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Timing of Initiation of Low-Molecular-Weight Heparin (LMWH) And Aspirin Administration on The Pregnancy Outcomes in Women with Antiphospholipid Syndrome (APS) And Recurrent Abortion

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ABSTRACT

Background: Recurrent miscarriages are common in around 1% of couples. Although the origin of antiphospholipid syndrome is unclear in the majority of instances, it is a preventable cause. Antiphospholipid antibody syndrome (APS) is a disorder marked by arterial and venous thrombosis, as well as gestation difficulties, when antiphospholipid (aPL) antibodies are present. Preeclampsia, placental inadequacy, and fetal development limitation are among the pregnancy difficulties in women with APS, as well as repeated miscarriages and fetal mortality.

Aim of the work: To see how varied timings for starting low-molecular-weight heparin (LMWH) and aspirin therapy affected pregnancy end results in women with antiphospholipid syndrome and recurring abortion.

Patients and methods: Randomized clinical trial study, the study was carried out on 100 participants was collected from outpatient clinic till fulfill sample size as they seek to be pregnant in next months, according to following criteria, the participants was collected from outpatient clinic of gynecological and obstetric department of Sayed Galal university hospitals.

Results: Our findings demonstrated that giving LMWH to gestational women with obstetrical APS early in the pregnancy decreased fetal loss by a substantial amount, while increase live birth but this results was insignificant; it was found that the two groups showed insignificant difference regarding maternal complication, but the neonatal complication was significantly lower in early administration of LMWH.

Conclusion: Early LMWH therapy for pregnant women with obstetrical APS lowers the risk of fetal loss and neonatal problems, but has little effect on the risk of late obstetrical difficulties.

Keywords: *Low-molecular; weight heparin; Aspirin -Antiphospholipid syndrome; recurrent abortion.*

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INTRODUCTION

Recurrent pregnancy loss (RPL) is characterized as two or more unsuccessful pregnancies in a row, causing emotional burden to women and their families. Approximately 5% of women lose two or more pregnancies in a row, and 1% of women lose three or more pregnancies in a row. Further examination is indicated after two consecutive clinical pregnancy failures; however, a clearly characterized cause is not established in 50% of RPL patients. RPL is caused by a combination of genetic, chromosomal, immunological, endocrinologic, anatomical, and structural factors.[1]

Obstetrical antiphospholipid syndrome (APS) is an autoimmune illness that impairs pregnancy and leads to repeated abortions, intrauterine growth restriction (IUGR), stillbirth, or extreme preeclampsia with or without artery and/or venous clotting. Antiphospholipid antibodies were discovered in 1%–5% of the population as usual variations, but their incidence soared to 15% in women who had repeated abortions and 40percent in women having systemic lupus erythematosus (SLE).[2]

Thrombosis in the vascular beds, whether arterial, venous, or placental, was long assumed to be the cause of APS, leading in placental inadequacy, [3] but this concept was called into question in obstetrical APS, especially in the lack of clinical findings of vascular thrombosis or infarction in the placental tissues of certain instances, allowing obstetrical APS to be classified as an autoimmune disease. [4]

Endothelial cells are activated when APS auto-antibodies attach to negatively charged macromolecules in cell membranes, like phospholipids. Defective placentation or complement activation may set off a chain of events, each of which creates pro-inflammatory molecules that injure the developing of the placenta or the baby. [4]

In women with APS, the efficacy of anticoagulation therapy with LMWH and/or aspirin is still debated. a protective effect of aspirin in those at increased incidence of heart disease or intrauterine growth [(5)]. Furthermore, for women with either main or secondary APS, therapy with LMWH in addition to aspirin was recommended. [6-8]

At the cellular level, LMWH is thought to reduce trophoblast apoptosis and increase the synthesis of proteases participating in trophoblast invasion of the maternal endometrium.[9, 10]

In vitro investigations have demonstrated that LMWH affects angiogenesis in the placental villi and has an impact on soluble vascular endothelial growth factor dysregulation[11.] Heparin also has an inhibitory impact on complement activation, which may minimize the incidence of pregnancy problems. [12]. LMWH, on the other hand, may have a negative impact by boosting soluble FMS-like tyrosine-kinase-1 , which is linked to HD [13]. Aspirin is believed to enhance trophoblastic invasion of the uterine spiral arteries by inhibiting thrombocyte aggregation and/or acting as an anti-inflammatory. This might help the placenta form and operate more effectively. [1]

Several studies have looked at the effects of aspirin and/or LMWH on pregnancy end results; for example, one study found that the prenatal and maternal results of the total cohort revealed that anticoagulant treatment subgroups had greater maternal and perinatal problems than those who did not. [14.]

Another recent research showed that the early initiation group (aspirin and LMWH) had a considerably greater incidence of continued pregnancy than the later initiation group. However, the rates of pregnancy loss, premature labor before 34 weeks of pregnancy, and IUGR were identical in both groups, as was the live birth rate.[2]

Numerous studies indicated that pre-conception enoxaparin treatment resulted in a considerable enhancement in the clinical gestation rate and a decrease in the frequency of repeated miscarriage as compared to individuals received placebo at the preconception phase.[15, 16]

Because the effects of aspirin and LMWH, as well as the time of beginning, are debatable, we conducted our research.

The purpose of this research was to see how varied timings for starting low-molecular-weight heparin (LMWH) and aspirin therapy affected pregnancy end results in women with antiphospholipid syndrome (APS) and recurrent abortion.

PATIENTS AND METHODS

Study type: randomized clinical trial study

Study site: the participants was collected from outpatient clinic of gynecological and obstetric department of Sayed Galal and Etay Elbarod hospitals

Study population:

The participants was collected from outpatient clinic till fulfill sample size as they seek to be pregnant in next months, according to following criteria.

Inclusion criteria:

A history of 3 successive early abortions (before the 10th week of pregnancy), and/or one morphologically normal fetus fatality from an unknown cause at or beyond the 10th week of pregnancy, and/or one preterm born of a morphologically normal neonate before 34 weeks of gestation due to serious preeclampsia, eclampsia, or placental inadequacies;

Anticardiolipin antibodies (immunoglobulin m and/or immunoglobulin g) in high or medium titer (>40 mL/L or >99 %) in plasma or serum on ≥two separate occasions at a minimum of 12 weeks apart, and/or lupus anticoagulant in plasma on≥ two separate occasions at a minimum of 12 weeks apart. The occurrence of lupus anticoagulant was determined using the dilute Russell viper venom time and the titer of anticardiolipin antibodies was assessed using a conventional ELISA.

Exclusion criteria:

Under the age of 20 or above the age of 38.

Body weight in the first trimester of pregnancy: 50 kg or >90 kg

SLE

Thromboembolic diseases that are active

Previous thromboembolic disease history

Coexisting Hereditary thrombophilia

Pregnancy loss due to genetic or hormonal factors

Uterine aberration or malformation, as uterine septum, bicornuate uterus, or unicornuate uterus that might cause improper placentation, early gestation loss, or premature delivery.

Uterine myoma, which might cause complications during pregnancy.

Cervical insufficiency.

A medical problem that has an impact on the pregnancy's outcome

Known LMWH or aspirin allergic or contraindication.

All eligible individuals were split into two groups at random. They asked to be notified once a positive pregnancy test was confirmed.

Study Procedures

Taking all participants demographic data, medical history and gynecological and obstetric history

A quantitative measurement of serum beta component of human chorionic gonadotropin was used to confirm biochemical gestation.

All participating women in the investigation was divided into two groups;

Group I (50 cases): Early LMWH initiation group; aspirin (81 mg/day) and LMWH (enoxaparin; Clexane®; Sanofi-Aventis, Paris, France) were administered subcutaneously at a dosage of 40 mg/day until the end of the first trimester. The aspirin and LMWH was started before being pregnant by 2 to 3 months.

Group II (50 cases): later LMWH initiation group (start aspirin and LMWH in same doses in group A, but started once pregnancy test be positive).

Two weeks after a positive pregnancy test, all participants had a transvaginal sonography (TVS) scan to confirm clinical intrauterine embryo, which was known as the availability of at least one intrauterine gestational sac with fetal pole and cardiac function on a TVS scan at 6–7 weeks of pregnancy.

Every 2–3 weeks, all women got regular prenatal care and supplements, as well as follow-up. Women were asked at each follow-up appointment to ascertain whether they had had vaginal bleeding or any other adverse events.

At each follow-up appointment, ultrasonography was used to verify fetus viability and evaluate fetus development and well-being.

To establish compliance with LMWH for each individual, the numbers of ampoules really used was divided by the total number of ampoules that should have been used.

Follow up visits was continued till the last of 1st trimester after stabilization of heart pulsation.

Statistical analysis:

The information was gathered and input into a computer. The Statistical Package for Social Sciences (SPSS/version 22) software was employed to conduct statistical analysis. To compare two groups, the mathematical mean, standard deviation, and chai square test were employed for classified parameters, while the t-test was utilized for numerical data. The relevance threshold was set at> 0.05.

RESULTS

The basic demographic and clinical data showed that the mean age of group I was 26.2±2.56 years, and in group II was 27.12±2.36 years, the BMI in group I was 28.22±2.27 and in group II was 27.22±2.56, In terms of age and BMI, there was no substantial distinction between the tested groups. Regarding maternal history, parity in group I ranged from 0-7 with mean value 3.18±2.057 and in group II ranged from 0-7 with median value 1.96±1.85. There was statistical substantial distinction between the two studied groups regarding parity ($p < 0.05$) while there was no statistical substantial distinction regarding gravidity and nulliparous ($p > 0.05$).

The comparison between the two groups regarding miscarriages, showed that the previous 1st trimester miscarriages in group I ranged from 2-4 with median value 3.46±0.613 and in group II ranged from 2-7 with mean value 4.52±1.40. There was statistical substantial distinction between the two groups according to Previous 1st trimester miscarriages ($p < 0.05$) while there was no statistical substantial distinction regarding women with previous second trimester miscarriages, preterm labor and previous fetal loss ($p > 0.05$)

Table (1) shows that gestational age at start of treatment in group I ranged from 4-6 with mean value 4.9±0.814 and in group II ranged from 5-7 with mean value 5.92±0.85. There was statistical substantial distinction between the two studied groups according gestational age at start of treatment ($p < 0.05$). Also, this table shows that there was no statistical substantial distinction between the two investigated groups regarding bleeding ($p > 0.05$). Also it was found that there was no substantial distinction between the two studied groups regarding pregnancy ($p > 0.05$). Table (1) shows also that there was no statistical substantial distinction between the two investigated groups regarding miscarriage ($p > 0.05$). There was a statistical substantial distinction between the two groups according fetal loss while live birth show insignificants difference ($p > 0.05$).

	Group I "n=50"		Group II "n=50"		p value
Gestational age at start of treatment (weeks)	4.9±0.814		5.92±0.85		0.001*
Bleeding	No.	%	No.	%	
First trimester bleeding	9	18	7	14	0.294
Second trimester bleeding	4	8	8	16	0.11
Pregnancy					
Clinical pregnancy	48	96	46	92	0.202 N.S.
Ongoing pregnancy	47	94	44	88	0.149 N.S.
Miscarriage	9	18	12	24	0.233 N.S.
First trimester miscarriage					
Second trimester miscarriage	5	10	4	8	0.365 N.S.
Gestational age at miscarriage (wks)	14.21±4.74		12.12±3.91		0.098 N.S.
Out come	3	6.0	6	12.0	0.049*
Fetal loss					
Live birth	32	64	28	56	0.209N.S.

Table 1: Comparing the two investigated groups in accordance of gestational age at start of therapy (weeks) and incidence of bleeding, pregnancy and miscarriage and final outcome.

	Group I "n=32"		Group II "n=28"		p value
	No	%	No	%	
Gestational age at delivery (weeks)	33.9±3.104		34.67±3.75		0.193 N.S.
Delivery before 34 weeks	14	43.75	9	32.14	0.18 N.S.
IUGR	9	28.1	6	21.43	0.279 N.S.
Complication					
Gestational hypertension	2	6.3	3	10.7	0.270 N.S.
Preeclampsia	9	28.1	7	25.0	0.394 N.S.
Placental abruption	5	15.6	2	7.14	0.157 N.S.

Table 2: Comparing the two investigated groups in basis of gestational age at delivery and incidence of complication.

Neonatal data	Group I "n=32"		Group II "n=28"		test p value
	No	%	No	%	
Birth weight (g)	2362.22±726.705		2298.11±802.11		0.334 N.S.
Congenital malformation	0	0.0	1	3.6	0.064 N.S.
Neonatal RDs	4	12.5	9	32.1	0.033 N.S.
Admission to NICU	5	15.6	15	53.6	0.0007*
Mechanical ventilation	0	0.0	10	35.7	0.001*
Early neonatal death	0	0.0	5	17.9	0.002*

Table 3: Comparing the two investigated groups in basis of neonatal data.

Table (3) shows that the birth weight in the two groups showed insignificant difference between the two groups. Only one case had congenital malformation in group II. Neonatal RDs in group I was 4 (12.5%) while in group II was 9(32.1%) respectively. Admission to NICU in group I was 5 cases (15.6%) while in group II was 15 (53.6%), there was a substantial increase in NICU in group II more than group I. Mechanical ventilation in group I was none while in group II was 10 cases (35.7%), there was a highly substantial increase in mechanical ventilation neonate in group II more than group I. Early neonatal death in group I was none while in group II was 5 (17.9%), there was a substantial increase in early death neonatal in group II more than group I.

DISCUSSION

The findings of our study revealed that early LMWH administration for pregnant women with obstetrical APS reduced fetal loss by a substantial amount while increasing live birth, though the difference was insubstantial. It was also discovered that the two groups showed no substantial difference in terms of maternal complication, but neonatal complication was significantly lower in the early LMWH administration group.

By lowering trophoblast apoptosis and boosting the generation of proteases involved in trophoblast invasion of the maternal endometrium, LMWH is likely to have an early impact at the cellular level. [17]

In vitro investigations have demonstrated that LMWH affects angiogenesis in the placental villi and has an impact on soluble vascular endothelial growth factor dysregulation (25, 26). [18]

Heparin also has an inhibitory impact on complement activation, which might lower the risk of pregnancy problems. [19]

LMWH, on the other hand, may cause HD via raising soluble fms-like tyrosine-kinase-1 (a splice variation of vascular endothelial growth factor receptor). [20]

The anticlotting mode of action of LMWH is most likely not the only one. When compared to healthy one, the rate of problems was high in all therapy groups. [21]

A favorable impact of LMWH on second and third trimester pregnancy results in women with primary APS has also not been shown. [22] Treating with LMWH during pregnancy is suggested for women with APS who have had a thrombotic episode in the past, since LMWH has been shown to be beneficial in avoiding venous thrombosis during gestation. [23]

One of the most prevalent and treatable reasons for recurrent miscarriage is APS. Late fetal loss is explained by thrombosis in the placental bed, whereas early pregnancy loss is explained by a variety of processes, including inadequate trophoblastic differentiation, invasion and migration, and complement-induced inflammation in the decidua. [24]

The latter pathophysiology explains heparin's efficacy in treating repeated early pregnancy miscarriage, since it has been shown that heparin, in addition to its antithrombotic activity, has an anti-inflammatory impact via suppressing complement activation and a trophic effect on trophoblast in vitro. [25]

As a result, we hypothesized in our research that the sooner heparin medication is started, the better the prognosis in individuals with APS who had experienced early gestation losses. In this research, we discovered that women in the study group who began LMWH medication after a positive pregnancy test had a lower rate of early pregnancy loss than control group women who began LMWH medication after Sonographic confirmation of fetal heart pulse. [25]

Anti-lupus anticoagulant antibodies have been linked to a higher incidence of first-trimester abortion. [21] We believe that the substantial decrease in early pregnancy losses in the study group is due to the timing of LMWH therapy initiation, rather than the occurrence of lupus anticoagulant antibodies in both groups, due to the lack of a substantial variation in the occurrence of lupus anticoagulant antibodies between the studied groups in our analysis. [26]

Ismail et al.[22] evaluated the impact of preconceptional LMWH beginning in individuals with APS and repeated fetal loss, which supports our hypothesis that earlier LMWH medication is beneficial in reducing early pregnancy losses. When daily injection of 40 mg enoxaparin subcutaneously with 81 mg aspirin was begun following verification of ovulation, they discovered a substantial decrease in early gestation loss. However, preconceptional LMWH starting has the disadvantage of administering LMWH to a proportion of women who will not become pregnant. As a result, we recommend starting LMWH dosing when a biochemical diagnosis of pregnancy was made, in order to prevent giving LMWH to women who may or may not get pregnant before they are ready. [27]

Late obstetrical problems linked to antiphospholipid antibodies, as IUGR, intrauterine fetal mortality, preeclampsia, placental abruption, and premature birth before 34 weeks of pregnancy, were not shown to be significantly different. This is due to the administration of low-dose aspirin in both groups, which has been shown to be effective in reducing IUGR and preeclampsia in APS patients [28,] since low-dose aspirin increases the production of IL-3, a cytokine that promotes placental and fetus growth. [29]

Our research's key strength was that it was a randomized trial with reliable randomization and allocation concealment procedures. The findings were likewise reported on an intention-to-treat basis, with a low percentage of loss to follow-up. Our investigation was limited by the fact that it was not conducted as a placebo-controlled trial with participants and assessors not being blinded. However, we do not believe that this has resulted in a considerable amount of bias since the results examined were hard clinical findings with high compliance rates in both groups, thereby eliminating the possibility of verification and effectiveness bias. Another research drawback is the small sample size, which restricts the investigation capacity to identify substantial variation in the results of live delivery and may have hampered the investigation power to discover other clinically relevant abnormalities such as preeclampsia and IUGR. Even with this restriction, this research found a substantial variation in effect size between reducing pregnancy losses and improving continuing gestation. [30]

CONCLUSION

Early LMWH therapy for pregnant women with obstetrical APS lowers the risk of fetal loss and neonatal problems, but has little effect on the risk of late obstetrical difficulties.

Conflict of interest : none

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