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Pregnancy Complications and Side Effects of Aspirin alone and Aspirin Plus Low Molecular Heparin in patients of Bad Obstetric History with elevated Anti-Phospholipid antibodies

Dr. Anjanadevi Santpure[1], Dr. Shivkumar Santpure[2] ,Dr. Mahesh Tandale[3]
[1,2,3]Associate Professor,JIIU's Indian Institute of Medical Science and Research, Badnapur Dist. Jalna, Maharashtra, India
Corresponding Author:Dr. Anjanadevi Santpure[1]Email:anjanasantpure@yahoo.com

Abstract

Background: Obstetric complications are the hallmark of antiphospholipid syndrome. Recurrent miscarriage, pre-term birth, oligohydramnios, prematurity, intrauterine growth restriction, pre-eclampsia/eclampsia, thrombosis and placental insufficiency are the most severe complications in patients of bad Obstetric history with elevated anti-phospholipid antibodies. Hence this single-center study was carried out to identify the pregnancy complications and side effects of aspirin alone and aspirin plus low molecular weight heparin (LMWH) in spite of the treatment.

Methods and Methods: This prospective, single-center study was conducted among 57 patients in the Department of Obstetrics and Gynaecology, Kasturba Medical College Hospital, Manipal, Karnataka, India during the period of November 2000 to November 2002. Recruitment of patients was done depending upon the bad obstetric history. They underwent test for anticardiolipin antibodies (ACA) and Lupus anticoagulant (LA).Out of 111 patients 57 patients were positive for anti-phospholipid antibodies (APA). They were further divided into aspirin alone group and aspirin plus low molecular heparin group randomly after confirmation of pregnancy. The complication like Intrauterine growth restriction (IUGR),pregnancy induced hypertension (PIH), oligohydramnios and preterm were studied.The data was entered and tabulated in MS-Excel 2007, and statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS 22.0) version.

Results: Comparison of pregnancy complications in aspirin alone and aspirin plus low molecular weight heparin(LMWH)group showed that Intrauterine growth restriction(IUGR) was seen in 27.3% and 14.3%, Pregnancy induced hypertension(PIH) in 27.3% and 7.1% and oligohydramnios in 9% and 14.3% in aspirin alone and aspirin plus LMWH groups respectively. The results were not statistically significant. Local pain was recorded in 10(50%) of patients in LMWH group. Around 10(27%) of aspirin patients experienced an epigastric pain. No patient had bleeding disorder.

Conclusion: Over period of time not much change in pregnancy complication rate seen despite medication with aspirin alone and aspirin plus LMWH.

Keywords: Aspirin, Anti-phospholipid antibodies, low molecular weight heparin (LMWH), Pregnancy complications

Introduction:

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and venous thrombosis, gestational morbidity and presence of elevated and persistently positive serum titres of antiphospholipid antibodies.[1] Women with APS have an increased risk for pregnancy complications like hypertensive disorders of pregnancy, preterm birth, intrauterine fetal death (IUFD) and small-for-gestational age (SGA) infants.[2]Nowadays, APS is recognized as the most significant cause of RPL (recurrent

pregnancy loss). Thrombophilia including antiphospholipid syndrome has been identified in about 50% of women with recurrent miscarriage. Upto 15-20% women with recurrent pregnancy loss have antiphospholipid antibodies (APA).[3]Women with APS have a spontaneous abortion rate as high as 90% for pregnancies without pharmacologic treatment.[4] APS is strongly associated with recurrent abortion and pregnancy complications such as intrauterine growth restriction (IUGR), preterm labor, preeclampsia, and intrauterine fetal death. The adverse effects of antiphospholipid antibodies is on trophoblast differentiation and invasion, placental infarctions, and thrombosis, and are thought to be responsible for recurrent abortion and pregnancy complications associated with APS.[5] Antiphospholipid antibodies include anticardiolipin antibodies and lupus anticoagulant.

There are three main subtypes (isotypes) of Anticardiolipin antibodies(ACA)-IgG,IgM and IgA[6].Testing of IgM and IgG is most widely used. IgG subtype is predictive for fetal loss and thrombosis[7] .These antibodies are directed against a cardiolipin or against phospholipid binding proteins such as β_2-glycoprotein I (β_2-GPI). The major activity of β_2-GPI appears to be its phospholipid-dependent anticoagulant inhibition of prothrombinase activity of platelets and adenosine diphosphate-inducted platelet aggregation. This results from the binding of this protein to negatively charged phospholipid surfaces such as activated platelets. Then β_2-GPI competitively inhibits the binding of coagulation factors, especially factor XII and the prothrombinase complex to negatively charged phospholipid surfaces and prevents activation of the coagulation cascade. An antibody directed against β_2-GPI would bind and prevent it from acting as phospholipid-dependent anticoagulant[8]. Detection of ACA and β_2-GPI antibodies are by solid phase assays. The ACA ELISA test, have been gradually refined. The ELISA format allows bulk testing and the results are not effected by factor deficiency or the use of anticoagulants. Important methodological considerations are the quality of the cardiolipin used and the technique for coating the microtitre plates. International consensus criteria, requires that patient with > 20 units anticardiolipin antibody to be identified as having definite APS[9].

The lupus anticoagulant is an immunoglobulin of IgG or IgM type. These antibodies prolong phospholipid dependent coagulation assays by binding to the epitopes of the anionic phospholipid portion of the prothrombinase complex. Prothrombinase complex: prothrombin, factor Xa and V, and calcium, which converts prothrombin to thrombin in the coagulation pathway[7].Screen test for the detection of LAC are : APTT (Activated Partial Thromboplastin Time), DRVVT (Dilute Russel's Viper Venom test), KCT (Kaolin Clotting Time) and TTI (Tissue Thromboplastin Inhibition Time) .The presence of APAs is associated with thrombosis. The most common theories for their mechanism of action is divided into:

i) Those that ascribe APAs to disrupt platelet function. The effects on platelet function is by activation of platelets leading to release of the procoagulant thromboxane[10] and interference with the complex of phospholipid and β_2-GPI [11].

ii) Those that interfere with function of endothelial cells. This is done by inhibition of prostacyclin by vascular endothelial cells[11]. Endothelial cell damage leading to increased procoagulant activity or impaired fibrinolytic responses[6].

iii) Effects on Coagulation : This action is through inhibition of the protein C, free protein S anticoagulant system. [12] APAs interfere with thrombomodulin production and by inhibition of antithrombinIII activity .

The prospective fetal loss rate in women with APAs has been reported to be in the range of 50-75%. Although fetal demise can occur in any of the three trimesters of pregnancy, first trimester loss is more common. The actions of APAs in causing adverse pregnancy outcome may be divided intro their effects on implantation and their effects inpostimplantation period. The post-implantation effect of APAs leads to adverse pregnancy

outcome. They are related to their thrombogenic action and vasculopathy leading to decreased placental perfusion. This vasculopathy was characterized by fibrinoid necrosis, atherosis of decidual vessels and intimal thickening of blood vessels.Pregnancies affected by antiphospholipid syndrome (APS) are managed with low molecular weight heparin (LMWH), either alone or in combination with aspirinwith prevention of maternal and fetal adverse outcomes as the goal.[13]

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that works primarily through its inhibition of two cyclooxygenase isoenzymes (COX-1 and COX-2), which are necessary for prostaglandin biosynthesis. The COX-1 isoform is present in the vascular endothelium and regulates the production of prostacyclin and thromboxane A_2, prostaglandins with opposing regulatory effects on vascular homeostasis and platelet function. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, whereas thromboxane A_2 (TXA2) is a potent vasoconstrictor and promotes platelet aggregation. The COX-2 isoform is inducible and expressed almost exclusively following exposure to cytokines or other inflammatory mediators. The effect of aspirin on COX-dependent prostaglandin synthesis depends on dose. At lower dosages (60–150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of prostacyclin**.** At higher doses, aspirin inhibits both COX-1 and COX-2, effectively blocking all prostaglandin production[14].Low dose of aspirin preferentially inhibit platelet thromboxane synthesis leaving endothelial prostacyclin synthesis relatively intact.[15] Aspirin inhibits platelet adhesion to collagen under condition of stasis or low flow but not under normal conditions. Aspirin also inhibits second wave aggregation and the associated release reactions inducted by agents such as collagen, ADP and adrenaline.[15] Low dose aspirin inhibit the release of ADP (adenosine di phosphate) from platelet and sticking to each other.[16]Low dose aspirin is a potent stimulator of IL-3. Cytokines have role in endocrine and immune system. This helps in endometrial development leading to better implantation of zygote. It also restores GnRH induced β hCG secretion.[16]LMWH is standard with a history of thromboembolism, yet studies regarding its effectiveness for the prevention of APS-associated adverse pregnancy outcomes have been fraught with contradiction.[18] Furthermore, the majority of systematic reviews of randomized controlled trials (RCTs) have found no increase in hemorrhagic complications associated with low-dose aspirin during pregnancy.[14] A USPSTF report on low-dose aspirin for prevention of preeclampsia identified no increased risk of placental abruption (11 trials [23,332 women]; relative risk [RR], 1.17; CI, 0.93–1.48), postpartum hemorrhage (nine trials [22,760 participants]; RR, 1.02; CI, 0.96–1.09), or mean blood loss (five trials, [2,478 women]; RR not reported).[19]Low molecular weight heparins (LMWH) are manufactured from unfractionated (UFH) by controlled depolymerization using either enzymatic (heparinase) or chemical (nitrous acid or alkaline hydrolysis.)[20] The action of LMWH is by anticoagulant action is by anticoagulation.

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides. It binds to endothelial cell surfaces. Its biologic activity is dependent upon the plasma protease inhibitor antithrombin III. Antithrombin inhibits clotting factor protein by forming equimolar stable complex with them. In the absence of heparin, these reactions are slow, in the presence of heparin, they are accelerated 1000-fold. The active heparin molecules binds tightly to antithrombin and cause a conformational change in this inhibitor. The conformational change of antithrombin exposes its active site for more rapid interaction with the proteases which activates clotting factors[21]. It inhibits platelet function.It inhibits the proliferation of vascular smooth muscle cells, an effect that is independent of its anticoagulant activity.[21] It increases protein C and S activity[22].It decreases the coagulation activation by factor V

Leiden mutation. Adverse effects of LMWH are hematologic bleeding (2.7 – 4.6%), wound hematoma (0.1-3.4%), local pain at injection site (12%), injection site hematoma (0.2-7.5%), allergic reaction <1% and osteoporosis in post natal period.[23]

Obstetric complications remain prevalent despite heparin therapy.[24]In view of this, the current prospective, single-center study was carried out to identify the pregnancy complications and side effects of aspirin alone and aspirin plus low molecular weight heparin (LMWH) in patients of bad obstetric history with elevated Anti-phospholipid antibodies.

Materials and Methods:

This prospective, single-center study was conducted in the Department of Obstetrics and Gynaecology, Kasturba Medical College Hospital, Manipal, Karnataka, India. The study period was of 24 months from November 2000 to November 2002. Recruitment of patients was done depending upon their past obstetric history with 2 or more consecutive abortions, 1 or more neonatal death, 1 or more intrauterine death. Patients with Diabetes mellitus, any bleeding disorders, HIV and Chronic hypertension were excluded. A total of 111 patients were enrolled in the study who fulfils the inclusion criteria. They underwent: Anticardiolipin antibody assay (ACA) by Enzyme immune assay, a quantitative study using a NOVAMED kit which allows rapid sampling. Lupus anticoagulant was detected by estimation of APTT. (Activated partial thromboplastin time). Out of 111 patients, 57 had elevated antiphospholipid antibodies. Hence 57 was sample size for the present study. These 57 were randomly divided into aspirin only group and aspirin plus LMWH group. Out of 57 patients with elevated antiphospholipid antibodies, 37 patients received aspirin and 20 patients received aspirin plus LMWH.

Aspirin75mg once a day orally was given from confirmation of pregnancy till 34 weeks in post conception period, Low molecular weight heparin 0.3 CC Containing 2850 anti-Xa activity given subcutaneously once a day for 6 weeks from the day of cardiac activity till 12 weeks in the post-conception period. All patients underwent a transvaginal ultrasound at 6 to 7 weeks gestation to rule out an ectopic pregnancy and to determine fetal viability. Patients with vaginal bleeding or pelvic pain were evaluated at an earlier date. If a missed abortion was diagnosed, the patients were offered a dilation and curettage, and the tissue was submitted for chromosome analysis. All patients had regular antenatal checkups. Patients were offered baseline investigation like complete blood count, HIV, HBsAg, urine routine. The objective of antenatal care was to detect maternal hypertension, IUGR, oligohydramnios, preterm and other obstetric complications. Serial Obstetric ultrasound done for growth monitoring. Pregnancy induced hypertension was diagnosed based on elevated blood pressure more than 140/90 mmHg beyond 20 weeks of gestation.Intrauterine growth restriction (IUGR) was diagnosed,based on ultrasonography. Preterm deliveries include deliveries below 37 weeks. Oligohydramnios was diagnosed clinically and confirmed by amniotic fluid index by ultrasound. Informed consent was taken from the patients in the study group. The study protocol was performed in accordance with the principle of the declaration of Helsinki and after approval by the institutional ethical scientific committee.

Statistical analysis: The data was entered and tabulated in MS-Excel 2007, and statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS version-22.0). Data had been summarized as mean for numerical variables and count and percentages for categorical variables and $p<0.05$ is considered as statistical significance.

Results:
A prospective, single-center study' was conducted in Department of Obstetrics and Gynaecology, Kasturba Medical College Hospital, Manipal, Karnataka, India. The study period was of 24 months from November 2000 to November 2002.
Table 1. IUGR was seen in 27.3% and 15.0%, PIH in 27.3% and 10.0% and oligohydramnios in 10.8% and 15.0%, Preterm in 8.1% and 5.0% in aspirin and aspirin plus LMWH groups respectively. The results were not statistically significant in any group.

Table 1: Comparison of pregnancy complications in Aspirin alone and Aspirin plus LMWH group

Pregnancy complications	Aspirin alone (n=37)	Aspirin plus LMWH (n=20)	p-value
IUGR	10 (27.3%)	03(15%)	P>0.05
PIH	10 (27.3%)	02 (10%)	P>0.05
Oligohydramnios	04 (10.8%)	03 (15%)	P>0.05
Preterm	03 (8.1%)	01 (5.0%)	P>0.05

Table 2. Local pain was recorded in 10(50%) of patients in LMWH group. Local bruise in 1. (5.0%) Around 10(27.3%) of aspirin alone patients experienced epigastric pain. Only 1 patient (2.7%) had hypersensitivity reaction.

Table 2: Comparison of Side Effects of Aspirin alone and Aspirin plus LMWH

Side effects of Aspirin alone & Aspirin plus LMWH	Aspirin alone (n=37)	Aspirin plus LMWH (n=20)
Local Pain	-	10 (50.0%)
Local Bruise	-	01 (5.0%)
Hypersensitivity	01 (2.7%)	-
Epigastric pain	10 (27.3%)	-
Nausea	02 (5.4%)	-

Discussion:
Aspirin is thought to improve the trophoblastic invasion of the uterine spiral arteries and might subsequently improve the development and efficacy of the placenta probably due to thrombocyte aggregation inhibition and/or an anti-inflammatory working mechanism.[25.26] These results, however, have been found in experimental setting and it is unknown what the relevance is for clinical practice.

In present study, incidence of IUGR is seen in 27.3% and 15.0% after treatment with aspirin and aspirin plus LMWH group in antiphospholipid antibody positive patients. R.D. franklin etal[27]study showed the incidence of IUGR in 10.5% and 8.3% in aspirin plus LMWH and aspirin alone group.There was an increased risk of IUGR if treatment was taken. In another

study by GlasnovićMetal[28] observed that 8.3% cases of IUGR after treatment with low dose aspirin and LMWH. One more study by Backos Metal[18] also found that 15.0% of infants were small for gestational age when treated with LDA and heparin. In Khalid Abd Aziz[29]showed that 33% of the aspirin group and 12% of aspirin plus LMWH had IUGR. Sasmita Swain etal study[31] also showed similar result of IUGR in 15% of aspirin plus LMWH group. In the present study,there were 27.3% and 10.0% developed pregnancy induced hypertension (PIH) after treatment with aspirin and aspirin plus LMWH in antiphospholipid antibody positive patients. Similarly a study by Jeremic etal[31] revealed that preeclampsia occurs 15.0% despite treatment with low dose aspirin and LMWH. In a study by Fawad S[32] observed that only 7% patients developed preeclampsia despite treated with low dose aspirin and LMWH.Anotherstudy by Serrano Fetal[33]in Portugal, shows that incidence of preeclampsia was 19.4% with medication.Yagoub etal[34] showedlow rate of 5.1%in patient on aspirin plus LMWH group. Our study result were matched with Beckos et al[18] study which showed 17% of preeclampsia in aspirin plus LMWH group. Obstetric manifestations of APS are not restricted to fetal loss. Current APS criteria include early delivery and oligohydramnios is a frequent finding in pregnancies involving IUGR and is more likely due to decrease fetal blood volume, renal blood flow and fetal urine output. Pregnancies complicated by severe oligohydramnios have been shown at increased risk of fetal morbidity.

In the present study, 10.8% and 15.0% developed oligohydramnios after treatment with aspirin and aspirin plus LMWH in antiphospholipid antibody positive patients. Similar results are recorded in the study conducted by Al-Assady NS.[35]A study by Yagoub M etal[34] showed13.8% had oligohydramnios in their study. In our study preterm delivery were seen in 8.1% and 5.0% in Aspirin and aspirin plus LMWH group. Sasmita Swain etal[30] also had 9% of preterm delivery in aspirin plus LMWH group. Mo D, Saravelosetal[36] had 5% preterm birth in aspirin plus LMWH. Khalid Abd Aziz etal[29]. study showed 20% and 14% of incidence of preterm in Aspirin and Aspirin plus LMWH group. In contrast to our study Beckos etal[18]had 24% of preterm in Aspirin plus LMWH group. The most common side effects of heparin are bleeding, osteoporosis, and heparin-induced thrombocytopenia. The LMWHs have weaker interactions with platelets and inhibits bone formation less than unfractionated heparin.[37] In the present study, 50% and 5% patients' experienced local pain and local bruise in LMWH group, whereas 2.7%, 27% and 5.4% patients experienced hypersensitivity, epigastric pain and nausea in aspirin group. A study byPaulien G de Jong[38] showed 40%patient had local skin reaction.The current study implies that reporting the pregnancy complications and side effects of aspirin and LMWH will add to available literature.

Conclusion:

Maternal and perinatal complications occurred frequently, despite LMWH and aspirin use. However, 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 the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation which leads to decrease percentage of IUGR and PIH.

Limitations:

In this study, we did not give LMWH till 34 weeks of gestation. Being a small sample size and single center study, who do not represent or generalize the whole population.

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References:

1. Schreiber K, Sciascia S, De Groot PG, Devreese K, Jacobsen S, Ruiz-Irastorza G, Salmon JE, Shoenfeld Y, Shovman O, Hunt BJ. Antiphospholipid syndrome. Nature reviews Disease primers. 2018;4(1):1-20.
2. Rodziewicz M, D'Cruz DP. An update on the management of antiphospholipid syndrome. Therapeutic Advances in Musculoskeletal Disease. 2020;5:122-27.
3. Ghosh A, Ghosh M, Bhattacharya SM. Anti-phospholipid antibodies as a cause of recurrent pregnancy loss: a study in Calcutta, India. Journal of Obstetrics and Gynecology. 2006;26(5):407-10.
4. Kaplan YC, Ozsarfati J, Nickel C, Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2016;81(5):835-48.
5. Matsuki Y, Atsumi T, Yamaguchi K, Hisano M, Arata N, Oku K, Watanabe N, Sago H, Takasaki Y, Murashima A. Clinical features and pregnancy outcome in antiphospholipid syndrome patients with history of severe pregnancy complications. Modern Rheumatology 2015;25(2):215-18.
6. McCrae KR, Feinstein Pl and Cines DB. Antiphospholipid antibodies 6. and the antiphospholipid syndrome. In: Colman RW, editor. Hemostasis and thrombosis. Basic principles and clinical practice. 4ed. Philadelphia: Lippincot: 2000.p.1339-1356.
7. Brown HL. Antiphospholipid antibodies and recurrent pregnancy loss. Clin ObstetGynecol 8. 1991:34:17-26. Schramm AM, Clowse ME. Aspirin for prevention of preeclampsia in lupus pregnancy. Autoimmune diseases2014;20:14-19.
8. Connective tissue disorders . In:Cunningham GF, Gant NF, Leveno KJ, Gilstrap Ill LC, Kauth JC, Wenstrom KD, editors. William's obstetrics, 21st ed. New York: McGraw Hill; 9. 2001.p.1390-1391.
9. Gris W and Bronch DW. Obstetric implications of antiphospholipid antibodies: Pregnancy loss and other complicatie ns. Clin ObstetGynecol 2001:44:2-10.
10. Rai R, Regan L. Antiphospholipid antibodies and adverse pregnancy outcome. In: Studd J, editor. Progress in Obstetrics and Gynecology No.12.p.135-152.
11. Carreras LO, Vermylen J, Spitz B, Van Assche A. Lupus anticoagulant and inhibition of prostacyclin formation in patients with repeated abortion, intrauterine growth retardation and intrauterine death. Br J ObstetGynecol1981;88:890-894.
12. Hampton KK, Preston FE, Greaves M. Resistance to activated protein C. 9 NEng J Med 1994;337:129-130.
13. Van Hoorn ME, Hague WM, van Pampus MG, Bezemer D, de Vries JI. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. European Journal of Obstetrics & Gynecology Reproductive Biology. 2016;197:168-73.
14. ACOG Committee opinion; low dose aspirin used during pregnancy; Volume. 132; No. 1; July 2018; e44-e52

15. McParland P, Pearce JM. Prostaglandins, aspirin and In: Stud pre-eclampsia. J, editor. Progress in Obstetrics and Gynecology; 9.p.55-81.
16. Antiplatelet drug. In: Tripathi KD, editor. Essentials of Medical Pharmacology, 4"ed. New Delhi: Jaypee Brothers; 2001: p.613.
17. Simone ND, Ferrazzani S, Castellani R, Carolis SD, Manuso S and 17 Caruso A. Heparin and low dose aspirin restores placental human chorionic gonadotrophin secretion abolished by antiphospholipid antibody containing sera. Human Reproduction 22 De Wolf 1997;12:2061-2065.
18. 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. International Journal of Obstetrics &Gynecology. 1999;106(2):102-07.
19. US Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M, Li L, Ogedegbe G, Pbert L, Silverstein M, Simon MA, Stevermer J, Tseng CW, Wong JB. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: US Preventive Services Task Force Recommendation Statement. JAMA. 2021 Sep 28;326(12):1186-1191. doi: 10.1001/jama.2021.14781. PMID: 34581729.
20. Weitz JI. Low molecular weight heparins. N Eng J Med1997;337: 688-698.
21. Hambleton J, O'Reilly RA. Drugs used in disorders of coagulation. In: Katzung BG, editor. Basic and Clinical Pharmacology. 8" ed. New York: Lange Medical Book; 2001. p.567.
22. Schambek CM, Eberl E, Geison U, Grossmann R, Keller F. The impact of Dalteparin (Fragmin) on thrombin generation in pregnant women with venous thromboembolism: Significance of the factor V leiden mutation. ThrombHaemost2001;85:782-786.
23. Carles LF, editor. Drug Information Handbook.9"ed.Americal Pharmaceutical Association; 2001. P.326-327.
24. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology 2002;41(8):924-29.
25. Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenatal diagnosis 2014;34(7):642-48.
26. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguere Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstetrics & Gynecology 2010;116(2):402-14.
27. R.D. Franklin and W.H. Kutteh, Antiphospholipid antibodies (APA) and recurrent pregnancy loss : treating a unique APA positive population. Human reproduction 2002 Vl. 17, No. 11 pp. 2981-2985,
28. Glasnović M, Bošnjak I, Včev A, Soldo I, Košuta M, Lenz B, Glasnović-Horvatić E, Soldo-Butković S, Mićunović N. Antibody profile of pregnant women with antiphospholipid syndrome and pregnancy outcome after treatment with low dose aspirin and low-weight-molecular heparin. Collegium Antropologicum 2007;31(1):173-77.
29. Khalid Abd Aziz MohamedAhmed Samy Saad, Enoxaparin and aspirin therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS) Middle East Fertility Society JournalVolume 19, Issue 3, September 2014, Pages 176-18
30. Sasmita Swain, Sujata SinghThe effect of low dose aspirin and low molecular weight heparin (enoxaparin) in recurrent pregnancy loss associated with antiphospholipid antibody syndrome,International Journal Of Reproduction, Contraception, Obstetrics And Gynecology,2017 nov; Vol 6(11):4830-4834.

31. Jeremić K, Pervulov M, Gojnić M, Dukanac J, Ljubić A, Stojnić J. Comparison of two therapeutic protocols in patients with antiphospholipid antibodies and recurrent miscariages. Vojnosanitetskipregled 2005;62(6):435-39.
32. Fawad S. Role of anti-thrombotic therapy for recurrent pregnancy loss due to anti-phospholipid syndrome. Journal of Ayub Medical College Abbottabad. 2010;22(3):197-200.
33. Serrano F, Nogueira I, Borges A, Branco J. Primary antipholipid syndrome: Pregnancy outcome in a Portuguese population. Acta Reumatologica Portuguesa 2009;34(3):492-97.
34. Yagoub M. A. MagidElsir A. ElusseinMaha M. OmerSamaan I. SamaanIshag AdamFawzi A. RahimHeparin and aspirin in pregnant Sudanese women with recurrent miscarriage associated with antiphospholipid antibodies : original research articleAfrican Journal of Reproductive HealthVol. 11, No. 2 2007
35. AL-Assady NS. Evaluation the Efficacy of Aspirin and Low Molecular Weight Heparin in Patients with Unexplained Intrauterine Growth Restriction accompanied by Early Onset Oligohydramnios. Thi-Qar Med J. 2017;13(1):147-56.
36. Mo D, Saravelos S, Metwally M, Makris M, Li TC. Treatment of recurrent miscarriage and antiphospholipid syndrome with low-dose enoxaparin and aspirin. Reprod Biomed Online. 2009 Jan 1;19(2):216-20.
37. Many A, Koren G. Low-molecular-weight heparins during pregnancy. Canadian Family Physician 2005;51(2):199-201.
38. Paulien G de Jong,Stef Kaandorp, Marcello Di Nisio, MariëtteGoddijn, Saskia MiddeldorpAspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophiliaCochrane Database Syst Rev. 2014 Jul; 2014(7): CD004734.