# Comparative Study between Three Different Thromboprophylactic Treatments in the Management of Patients with Recurrent Miscarriage

Farid Ibrahim Hassan[1], Emad Marouf Abd El Latif[1], Ahmed Abdou Ellawah[1], Mofeed Fawzy Mohamed[1] and Alaa Elsayed Saleh[2]
[1] Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[2] Obstetrics and Gynecology Department, Mubarak Central Hospital, Giza, Egypt
alaa.elsayed2050@yahoo.com

**Abstract:** Purpose: Recurrent miscarriage is a major women's health problem. The aim of this study is to evaluate the efficacy and safety of low dose aspirin (LDA) alone, unfractionated heparin alone or a combination of both anticoagulant agents as a preventive measure in women with a history of at least two unexplained miscarriages with or without antiphospholipid syndrome. **Methods:** This randomized trial included 75 pregnant women between the ages of 18 and 42 years, who hada history of at least two recurrent miscarriages. Patients were recruited by the closed-envelope method from the outpatient clinics of El-Hussein University Hospital during December 2015 - august 2017. Results: Compared with the group who received LDA or unfractionated heparin alone, the combination group had a significantly greater number of live births than Groups I and II [ (23/25(92%) versus 16/25(64%) and 20/25(80%); p =0.003)], and had a significantly lower number of miscarriages (9 miscarriage in Groups I (36%), 5 miscarriages in Group II (20%), 2 miscarriages in Group III (20%); [p =0.001]. The mean gestational age at delivery in Group III [37.97 ± 1.9 versus 36.01± 1.7 and 36.23±2.42 weeks] in Groups I and II respectively; [p = 0.004]. The mean birth weight in Group III was 3687± 503 versus 2818±379 and 3281± 363g in Groups I and II; [p = 0.025]. Six babies were admitted to the neonatal unit (3 (12%) in Group I, 2 (8%) in Group II and 1(4%) in Group III). There were no intrauterine or neonatal deaths in the study. Conclusion: The use of anticoagulants (calheparin) and/or aspirin (aspocid) could potentially improve the pregnancy outcome and increase live-birth rate, the combination of calheparin and aspirin is superior to aspirin alone orcalheparin alone in achieving more live births in patients with/without thrombophilia.

**[**Farid Ibrahim Hassan, Emad Marouf Abd El Latif, Ahmed Abdou Ellawah, Mofeed Fawzy Mohamed and Alaa Elsayed Saleh. **Comparative Study between Three Different Thromboprophylactic Treatments in the Management of Patients with Recurrent Miscarriage.** *Nat Sci* 2018;16(12):77-82]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 13. doi:10.7537/marsnsj161218.13.

**Keywords:** aspirin, low-molecular-weight heparin, recurrent miscarriage, thrombophilia

## 1. Introduction

Recurrent miscarriage is a major women's health issue; 1% to 2% of women of reproductive age have experienced three or more successive miscarriage, and approximately 5% have lost at least two successive pregnancies [1].

In half of such patients, no underlying cause of miscarriage can be identified[2]. The etiology of most recurrent miscarriages remains unclear. The majority of cases−after excluding anatomical, genetic, microbiological, and hormonal causes of abortions and complete medical, surgical, and social history − remain idiopathic [3,4].

Although controversial, various reports have claimed that hereditary thrombophilias may predispose to thrombosis in decidual vessels, and subsequent fetal hypoxia and pregnancy loss [5,6]. Various interventions have been suggested to improve rates of live birth in such cases, no effective treatment has been identified. Pregnancy itself is a hypercoagulable state associated with increased levels of procoagulant factors and decreased levels of naturally occurring anticoagulants such as protein S. The overall fibrinolytic activity is impaired due to increase in plasminogen activator inhibitor-2 [7–9].

It has been suggested that in women with recurrent miscarriage and a diagnosis of the antiphospholipid syndrome, treatment with aspirin and unfractionated heparin may improve the pregnancy outcome, although findings from available randomized trials have been inconsistent[10,11].

Heparin has been shown to have potentially beneficial effects on trophoblast implantation and influence trophoblast apoptosis. To be beneficial, heparin may need to be given at the time of implantation[12–14].

Aspirin is increasingly used to reduce the risk of miscarriage and improve pregnancy outcome in women who have suffered a recurrent miscarriage. An important factor controlling tissue perfusion is the equilibrium between thromboxane A2 (in addition to its platelet aggregating properties, it also has a vasoconstrictor effect) and prostacyclin (has vasodilatory properties) [1,15,16].

We aimed to assess the efficacy and safety of low dose aspirin alone, unfractionated heparin alone or

a combination of aspirin and unfractionated heparin as a preventive measure in women with recurrent miscarriage with and without thrombophilia.

## 2. Patients and Methods

This prospective study was conducted at the outpatient clinics of El-Hussein University Hospitalin the Department of Obstetrics and Gynecology from December 2015-August 2017. The previous miscarriage was defined as pregnancy loss at a gestational age of 20 weeks or less. The definition of miscarriage included documentation of pregnancy by a positive pregnancy test and clinical manifestations of miscarriage (e.g., abdominal pain, cramps, and vagina bleeding); it did not include the loss of a biochemical pregnancy. The recurrent miscarriage was defined as at least two miscarriages. Selected patients were divided randomly into three groups:

- **Group I ( 25 patients)**: this group received low dose aspirin ( 75 mg oral once daily ) ( Aspocid pediatric, chemical industries development, Giza, Egypt ) until the end of the third month of pregnancy.
- **Group II ( 25 patients)**: this group received heparin calcium ( 5000 IU subcutaneous twice daily ) (cal-heparin, amounpharmaceutical, Cairo, Egypt ) until the end of the third month of pregnancy.
- **Group III ( 25 patients )**: this group received low dose aspirin (75 mg oral once daily) (Aspocid pediatric, chemical industries development, Giza, Egypt ) plus heparin calcium (5000 IU subcutaneous twice daily) (cal-heparin, amoun pharmaceutical, Cairo, Egypt) until the end of the third month of pregnancy.

**Inclusion criteria**

Women were eligible for this study if they had a history of two or more consecutive miscarriage, unexplained miscarriage or documented thrombophilia.

**Exclusion criteria**

Women with a history of chronic disease like renal or cardiac disorders, thromboembolism, DM, hypertension, uterine abnormalities. In addition, patients with ahistory of sensitivity to aspirin or heparin were excluded.

**Data collected to determine:**

Socio-demographic, obstetric, and medical data were gathered from the study participants using pre-tested questionnaires.

**Intervention**:

Treatment was started as soon as pregnancy test become positive. follow up included early dating scan for assessment of gestational age and viability at 6-7 weeks gestation. Antenatal visits were planned every 2 weeks from time of enrollment in the study till 32 weeks gestation, then weekly until delivery. To detect thrombocytopenia, baseline platelet count was checked before therapy, then every two weeks during the treatment period. Heparin therapy was planned to be discontinued if platelet count becomes less than 100,000/ml or if there is a 50% drop in the baseline platelet count.

**Primary outcome measures:**

The primary outcome measure was the live-birth rate.

**Secondary outcome measures:**

Secondary outcome measures were as follows:

- ✓ Miscarriage of less than 20 weeks.
- ✓ Preterm delivery less than 37 weeks.
- ✓ Thrombocytopenia (platelet count less than 100,000/ml).
- ✓ Obstetric complications (pre-eclampsia, IUFD and intrauterine growth restriction (IUGR).

**Statistical analysis**

Data are statistically described as mean±SD or as ranges, frequencies (number of cases), and percentages as appropriate. It was performed using Microsoft® Excel® version 2016and Statistical Package for Social Sciences (SPSS®) for Windows® version 22.0. P-value <0.05 was considered statistically significant.

**Ethical Consideration**

Agreement for the study obtained from the ethical committee of El-Hussein University hospital and the purpose of the study and the protocols used were explained to each woman, and consent was obtained from all of them.

## 3. Results

Seventy-five women with recurrent miscarriage were included in the study: Group I (25 patients); received low dose aspirin (75 mg oral once daily). Group II (25 patients); heparin calcium (5000 IU subcutaneous twice daily). Group III (25 patients); received low dose aspirin plus heparin calcium.

As exposed in Table2, In the Group III there were a significantly greater number of live births than Groups I and II [ (23/25(92%) versus 16/25(64%) and 20/25(80%); p=0.003)].

The mean gestation algae and the neonatal birth weight were significantly higher in Group III than Groups I and II. The mean gestation alage at delivery in Group III [37.97±1.9 versus 36.01± 1.7 and 36.23±2.42 weeks] in-groups I and II respectively; [p=0.004]. The mean birth weight in Group III was 3687± 503 versus 2818±379 and 3281± 363 gin Groups I and II; [p =0.025].

There was a highly significant difference between Groups I, II and III in the rate of miscarriages (9miscarriagein Groups I (36%), 5miscarriages in Group II (20%), 2 miscarriages in Group III (20%); [p=0.001]. Most miscarriages in Groups I, II occurred in the first trimester while in Group III; most occurred

in the second trimester. There were no intrauterineorneonatal deaths in the study.

**Table1: Shows Age and pregnancy characteristics of the participants.**

| VARIABLES | | GROUP I (N=25) | GROUP II (N=25) | GROUP III (N=25) | P-Value |
|---|---|---|---|---|---|
| **Maternal Age (Years)** | **Mean±SD** | 29.3±4 | 28.1±4.4 | 29.1±4.1 | **0.11** |
| | **Range** | 22–38 | 21–39 | 21-40 | |
| **BMI** | | 25.4±4.9 | 25.0±4.8 | 24.6±4.1 | **0.26** |
| **Previous Miscarriages (No.)** | **Median** | 3 | 3 | 3 | **0.29** |
| | **Range** | ( 3–6) | (3–5) | (2-5) | |
| **Prior Live Births** | | 14 (56%) | 13 (52%) | 12 (48%) | **0.99** |
| **Prior IUFD (No.)** | | 9 (36%) | 11 (44%) | 10 (40%) | **0.95** |
| **Total Pregnancies** | | 3.81 ±1.54 | 4.19±1.92 | 3.81 ±1.54 | **0.53** |

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

There were no significant differences in the patient's age, body mass index, prior miscarriages, prior live births, prior IUFD and prior total pregnancies.

**Table 2: Final outcome data from participants:**

| Variables | Group I (n=25) | Group II (n=25) | Group III (n=25) | p-Value |
|---|---|---|---|---|
| **Live Births (%)** | 16 (64%) | 20(80%) | 23 (92%) | **0.003** |
| **Gestational Age At Birth (Weeks)** | 36.01± 1.7 | 36.23±2.42 | 37.97± 1.9 | **0.004** |
| **Miscarriages (%)** | 9 (36%) | 5 (20%) | 2 (8%) | **0.001** |
| **Gestational Age At Loss (Weeks)** | 9.71± 3.79 | 11.23±3.33 | 13.67±3.12 | **0.621** |
| **Birth Weight (Grams)** | 2818±379 | 3281± 363 | 3687± 503 | **0.025** |

***Data is expressed as number (%).**

**Table 3 Obstetric, maternal and Neonatal complications:**

| Variables | GROUP I | GROUP II | GROUP III | P-VALUE |
|---|---|---|---|---|
| **Pre-Eclampsia** | 2 (8%) | 1 (4%) | 1 (4%) | **0.91** |
| **IUGR** | 1(4%) | 1 (4%) | 2 (8%) | **0.79** |
| **PRETERM LABOUR** | 3 (12%) | 2 (8%) | 1 (4%) | **0.13** |
| **IUFD** | 0 (0%) | 0 (0%) | 0 (0%) | **0.23** |
| **Admission To NICU** | 3 (12%) | 2 (8%) | 1 (4% ) | **0.88** |

***Data is expressed as number (%).**

Nevertheless not statistically significant, women in Group III tended to have lower rates of preterm births [ (1/25 (4%) versus 3/25 (12%) and 2/25 (8%); p = 0.13]. There were no statistically significant relations regarding Pre-eclampsia, IUGR, and IUFD. Six babies were admitted to the neonatal unit (3 (12%) in Group I, 2 (8%) in Group II and 1(4%) in Group III).

**4. Discussion**

Recurrent miscarriages are the loss of more than two consecutive pregnancies before the 24th week of gestation. It is either primary (in women without a previous live-born infant) or secondary (in women with at least one previous live-born infant) [8,17,18].

75 women were included in this study randomized into three groups; Group I (25 patients); received low dose aspirin (75 mg oral once daily). Group II (25 patients); heparin calcium (5000 IU subcutaneous twice daily). Group III (25 patients); received low dose aspirin plus heparin calcium. The age of participants ranges between 18 and 42 (mean±SD 29.3±4 in group I,28.1±4.4 in group II and 29.1±4.1 in group III); There were no significant differences in the patient's age, body mass index, prior miscarriages, prior live births, prior IUFD and prior total pregnancies.

Many trials were carried out on the randomized use of low dose aspirin (aspocid) and Heparin on women with unexplained recurrent pregnancy loss (RPL) found that the regimen was associated with high live-birth rates and a few late pregnancy complications [19–21].

Therefore, the present study was conducted to evaluate the effectiveness of three different anticoagulant agent's regimen in women with recurrent

miscarriage who have either confirmed thrombophilia or unexplained recurrent miscarriage.

In the present study, the combination of Heparin plus LDA treatment resulted in a high live-birth rate in women with recurrent miscarriages; In Group III there were a significantly greater number of live births than Groups I and II [ (23/25(92%) versus 16/25(64%) and 20/25(80%); p =0.003)]. Several studies have revealed that LMWHs are effective in the treatment of pregnant women with thrombophilic disorders or APS.

This was in agreement with a study held in 2012 on 167 patients with recurrent pregnancy loss, where group one received acetylsalicylic acid, group two received low molecular weight heparin and group three received both acetylsalicylic acid and low molecular weight heparin. Among women negative for thrombophilia, 19 patients of those taking aspirin alone with incidence 70.3% end in a live birth and 8 patients end in the fetal loss with incidence 29.7%. In group two (women receiving heparin alone), 22 patients with an incidence of 88% end in a live birth and 3 patients with an incidence of 12% end in a fetalloss. In the third group (women receiving aspirin and heparin), 28 patients with an incidence of 100 % end in live birth while no patients end in the fetal loss with the incidence of 0%[22].

**Brenner et al.,** prospectively evaluated the efficacy of LMWH (enoxaparin) plus LDA during 166 pregnancies in 166 thrombophilic women with recurrent pregnancy loss, including 9 women with APS. The dose of enoxaparin was 40mg for women with a solitary thrombophilic defect and 80 mg for women with combined thrombophilic defects. The enoxaparin dose of 40mg/day resulted in a live birth in 69% of gestations, compared with 83% of gestations for women treated with enoxaparin at 80mg/day[23,24].

**Backos et al.** agreed with our present study in that combination treatment with aspirin and heparin lead to a high live birth rate among women with recurrent miscarriage and antiphospholipid antibodies [25–27].

In addition, a randomized controlled trial comparing LMWH plus LDA with intravenous immunoglobulin in the treatment of women with recurrent pregnancy loss associated with APS revealed that LMWH plus LDA resulted in a significantly higher live-birth rate (72.5% versus 39.5%) [27–29].

However, these findings are not in agreement with a study conducted by **Tong et al., 2016** to evaluate the efficacy and safety of aspirin-heparin treatment for unexplained recurrent spontaneous abortion (URSA). There were 907 pregnant women with a diagnosis of URSA, 367 of them were pooled in the study group with aspirin-heparin therapy and 540 women in the control group with placebo. they stated that Live birth rates in the aspirin-heparin treated groups and placebo groups were compared and no significant difference was found [30].

**Kaandorp et al.** concluded in their recent review that there was no benefit of LDA over heparin treatment on the live-birth rate in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia [1].

Despite the treatment, Six babies were admitted to the neonatal unit (3 (12%) in Group I, 2 (8%) in Group II and 1(4%) in Group III). This confirms previous reports of a high incidence of pregnancy complications in patients with recurrent miscarriages, especially if phospholipid antibodies are detected [1,31–33], and emphasizes the need for close antenatal surveillance. Most of these miscarriages occurred before 14 weeks of gestation and occurred spontaneously, but in some cases, labor was induced prematurely because of preeclampsia. All premature infants were admitted to the neonatal unit, but all of them were later discharged in good condition.

A study conducted by **Kutteh** showed that there were no significant differences between the low-dose aspirin and the heparin plus low-dose aspirin Groups with respect to gestational age at delivery (37.2 ±3.4 weeks vs. 37.8 ±2.1)[32,34,35].

These disagreed with our results; the mean gestational age and the neonatal birth weight were significantly higher in Group III than Groups I and II. The mean gestational age at delivery in Group III [37.97 ± 1.9 versus 36.01± 1.7 and 36.23±2.42 weeks] in Groups I and II respectively; [p = 0.004]. The mean birth weight in Group III was 3687± 503 versus 2818±379 and 3281± 363g in Groups I and II; [p = 0.025].

In the current study, two women in the LDA group had pre-eclampsia while one case in each of the other groups. A link (perhaps through endothelial dysfunction and heptahelical G-protein-coupled receptors (GPCRs) has been postulated between pre-eclampsia and increased cardiovascular disease later in life and women with unexplained recurrent miscarriages who might be at increased cardiovascular risk [35,36]. The role of calcium/calmodulin-dependent kinase IV (CaMKIV) in blood pressure regulation (through the control of endothelial nitric oxide synthase activity), increased levels of G protein-coupled receptor kinase and action of heparin by acting as a GRK inhibitor was observed [37,38].

Regarding maternal outcomes, LDA and Heparin are safe drugs and were well tolerated in this study. Of those taking heparin, none developed thrombocytopenia or had symptomatic complications, apart from mild localized bruising at the injection site.

**Conclusion**

Combination treatment with aspirin and unfractionated heparin leads to a high live birth rate among women with recurrent miscarriage with and without Confirmed thrombophilia. This combination may indorse successful embryonic embedding in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation.

**References**


1 Elmahashi MO, Elbareg AM, Essadi FM, Ashur BM, Adam I. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. BMC Res Notes 2014;7:23. doi:10.1186/1756-0500-7-23.

2 Vlaanderen W. Is recurrent miscarriage a useful clinical concept? Acta Obstet Gynecol Scand 2014;93:848–51. doi:10.1111/aogs.12453.

3 Rajaram S, Gupta V, Loss BG-RP. Unexplained Recurrent Miscarriage: A Dilemma. Springer 2018.

4 Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harb Perspect Med 2015;5:a023119. doi:10.1101/cshperspect.a023119.

5 Martinelli I, Taioli E, Cetin I, Marinoni A, Gerosa S, Villa M V., et al. Mutations in Coagulation Factors in Women with Unexplained Late Fetal Loss. N Engl J Med 2000;343:1015–8. doi:10.1056/NEJM200010053431405.

6 Singla S, Jain S. Recurrent Pregnancy Loss and Inherited Thrombophilia. Recurr. Pregnancy Loss, Singapore: Springer Singapore; 2018, p. 113–28. doi:10.1007/978-981-10-7338-0_9.

7 Steven A. Savella, Jessica A. Kvasic and JFL. Anticoagulation Therapy. Anticoagulation Ther., Cham: Springer International Publishing; 2016, p. 2016. doi:10.1007/978-3-319-73709-6.

8 Elfattah A, Amer S,… WH-BM, 2017 undefined. Aspirin versus low-molecular-weight heparin in treating recurrent miscarriages in women without antiphospholipid antibody syndrome. Bmfj Eg Net 2017.

9 Kruithof EK, Tran-Thang C, Gudinchet a, Hauert J, Nicoloso G, Genton C, et al. Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors. Blood 1987;69:460–6.

10 Empson MB, Lassere M, Craig JC, Scott JR. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev 2005. doi:10.1002/14651858.CD002859.pub2.

11 Kaandorp SP, Goddijn M, Van Der Post JAM, Hutten BA, Verhoeve HR, Hamuly??k K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. Obstet Gynecol Surv 2010;65:621–2. doi:10.1097/OGX.0b013e3182021f71.

12 Bruno V, Rizzacasa B, Pietropolli A, Capogna MV, Massoud R, Ticconi C, et al. OLR1 and Loxin Expression in PBMCs of Women with a History of Unexplained Recurrent Miscarriage: A Pilot Study. Genet Test Mol Biomarkers 2017;21:363–72. doi:10.1089/gtmb.2016.0331.

13 Hills FA, Abrahams VM, González-Timón B, Francis J, Cloke B, Hinkson L, et al. Heparin prevents programmed cell death in human trophoblast. Mol Hum Reprod 2006;12:237–43. doi:10.1093/molehr/gal026.

14 Nelson SM, Greer IA. The potential role of heparin in assisted conception. Hum Reprod Update 2008;14:623–45. doi:10.1093/humupd/dmn031.

15 Bussolino F, Benedetto C, Massobrio M, Camussi G. Maternal Vascular Prostacyclin Activity in Pre-Eclampsia. Lancet 1980;316:702. doi:10.1016/S0140-6736(80)92746-4.

16 Navaratnam K. Platelet function and response to low-dose aspirin in pregnancy. Doctoral Diss Univ Liverpool 2017.

17 Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: A randomized, controlled trial of treatment. Obstet Gynecol 2002;100:408–13. doi:10.1016/S0029-7844(02)02165-8.

18 Ruffatti A, Salvan E, Ross T Del, Gerosa M, Andreoli L, Maina A, et al. Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positivity: A European multicentre retrospective study. Thromb Haemost 2014;112:727–35. doi:10.1160/TH14-03-0191.

19 Mekinian A, Cohen J, Alijotas-Reig J, Carbillon L, Nicaise-Roland P, Kayem G, et al. Unexplained Recurrent Miscarriage and Recurrent Implantation Failure: Is There a Place for Immunomodulation? Am J Reprod Immunol 2016;76:8–28. doi:10.1111/aji.12493.

20 Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. Fertil Steril 2006;86:362–6. doi:10.1016/j.fertnstert.2005.12.068.

21 Jain P, Dhodapkar SB, Daniel M. Combination of aspirin and heparin in unexplained recurrent miscarriages - “Empirical or evidence based”. J Hum Reprod Sci 2011;4:155–6.

doi:10.4103/0974-1208.92293.

22 Giancotti A, Torre R La, Spagnuolo A, D'Ambrosio V, Cerekja A, Piazze J, et al. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. J Matern Neonatal Med 2012;25:1191–4. doi:10.3109/14767058.2011.600366.

23 Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost 2000;83:693–7. doi:10.1055/s-0037-1613894.

24 Schleussner E, Kamin G, Seliger G, Rogenhofer N, Ebner S, Toth B, et al. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss a multicenter trial with a minimization randomization scheme. Ann Intern Med 2015;162:601–9. doi:10.7326/M14-2062.

25 Backos M, Rai R, Baxter N, Chilcott IT, Cohen H, Regan L. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. Br J Obstet Gynaecol 1999;106:102–7. doi:10.1111/j.1471-0528.1999.tb08208.x.

26 Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and pregnancy complications. Int J Mol Sci 2015;16:28418–28. doi:10.3390/ijms161226104.

27 Quao ZC, Tong M, Bryce E, Guller S, Chamley LW, Abrahams VM. Low molecular weight heparin and aspirin exacerbate human endometrial endothelial cell responses to antiphospholipid antibodies. Am J Reprod Immunol 2018;79:e12785. doi:10.1111/aji.12785.

28 Dendrinos S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. Int J Gynecol Obstet 2009;104:223–5. doi:10.1016/j.ijgo.2008.11.010.

29 Nazari Z, Ghaffari J, Ebadi A. Comparison of the effect of aspirin and heparin with or without intravenous immunoglobulin in treatment of recurrent abortion with unknown etiology: A clinical study. J Nat Sci Biol Med 2015;6:17. doi:10.4103/0976-9668.166054.

30 Tong L, Wei X jiang. Meta-analysis of aspirin-heparin therapy for un-explained recurrent miscarriage. Chinese Med Sci J 2016;31:239–46. doi:10.1016/S1001-9294(17)30007-X.

31 Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80:614–20.

32 Out HJ, Kooijman CD, Bruinse HW, Derksen RHWM. Histopathological findings in placentae from patients with intra-uterine fetal death and anti-phospholipid antibodies. Eur J Obstet Gynecol Reprod Biol 1991;41:179–86. doi:10.1016/0028-2243(91)90021-C.

33 de Wolf F, Carreras LO, Moerman P, Vermylen J, Van Assche A, Renaer M. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant. Am J Obstet Gynecol 1982;142:829–34. doi:10.1016/S0002-9378(16)32527-3.

34 Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: Treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 1996;174:1584–9. doi:10.1016/S0002-9378(96)70610-5.

35 Arachchillage DRJ, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thromb Haemost 2015;113:13–9. doi:10.1160/TH14-05-0416.

36 Santulli G, Trimarco B, Iaccarino G. G-Protein-Coupled Receptor Kinase 2 and Hypertension. High Blood Press Cardiovasc Prev 2013;20:5–12. doi:10.1007/s40292-013-0001-8.

37 Izzo R, Cipolletta E, Ciccarelli M, Campanile A, Santulli G, Palumbo G, et al. Enhanced GRK2 expression and desensitization of βAr vasodilatation in hypertensive patients. Clin Transl Sci 2008;1:215–20. doi:10.1111/j.1752-8062.2008.00050.x.

38 Santulli G, Cipolletta E, Sorriento D, Del Giudice C, Anastasio A, Monaco S, et al. CaMK4 gene deletion induces hypertension. J Am Heart Assoc 2012;1:e001081. doi:10.1161/JAHA.112.001081.

9/29/2018