Randomised Trial

Effects of low-dose aspirin and heparin on the pregnancy outcome in women with antiphospholipid syndrome

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ARTICLE INFO

Keywords:
Antiphospholipid syndrome
Anticardiolipin antibody
Lupus anticoagulant antibody
Anti-β2 glycoprotein I antibody
Thrombosis
Pregnancy morbidity
Low-dose aspirin
Prednisone
Heparin

ABSTRACT

Objective: The purpose of this study was to compare the use of low-dose aspirin alone versus prednisone and low-dose aspirin versus heparin and low-dose aspirin in the treatment of the antiphospholipid antibody syndrome in pregnant women.

Study design: A prospective, single-center randomized trial included 14 patients who were alternately assigned to treatment. Each patient had a history of recurrent miscarriage diagnosed with antiphospholipid syndrome. 5 accepted the treatment of aspirin alone, 5 accepted the combination treatment of aspirin + prednisone, and 4 accepted the combination therapy of aspirin + heparin. Data were compared by the One-way ANOVA test using IBM SPSS stats 19.

Results: There were no significant differences in patient outcome data, obstetric complications, and gestational age at delivery in live births between the 3 groups (P > 0.05). However, treatment with aspirin + heparin increased neonatal weight (P < 0.05).

Conclusions: Our data demonstrate the non-superiority one on each other of the three different regimens, except in terms of neonatal weight when aspirin + heparin were used. These findings raise questions about the need for therapies such as heparin and corticosteroids for women with antiphospholipid antibody syndrome, especially in resource-limited settings similar to Syria.

1. Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune disease that classically manifests as thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) which include immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin (aCL) and/or lupus anticoagulant antibodies (LA) and/or anti-β2 glycoprotein I (anti-β2GPI) [1]. In the early 1980s, APS was first described in patients with systemic lupus erythematosus (SLE) [2]. It occurs either as an isolated disorder (primary APS) or in the setting of another autoimmune disorder (secondary APS) such as SLE [3,4]. APS is usually associated with recurrent miscarriage, and other pregnancy complications include Intrauterine growth restriction (IUGR), pre-eclampsia, and preterm labor [3,5]. Recently proposed mechanisms of pregnancy loss include thromboses of placental vasculature that may affect the protein C pathway and/or annexin V, or inhibit syncytia formation due to antiphospholipid antibodies acting on trophoblasts [6].

The combined treatment with heparin and a low dose of aspirin results in successful pregnancies in most cases. Nevertheless, a minority of patients require alternative therapies such as low-dose glucocorticoids, hydroxychloroquine (HCQ), immunoglobulin, pravastatin, and plasmapheresis, to decrease obstetric complications [7]. Many studies have evaluated the efficacy of several treatment strategies, both single agents and combinations. However, the findings have not been consistent [3,5], and therapeutic interventions to prevent late obstetric complications are not yet known [7].

The present clinical comparative study aimed to evaluate the effect of treatment with aspirin + heparin. APS patients were observed from the time of positive pregnancy testing until delivery or miscarriage. To the best of our knowledge, this study is the first randomized trial in Syria to evaluate the effect of treatment with aspirin + heparin in patients with APS.
2. Methods

The patients who participated in this clinical comparative study were referred to a private obstetrics and gynecology clinic in Lattakia, Syria between January 2020 and June 2022, with a history of recurrent miscarriage, due to a known diagnosis of antiphospholipid antibody syndrome according to the laboratory and clinical criteria which were published in an international consensus statement in 2006 [1]. Patients had to have at least one clinical criterion and one laboratory criterion.

- Clinical criteria:
  1. Vascular thrombosis.
  2. Pregnancy morbidity:
     (a) 1 or more late termination spontaneous miscarriages of a morphologically normal fetus (≥10 weeks of gestation).
     or (b) 1 or more premature births of a morphologically healthy neonate (≤34 weeks of gestation) due to severe placental insufficiency or severe preeclampsia or eclampsia.
     or (c) 3 or more unexplained, consecutive, spontaneous miscarriages (<10 weeks of gestation).

- Laboratory criteria on 2 or more occasions at least 12 weeks apart:
  1. Lupus anticoagulant (LA).
  2. Medium to high levels of anticardiolipin (aCL) antibody of IgG and/or IgM isotype.
  3. Anti-b2 glycoprotein-I antibody (anti-b2GPI) of IgG and/or IgM isotype.

Maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes associated with recurrent pregnancy loss were excluded from this study.

The study was a prospective, single-center trial approved by the ethics committee of Tishreen University and all patients provided informed consent.

In total, 16 patients were investigated and randomized into 3 groups. Of these, 2 patients were lost to follow-up, ultimately only 14 patients were analyzed. Of the 14 patients, 5 accepted the combination treatment of aspirin (a low dose of 100 mg once daily orally) and prednisone (a low dose of 10 mg once daily orally), and 4 accepted the combination treatment of aspirin (a low dose of 100 mg once daily orally), and heparin (5000 IU subcutaneously once daily).

Patients were given treatment as soon as a positive pregnancy test as identified by urine human chorionic gonadotropin testing at approximately 5 weeks of gestation was achieved. The subjects were tested each month for aPL antibodies. If aPL antibodies were negative, treatment was ceased. When aPL antibodies remained positive during pregnancy, the therapy was continued throughout the gestational period. Pregnancy in the 3 groups was confirmed by two rising quantitative β-human chorionic gonadotropin hormone levels measured 48 h apart, or by ultrasound confirmation of fetal heart activity at 7–8 weeks. The patients were evaluated every 2–4 weeks during pregnancy. The patients were interviewed, and medical records were reviewed to confirm pregnancy histories. Prenatal diagnosis was performed at 8–20 weeks. Multicolor ultrasonography was conducted at 24–28 weeks and performed serially to assess fetal growth and amniotic fluid volume every 4 weeks. Uterine and umbilical artery blood velocity waveforms were assessed every 2–4 weeks from 28 weeks. Weekly, non-stress testing was performed from 28 weeks. When complications were identified, the patient was provided with the appropriate treatment.

A positive pregnancy outcome was the birth of a live infant, a negative pregnancy outcome was considered to be a fetal loss (miscarriage, fetal death, or stillbirth). An obstetric complication was classified as one of the following events: preeclampsia, preterm labor, Intrauterine growth restriction IUGR, premature rupture of membrane PROM, gestational diabetes mellitus GDM, major bleeding, and fetal malformation.

For fetal outcome, we recorded the live birth ratio, gestational age at delivery, and neonatal weight. Statistical analysis was performed using IBM SPSS stats 19. Variables were analyzed using the One-way ANOVA test. P < 0.05 was considered significant.

3. Results

Patient characteristics: All 14 patients enrolled in the study had a history of miscarriage before 12 weeks of gestational age. The age of the patients ranged from 25 to 32 years old. There were no significant differences in patient age, the total number of prior pregnancies, prior live births, or miscarriages between the 3 groups (Table 1). Each patient had a positive result for aPL antibody testing.

Pregnancy outcome: Of the 14 patients, 5 had live births. 4 patients had an abortion before 10 weeks, 5 patients had a stillbirth and none had fetal death. The live birth rate was 35.71% (5/14), and the fetal loss rate was 64.28% (9/14).

Of the 5 patients treated with aspirin alone, 2 had live births. 2 had an abortion prior to 10 weeks, and 1 patient had a stillbirth. The live birth rate was 40% (2/5) and the fetal loss rate was 60% (3/5).

Of the 5 patients treated with aspirin + prednisone, none had live births. 2 had an abortion prior to 10 weeks, and 3 had stillbirths. The live birth rate was 0% and the fetal loss rate was 100%(5/5).

Of the 4 patients treated with aspirin + heparin, 2 had live births. only 1 had a stillbirth. The live birth rate was 75% (3/4) and the fetal loss rate was 25% (1/4). As shown in (Table 2), There were no significant differences between the 3 groups (P > 0.05).

Obstetric complications: Of the 14 patients, 3 patients from group A had pregnancy complications, of which 2 had premature labor, and one had GDM. 2 patients from group B had pregnancy complications, of which one had premature labor, and one had preeclampsia. There were no pregnancy complications in group C.

The total rate of pregnancy complications was 35.71%. There were no significant differences in the incidence of complications between the 3 groups (P > 0.05) (Table 3). There was no major bleeding, fetal malformation, IUGR, or PROM in either group (data not shown).

Fetal outcome: To assess the fetal outcome, gestational age was recorded at delivery, as well as neonatal weight. Neonatal weight in group C was significantly increased compared with group A (P < 0.05), but there were no differences in gestational age at delivery (P > 0.05) (Table 4).

4. Discussion

APS is considered a challenging issue for clinicians, and women of childbearing age. Since its original description, It has emerged as the most important treatable cause of recurrent miscarriage [3,8]. The incidence of fetal loss in APS women is reported to be 34–76% [9], and the risk of subsequent fetal loss in women with aPL and previous fetal Table 1

| Variable                  | Group A Aspirin (n = 5) | Group B Aspirin + prednisone (n = 5) | Group C Aspirin + heparin (n = 4) | P-value |
|---------------------------|------------------------|-------------------------------------|----------------------------------|---------|
| Age                       | 29 ± 2                 | 26 ± 2.64                           | 27.5 ± 2.38                      | 0.178   |
| No. of prior pregnancies  | 2.6 ± 0.54             | 3.6 ± 2.07                         | 3.25 ± 1.5                      | 0.586   |
| No. of prior live births  | 0.2 ± 0.44             | 0                                  | 0.25 ± 0.5                      | 0.575   |
| No. of miscarriages       | 2.4 ± 0.54             | 3.6 ± 2.07                         | 3 ± 1.15                        | 0.441   |
randomized placebo-controlled trial, Pattison et al. showed that low-dose aspirin has no additional benefit when added to supportive care for patients for whom recurrent early fetal loss is the only pregnancy complication of APS [17].

5. Conclusion

This trial, like all other trials in small private clinics, is small, but it results raise questions about the need for therapies such as heparin and corticosteroids for women with APS in resource-limited settings similar to Syria.

The outlook for a successful pregnancy has much improved as a consequence of medical therapy. However, large-scale, high-quality RCTs, and further investigation of the pathogenetic mechanisms of complications in APS are needed, to identify the most appropriate treatment protocol for developing countries.

Registration of research studies

Researchregistry8251.

Ethical approval

The study was approved by the Ethics Committee of Tishreen University, Faculty of medicine.

Sources of funding for your research

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contribution

All authors contributed in all the phases of preparing the paper.

Consent

Written informed consent was obtained from all patients for publication of this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Researchregistry825.

You will find the registration here: https://www.researchregistry.com/browse-the-registry#home/

Guarantor

Dr. Latifa Baiazid.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

The Authors declare that there is no conflict of interest.

Acknowledgements

None.

Abbreviations

APS Antiphospholipid antibody syndrome
aPL Antiphospholipid antibodies
aCL Anticardiolipin antibodies
LA Lupus anticoagulant antibodies
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