (LMW self-administered injection; 4000 IU/day) plus low-dose aspirin (81 mg/day). Group B (23 patients) assigned to receive aspirin alone (81mg/day). From 20th week of gestation, pregnancies were monitored by serial ultrasonography and Doppler studies of the umbilical artery circulation, fetal growth and wellbeing. The husbands were all fertile and had normal sperm parameters.

Results

There was a highly significant difference between Groups A and B in the rate of miscarriages (4 miscarriage in Group A (9%) versus 8 miscarriages in Group B (35%); p = 0.02). Most abortion in the two Groups occurred in the first trimester (3 in Group A and 5 in Group B). In the low-dose aspirin plus LMWH (Group A) there were a significantly greater number of live births (43/47(91%) versus 15/23(65%) in group B; p =0.02).

The mean gestational age and the neonatal birth weight were significantly higher in Group A than in Group B. The mean gestational age at delivery in Group A was 37.86± 1.8 versus 36.13 ±2.39 weeks in Group B; p= 0.005. The mean birth weight in Groups A was 3252 ±459 versus 2907 ± 618 g in Group B; p =0.03.

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Significant difference in the mode of delivery. Nineteen (19) of the 58 women with successful pregnancies (33%) delivered prematurely (<37 weeks' gestation). Eleven of them were in Group A [6/43 (14%) due to preterm labour, 4/43(9%) due to IUGR, and 1/43(2%) due to pre-eclampsia] and the remaining 8 were in Group B [3/15(20%) due to preterm labour, 3/15(20%) due to IUGR and 2/15 (13%) due to pre-eclampsia]. No woman developed a thromboembolic complication during pregnancy or the puerperium.

Both low dose aspirin and LMWH were well tolerated. Of those taking heparin, none developed thrombocytopenia or had symptomatic complications apart from mild bruising localized to the injection site.

Conclusion

Combination treatment with aspirin and LMWH leads to a high live birth rate among women with recurrent abortion and antiphospholipid antibodies. This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation.

Recommendation

Future studies should be aimed at refining the protocol used in this trial to determine the benefits of preconceptional administration of heparin and whether it can be stopped after 13 weeks of gestation without adversely affecting the rate of live births.

However, successful pregnancies are prone to a high risk of complications during all pregnancy. Close antenatal surveillance and planned delivery of these pregnancies in a unit with specialist obstetric and neonatal intensive care are indicated.

A larger randomized control trial is needed.

KEYWORDS: antiphospholipid antibodies; recurrent abortion.

INTRODUCTION

Recurrent abortion is defined as the occurrence of three consecutive spontaneous abortions prior or during the 20th week of pregnancy. It occured in about 1 in 300 pregnancies and in up to 1% of gravida three or more women. [1]

Approximately 15% of clinically recognized pregnancies result in spontaneous loss, and there are many more pregnancies that fail before to being clinically recognized. Only 30% of all conceptions result in a live birth. The risk of miscarriage is 30% after two previous losses and 35% after the third loss. This strongly suggests a need for evaluation after just two losses in patients with no prior live births. An earlier evaluation may further indicate whether the fetal cardiac activity is recognised prior to a loss, if the woman is older than 35 years, or the couple has had difficulty to conceiving. [2]

The cause is unexplained in up to 60% of couples. It has been suggested that the fetal-placental semiallograft is produced protection by local immunomodulating factors and that immunologic recurrent abortion may result from an imbalance or breakdown in the mechanisms responsible for immune homeostasis. [3, 4]

It is established that the presence of antiphospholipid antibodies represented by the lupus anticoagulant and or anticardiolipin antibody; what is called

antiphospholipid antibody syndrome (APA syndrome) is a major cause of such imbalance. These autoantibodies are also strongly associated with both venous and arterial thrombosis and or thrombocytopenia. [5, 6]

Antiphospholipid antibodies (APA) are a group of organ autoantibodies that bind to negatively charged phospholipids. Thrombosis occurs in up to 33% of people with the lupus coagulant and in over 75% of patients with elevated anticardiolipin antibodies. The presence of APA is asociated with recurrent spontaneous loss. [7-11]

Autoimmune function is an etiological factor in approximately 10% of patients with recurrent pregnancy loss and assessment of Antiphospholipid antibodies has become routine in the evaluation of women having recurrent abortion. [12, 13]

A series of complex immune mechanisms modulates implantation. Increased concentrations of prostaglandins (PGE2 and PGF2alpha) at the site of embryo implantation increase vascular permeability prior to implantation and this critical to the process. Platelet activation factor (PAF), an ether-linked phospholipid, is produced by the blastocyst, by invading trophoblast and adjacent decidua for a few days around the time of implantation. [14-16]

Platelet activation factor facilitates implantation by increasing local consumption of thrombocytes and promoting the release of PGE2. Phospholipids function as adhesion molecules in the formation of myoblasts and syncytiotrophoblasts. [17-19]

Exposure of surface phospholipids (especially phosphoserine and phosphoethanolamine in the hexagonal phase II form) creates an immunogenic

condition leading to delayed syncytialization of the trophoblast. This mechanism could play an important role in the pathogenesis of recurrent abortion through reducing the efficiency of implantation and promote autoimmune rejection of the conception. [20]

Several regimens have been proposed for the treatment of APS, including aspirin alone, prednisone and aspirin, heparin and aspirin and recently intravenous immunoglobulin (Ig). Recent studies have suggested that aspirin plus heparin may be superior to prednisone or aspirin alone for the treatment of APA associated recurrent pregnancy loss. [21]

The combination of aspirin and heparin may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the utero-placental vasculature after placentation. [22,23]

Aim of the study

To investigate the efficacy of combined aspirin and low molecular heparin as opposed to aspirin alone in the management of immunological recurrent abortion

Patients and methods

This is a prospective study of 70 female patients presented with recurrent pregnancy loss (RPL) or miscarriage (loss of three or more consecutive pregnancies before the 20th week of gestation) [1] and repeatedly positive test results for anticardiolipin or lupus anticoagulant (test performed at intervals of 3 months) and all of them have their loss in the first twenty weeks of gestation.

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The duration of the study was 3 years (February 2013-February 2016); the cases were presented both to the private clinic and the hospital (Al-Batool teaching hospital).

Criteria for inclusion were age 30–35 years, 3 fetal losses before 20th week gestation, and 2 positive results for anticardiolipin antibody (ACL) and lupus anticoagulant (LAC) this testing performed at intervals of 3 months.

Exclusion criteria were a chromosomal or anatomic abnormality, luteal phase defect, confirmed peptic ulcer, SLE, diabetes mellitus, abnormal results of an oral glucose tolerance test, previous thromboembolism, sensitivity to aspirin, hypertension or current treatment with antihypertensive drugs, previous prednisone therapy, an abnormal chest radiographic result, or a positive result of a tuberculin skin test.

The patients were randomly put in two groups. In two groups the patients started receiving treatment as soon as they had a positive result on a pregnancy test.

Group A (47 patients), the women given both low molecular weight heparin (LMW self-administered injection; 4000 IU/day) with low-dose aspirin (81 mg/day) as soon as they had a positive result on a pregnancy test; aspirin was discontinued at 36th week of gestation or at the time of miscarriage, and heparin at 37th week of gestation or at the time of miscarriage.

Group B (23 patients) assigned to receive aspirin alone (81mg/day); again aspirin was discontinued at 36th week of gestation or at the time of miscarriage.

Gestational age at delivery was determined by menstrual dates and confirmed by ultrasound examination. From 20th week of gestation, pregnancies were monitored by serial ultrasonography and Doppler studies of umbilical artery circulation, fetal growth and wellbeing. The first outcome measure was the rate of live births. Second outcomes included rates of miscarriage, intrauterine fetal death (fetal death after 20 weeks of gestation), and obstetrical complications.

Such complications included preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count), small for gestational age (birth weight below the 10th percentile for gestational age and sex), placental abruption, and premature delivery. Premature delivery was classified a priority in three subgroups according to gestational age (24 to <28, 28 to <32, and 32 to <37).

The rates of maternal thrombocytopenia (defined as a platelet count of <150,000 per cubic millimeter), bleeding episodes (i.e., bleeding from the gums, nose and the amount of vaginal blood loss at delivery), skin reactions were assessed by telephone at 3-month intervals and verified on the basis of obstetrical medical reports. All infants were examined by an pediatrician. In cases in which a congenital or neonatal abnormality was suspected, a neonatologist do the final diagnosis. [23]

All women were advised to take folic acid (400 µg daily), before conception and continuing until 10 weeks of gestation, as prophylaxis for neural-tube defects. Women received standard care provided by their obstetrician throughout pregnancy, including structural fetal ultrasonography(anomaly scan) at 18 to 22 weeks of gestation.

In addition, platelet counts performed at 12th and 30th weeks of gestation. Women contacted by telephone every 3 months throughout the study until completion of the first pregnancy; compliance and side effects addressed during these with the use of a structured form. [23]

Statistical analysis

Results were expressed as mean± SD, range, numbers and percentages. Intra-Group data was statistically analysed using t-test and inter-Group analysis was examined using Chi-square test (X2 test). Statistical analysis was conducted using SPSS program, (Version 10, 2002). P value <0.05 was considered statistically significant.

Discussion

The negative effect of APS on pregnancy is most likely due to abnormal placental function (24). Adverse pregnancy outcomes in women with APS may result from poor placental perfusion due to localized thrombosis, perhaps through interference by APA antibodies with trophoblastic annexin V. Activated endothelial cells induce adhesion molecules and, along with monocytes, up regulate the production of tissue factor. (25)

Our study investigated women with APS in the index pregnancy treated with both aspirin and LMWH together or aspirin only. Analysis of the data revealed statistically significant difference between the treatment Groups in terms of live birth rate (43/47(91%) versus 15/23(65%); p = 0.02), the mean gestational age at delivery (37.86 ±1.8 versus 36.13± 2.39 weeks; p =0.005) and the mean birth weight (3252± 459 versus 2907 ±618 gs; p =0.03). Preterm deliveries were experienced by 14% of women in Group A compared with 40% in Group B, while 12% and 33% of women complaine from IUGR in Groups A and B respectively. The rate of preeclampsia was significantly lower in Group A (7%) than in Group B (40%); (P <0.009).These results were comparable to international data (26,27,28,29).

A prospective study by Kutteh revealed that viable infants were delivered 20/25 (80%) women treated with heparin and aspirin and of 11/25 (44%) women treated with aspirin (p< 0.05) and this agreed with this our present study (43/ 47(91%) versus 15/23(65%); p = 0.02). But there were no significant differences between the low-dose aspirin and the heparin plus low-dose aspirin Groups in respect to gestational age at delivery (37.2± 3.4 weeks vs. 37.8± 2.1) these disagreed with our results (37.86± 1.8 versus 36.13 ±2.39 weeks; p= 0.005), while agreed with ours in difference in number of caesarean sections, and complications (21).

A comparable trial also found aspirin alone inferior to aspirin plus heparin (42% versus 71% live births) (30). But, Farquharson et al., found the birth rate be similar in both Groups (72% with aspirin alone compared with 78% when heparin was added to the regimen) (31).

Backos et al., agreed with our present study in that combination therapy with aspirin and heparin leads to a high live birth rate among women with recurrent miscarriage and antiphospholipid antibodies resulted(71%) in a live birth and (27%) miscarried, the majority in the first trimester (32).

Our study suggests that the women with APS and in pregnancy can be treated effectively with low-dose aspirin alone. (33,34).

To date, studies confirmed that treatment with LMWH plus aspirin should be considered as the standard therapy for

recurrent pregnancy loss due to APS (35,36).

The main limitation of this study that it was non randomized study which can be explained by the need of active participation of the patients in buying the medication (cost implication).

Conclusion

Combination treatment with aspirin and LMWH leads to a high live birth rate among women with recurrent miscarriage and antiphospholipid antibodies. This combination may promote successful embryonic implantation in early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation.

Recommendation

Future studies should be aimed at refining the protocol used in this trial to determine the benefits of preconceptional administration of heparin and whether it can be stopped after 13 weeks' gestation without adversely affecting the rate of live births.

However, successful pregnancies are prone to a high risk of complications during all pregnancy . Close antenatal surveillance and planned delivery of these pregnancies in a unit with specialist obstetric and neonatal intensive care are indicated.

A larger randomized control trial is needed.

Results

A total of 70 women with APS were included in the study: 47 women in Group A used low-dose aspirin (81 mg) plus LMWH (clexane 4000IU) and 23 women in Group B received aspirin only. Table 1 shows the

demographic details of the women. There were no significant differences in the patient's age at entry, weight, previous pregnancies, previous live births, prior miscarriages and prior intrauterine fetal death (IUFD).

As shown in Table 2, there was a highly significant difference between Groups A and B in the rate of abortion (4 miscarriage in Group A (9%) versus 8 miscarriages in Group B (35%); p = 0.02). Most abortion in the two Groups occurred in the first trimester (3 in Group A and 5 in Group B). In the low-dose aspirin plus LMWH (Group A) there were a significantly greater number of live births (43/47(91%) in group A versus 15/23(65%) in group B; p =0.02).

The mean gestational age and the neonatal birth weight were significantly higher in Group A than in Group B. The mean gestational age at delivery in Group A is 37.86± 1.8 versus 36.13 ±2.39 weeks in Group B; p= 0.005. The mean birth weight in Groups A is 3252 ±459 versus 2907 ± 618 g in Group B; p =0.03. There are no intrauterine or neonatal deaths in the study (Table 3). The rates of pre-eclampsia is significantly higher in Group A than in Group B (3/43 (7%) versus 6/15 (40%); p= 0.009).

Although not statistically significant, women in Group A have lower rates of preterm births (6/43 (14%) versus 3/15 (20%); p= 0.89) and IUGR (5/43 (12%) versus 5/15 (33%); p = 0.13) than in Group B

(Table 4). Also there is no statistically significant difference in the mode of delivery. Nineteen (19) of the 58 women with successful pregnancies (33%) delivered prematurely (<37 weeks' gestation). Eleven of them were in Group A [6/43 (14%) due to preterm labour, 4/43(9%) due to IUGR, and 1/43(2%) due to pre-eclampsia] and the remaining 8 were in Group B [3/15(20%) due to preterm labour, 3/15(20%) due to

IUGR and 2/15 (13%) due to pre-eclampsia]. No woman developed a thromboembolic complication during pregnancy and puerperium (Table 3).

Babies were examined by a paediatrician shortly after delivery. No congenital abnormalities were detected. Twelve babies were admitted to the neonatal care unit because of prematurity. Nine babies (5 in Group A and 4 in Group B), delivered by caesarean section for IUGR and preeclampsia, required ventilator support for one week. The other three babies (1 in Group A and 2 in Group B) were admitted to the neonatal unit to help for feeding.

Both low dose aspirin and LMWH were tolerated. Of those taking heparin, none developed thrombocytopenia or had symptomatic complications apart from mild bruising localized to the injection site.

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Table 1 Age and pregnancy criteria of women treated with aspirin plus LMWH or aspirin alon.

Variables	LMWH+aspirin Group A (n= 47)	Aspirin alone Group B (n= 23)	Test of significance	p-Value
Maternal age (years)	28.7±3.3	29.35± 3.55	T= 0.75	p=0.46
Weight (kg)	71.8±7.62	70.39± 8.38	T= _0.75	p=0.46
Total pregnancies	3.98±1.67	4.26± 1.89	T= 0.64	p=0.53
Prior abortions (No.)	2.98±1.33	3.22± 1.54	T= 0.73	p=0.47
Prior live births (%)	26/47(55%)	12/23(52%)	X2= 0.0004	p=0.99
prior IUFD (No.)	22/47(47%)	10/23(43%)	X2= 0.004	p=0.95

* Data are presented as percentage or mean±standard deviation.

Table 2 Outcome data from patients who had miscarriage.

Variables	LMWH+aspirin Group A (n= 47)	Aspirin Group B (n=23)	Test of significance	p-Value
Miscarriages (%)	4/47(9%)	8/23(35%)	X2= 5.77	p =0.02
Mean gestational age at loss	10.75±4.99	12.38±3.34	T= 0.68	p =0.51

Table 3 Outcome data from patients who had live births.

Variables	LMWH+aspirin Group A (n= 47)	Aspirin Group B (n=23)	Test of significance	p-Value
Live births (%)	43/47(91%)	15/23(65%)	X2= 5.77	p =0.02
Mean gestational age at birth (weeks)	37.86±1.8	36.13±2.39	T= _2.91	p =0.005
Birth weight (grams)	3252±459	2907±618	T= _2.28	p =0.03

Mode of delivery	(n =43)	(n= 15)		
1. Caesarean Section	30(70%)	10(67%)	X2= 0.01	p =0.92
2. Vaginal delivery	13(30%)	5(33%)		

Table 4 Obstetric and maternal complications of patients who delivered a live born.

Variables	LMWH+aspirin Group A (n=43)	Aspirin Group B (n= 15)	Test of significance	p-Value
Pre-eclampsia (No.)	3(7%)	6(40%)	X2 = 6.89	p =0.009
Preterm delivery (No.)	6(14%)	3(20%)	X2 = 0.02	p =0.89
IUGR (No.)	5(12%)	5(33%)	X2 = 2.3	p =0.13
Prematurity (No.)	11(26%)	8(53%)	X2 = 2.73	p =0.1