IMMUNOLOGICAL CAUSES OF BAD OBSTETRIC HISTORY

Champa Koppad[1], Lakshmi K. S[2]

HOW TO CITE THIS ARTICLE:
Champa Koppad, Lakshmi K. S. "Immunological Causes of Bad Obstetric History". Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 16, December 22, 2014; Page: 2086-2099.

ABSTRACT: Occurrence of three consecutive pregnancy losses constitutes the classic definition of bad obstetric history (BOH). One of the important causes of BOH is the presence of antiphospholipid antibodies, which enhance the coagulability of blood in pregnancy. The association between phospholipid antibodies and recurrent miscarriage is called Antiphospholipid Syndrome (APS). Pregnant women with thrombotic APS have higher rates of pregnancy complications. APS is responsible for first trimester pregnancy loss in 90% of patients. APS is associated with events like thrombosis, vascular injury and vasoconstriction, all of which can abnormally reduce maternal-fetal interface blood flow. APS is best treated by a combination of LMWH and low-dose aspirin. Controlled clinical studies have demonstrated the superiority of heparin plus aspirin over aspirin alone in improving the birth rate.
KEYWORDS: LMWH, Bad obstetric history, antiphospholipid syndrome.

INTRODUCTION: A woman is said to have 'bad obstetric history (BOH)' if she has experienced any of the following events on two or more occasions in the past:

- Consecutive spontaneous abortions.
- Early neonatal deaths.
- Stillbirths.
- Intrauterine fetal deaths.
- Intrauterine growth retardation.
- Congenital anomalies in the fetus.

However, it is the occurrence of three consecutive pregnancy losses that constitutes the classic definition of BOH. This condition is seen in 1-2% of couples.[1]

CAUSES: The most common causes of recurrent miscarriages are shown in Table 1.[2]

IMMUNOLOGICAL CAUSES OF BOH: The immune factors associated with pregnancy loss are classified as autoimmune and alloimmune factors.

AUTOIMMUNE FACTORS: These factors include the presence of certain autoantibodies, namely:

- Antiphospholipid antibodies: These antibodies enhance the coagulability of blood, making it clot more easily than is normal during pregnancy. The clots thus formed in the placental blood vessels may impede the fetus' blood supply, resulting in miscarriage. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. The association

between phospholipid antibodies and recurrent miscarriage is referred to as Antiphospholipid Syndrome (APS). The main types of antiphospholipid antibodies are:

- Lupus Anticoagulant (LA).
- Anticardiolipin (aCL) antibodies (IgG and IgM).
- Anti-β_2 Glycoprotein I antibodies.[1]

- Antinuclear antibodies: Anti-nuclear antibodies (ANAs) are circulating immunoglobulins, e.g., IgG, IgA and IgM, which attack the whole nucleus or its components.[1] These antibodies have also been associated with recurrent pregnancy loss, even in patients without evidence of overt autoimmune disease, but further investigation is needed into their exact role in causing recurrent miscarriages. Therefore, measuring ANAs is not recommended as part of an evaluation of recurrent miscarriage.[2]
- Antithyroid antibodies: Unlike ANA, antithyroid antibodies are known as independent markers for an increased risk of miscarriage. However, since the pathophysiology involved in this phenomenon is unclear, antithyroid antibody testing is not recommended in women with recurrent pregnancy loss.[2]

Table 1: Common causes of recurrent pregnancy loss[2]

- Genetic causes.
  - Aneuploidy.
  - Somatic.
  - Sex chromosome.
  - Mendelian disorders.
  - Multifactorial disorders.
  - Parental chromosomal abnormalities (translocations).
  - Chromosomal inversions.
- Immunologic causes.
  - Autoimmune causes.
  - Alloimmune causes.
- Anatomic causes.
  - Uterine mullerian anomaly.
- Uterine septum (the anomaly most commonly associated with pregnancy loss).
- Hemiuterus (unicornuate uterus).
- Bicornuate uterus.
  - Diethylstilbestrol-linked condition.
  - Acquired defects (e.g., Asherman syndrome).
  - Incompetent cervix.
  - Leiomyomas.
  - Uterine polyps.
- Infectious causes.
- Environmental causes.
  - Smoking.
  - Excessive alcohol consumption.

    - Caffeine.
- Endocrine factors.
    - Diabetes mellitus.
    - Antithyroid antibodies.
    - Luteal phase deficiency.
- Hematologic disorders

ALLOIMMUNE FACTORS: Alloimmune traits, such as abnormal maternal immune response to antigens of placental or fetal tissues, have been implicated in otherwise unexplained recurrent pregnancy loss. One such response is human leukocyte antigen (HLA) sharing,[3] which impairs the mother's ability to block antibodies. However, studies to date have proved no association between recurrent pregnancy loss and HLA.

THROMBOPHILIA: Thrombophilia is a term used to describe a group of conditions characterized by an increased tendency, often repeated and often over an extended period of time, for excessive clotting.[4] This can be due to either an excess of clotting factors or a deficiency of anti-clotting proteins that limit clot formation.

A thrombophilia can be inherited or acquired later in life. Acquired thrombophilias are less common than inherited. Thrombophilias may pose special risks in pregnancy.

INHERITED THROMBOPHILIAS:

- Factor V Leiden and prothrombin mutations: Factor V is a coagulation factor that is normally inactivated by activated protein C (APC). Patients with a single point mutation in the gene coding for factor V produce a mutated factor V, called FactorV Leiden, that is resistant to inactivation by APC, resulting in increased thrombin production and a hypercoagulable state. This mutated gene is inherited as an autosomal dominant trait and is the most common cause of thrombosis and familial thrombophilia, with a prevalence of 3-5% in the general population. In patients with a history of venous thrombosis, the prevalence rate is as high as 40%.[2] These thrombophilias are less common in African-Americans and Asians.[5]
- Antithrombin, protein C and protein S deficiencies: There is paucity of data on these types of thrombophilias, which affect less than 1% of the American population.[5]

The above thrombophilias are inherited in an autosomal dominant pattern, i.e., the gene is inherited from only one parent. Each child of an affected parent has a 50% chance of inheriting the thrombophilia.

ACQUIRED THROMBOPHILIAS: The most common acquired thrombophilia is antiphospholipid syndrome (APS), in which the body makes antibodies that attack certain fats (phospholipids) that line the blood vessels, sometimes leading to blood clots. APS is an autoimmune disorder like arthritis and systemic lupus erythematosus (SLE). Up to 40% of women with SLE have antiphospholipid antibodies in their blood, which may put them at increased risk of pregnancy complications.[6]

DIAGNOSIS AND MANAGEMENT: Current recommendations for evaluation and management based on current practices are listed below.[2]

- Genetic causes.
  - Perform karyotype of parents with family or personal history of genetic abnormalities.
  - Perform karyotype of the abortus in recurrent cases.
  - Provide genetic counseling for families with recurrent loss or familial history of genetic disease.
  - In patients with a high risk of recurrent, chromosomally abnormal conceptus, discuss the options of adoption, gamete donation, and PGD.
- Immunologic causes.
  - Perform APLA (antiphospholipid antibody) testing if indicated.
  - If APLA levels are elevated, counseling with a hematologist and a specialist in maternal fetal medicine is recommended.
  - Aspirin and heparin therapy for patients diagnosed with APS.
- Anatomic causes.
  - Imaging studies - HSG, hysteroscopy, ultrasonography, and/or MRI.
  - Surgical correction may be required.
- Infectious causes.
  - Cervical cultures should be obtained during the evaluation of infertility.
  - Empiric antibiotics should be given before invasive testing, such as HSG.
- Environmental causes - Encourage life-style changes and counselling for preventable exposures.
- Endocrine factors - Perform thyroid-stimulating hormone (TSH) screening in symptomatic patients.
- Thrombophilic disorders - Aspirin and heparin therapy may be given for proven diagnoses.

ANTIPHOSPHOLIPID SYNDROME: Antiphospholipid syndrome (APS) is an autoimmune disorder in which there is recurrent venous or arterial thrombosis and/or fetal loss. It is characterized by persistently high levels of antibodies directed against membrane anionic phospholipids (i.e., anticardiolipin [aCL] antibody, antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H); or evidence of a circulating anticoagulant.

APS is usually accompanied with systemic lupus erythematosus (SLE) or another rheumatic or autoimmune disorder, in which case it is termed secondary APS. When there is no associated disease, it is called primary APS.[10]

APS is more common in women than in men, and has been increasingly diagnosed in patients without underlying autoimmune disease. It is most frequently seen in obstetric patients suffering spontaneous abortion, preeclampsia and intrauterine growth restriction. Research into the pathophysiology of APS has shown that autoantibodies are not only the markers of the disease, but also directly contribute to the development of clinical features.[11]

PATHOPHYSIOLOGY: In this syndrome, antiphospholipid antibodies, namely, anticardiolipin antibodies and lupus anti-coagulant, react against proteins that bind to anionic phospholipids on plasma membranes. The exact cause is not known, but there is evidence of alteration of the homeostatic regulation of blood coagulation. Clinically important antiphospholipid antibodies (those that arise as a result of the autoimmune process) are associated with thrombosis and vascular disease.[12]

One hypothesis postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various plasma proteins, such as beta-2 glycoprotein I. Once bound, a phospholipid-protein complex is formed and a neoepitope is uncovered, which subsequently becomes the target of autoantibodies. Recent evidence suggests that oxidized beta-2 glycoprotein I is able to bind to and activate dendritic cells in a manner similar to activation triggered by Toll-like receptor 4 (TLR-4), which could amplify the production of autoantibodies.[13] Other proposed mechanisms for the hypercoagulable effect of aPL antibodies, which may or may not depend on beta-2 glycoprotein I, include the following:

- Production of antibodies against coagulation factors, including prothrombin, protein C, protein S, and annexins.
- Activation of platelets to enhance endothelial adherence.
- Activation of vascular endothelium, which, in turn, facilitates the binding of platelets and monocytes.
- Reaction of antibodies to oxidized low-density lipoprotein, thus predisposing to atherosclerosis and myocardial infarction.

Complement activation may play an important role in the pathogenesis of APS, leading to pregnancy loss.[14]

DIAGNOSTIC CRITERIA: According to the revised criteria for the diagnosis of APS, published in an international consensus statement in 2006,[15] at least one clinical criterion and one laboratory criterion must be present for a patient to be classified as having APS. These criteria are given below.

CLINICAL CRITERIA:

- Vascular thrombosis.
  - One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by findings from imaging studies, Doppler studies, or histopathology.
  - Thrombosis may involve the cerebral vascular system, coronary arteries, pulmonary system (emboli or thromboses), arterial or venous system in the extremities, hepatic veins, renal veins, ocular arteries or veins, or adrenal glands. Investigation is warranted if a history of DVT, PE, acute ischemia. Ml, or CVA (especially when recurrent) is present in a younger individual (males <55 y; females <65 y) or in the absence of other risk factors.

- Pregnancy morbidity.
  - One or more late-term (>10 weeks' gestation) spontaneous abortions
  - One or more premature births of a morphologically healthy neonate at or before 34 weeks' gestation because of severe preeclampsia or eclampsia or severe placental insufficiency
  - Three or more unexplained, consecutive, spontaneous abortions before 10 weeks' gestation.

LABORATORY CRITERIA:

- Presence of medium to high levels of immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin (aCL).
- Presence of anti-beta-2 glycoprotein I.
- Presence of Lupus anticoagulant on at least 2 occasions at least 12 weeks apart.
- Thus, a history of any of the following should raise suspicion for APS:
- Thrombosis (e.g., DVT/PE, Ml, transient ischemic attack [TIA], or CVA, especially if recurrent, at an earlier age, or in the absence of other known risk factors).
- Miscarriage (especially late trimester or recurrent) or premature birth.
- History of heart murmur or cardiac valvular vegetations.
- History of hematologic abnormalities, such as thrombocytopenia or hemolytic anemia.
- History of nephropathy.
- Nonthrombotic neurologic symptoms, such as migraine headaches, chorea, seizures, transverse myelitis, Guillain-Barre syndrome, or dementia (rare).
- Unexplained adrenal insufficiency.
- Avascular necrosis of bone in the absence of other risk factors.
- Pulmonary hypertension.

TREATMENT: Heparin (either unfractionated heparin or low-molecular-weight heparins) and low-dose aspirin are the treatments of choice for prevention of pregnancy loss in pregnant women with APS and previous pregnancy losses. The use of low-dose aspirin and low-molecular weight heparin during pregnancy and anticoagulants in the post-partum period has been recommended by the Advisory Board members (ABMs) of the 12th Congress of aPL and the Fifth Conference on Sex Hormones, Pregnancy and Rheumatic Diseases (Florence, Italy, April 2007), and all attendees of the above meetings.[16]

The dose schedule is as follows:[17]

- Unfractionated heparin: 15,000-20,000 U/day subcutaneously in 2 divided doses, plus low-dose aspirin.
- Low-molecular-weight heparins (e.g., enoxaparin): 40 mg/day subcutaneously plus low-dose aspirin.
- Aspirin: 1-2 mg/Kg/day orally - maximum 325 mg/day.

The effectiveness and safety of LMWHs (enoxaparin, dalteparin, nadroparin, tinzaparin) in comparison to unfractionated heparin have been demonstrated in several studies. Their advantages over unfractionated heparin are:[18]

- Less risk of bleeding.
- Less platelet activation.
- Control of markers of hemostatic system activation.
- No progression or regression of thrombus size.
- More comfortable for patients.
- Less time consuming for nurses and laboratories.
- More cost effective.

ROLE OF LMWH IN APS: Pregnancies in women with APS are known to be at a higher risk of complications, like spontaneous abortion, fetal growth restriction, stillbirth and pre-eclampsia.[19,20] The use of heparin can result in a significant reduction in pregnancy complications in these women. The beneficial effects of heparin in pregnancy can be attributed to its anticoagulant actions.[21-23] It may also act by other mechanisms, such as reducing antiphospholipid (aPL) antibody binding, inhibiting complement binding, inhibiting placental apoptosis and stimulating placental proliferation.[24,25] The relative success of heparin in improving pregnancy prognosis in women with previous APS-related pregnancy complications has led to the increased use of heparin, especially low molecular weight heparin (LMWH), in absence of confirmed thrombophilias.[26]

Hypercoagulability in APS can be ascribed to enhanced microvesiculation of cell membranes, as detected by reduced membrane adhesion. Frank and colleagues[27] found that LMWH completely restored beta2-glycoprotein I (beta2-GPI)-induced membrane adhesion in the presence of anti-beta2-GPI IgG antibodies. Thus, a novel anticoagulant mechanism of LMWH in APS was suggested that supplements its direct effect on the coagulation cascade. Restoration of adhesion between negatively charged membranes in the presence of LMWH might decrease shedding of microvesicles into the surrounding solution and could thus contribute to the efficacy of heparin treatment in APS.

Several studies have confirmed the safety of LMWH therapy during pregnancy. The risk of potential side effects is low for both the mother and the neonate.[28]

A study in Croatia[29] recruited 36 pregnant women with APS, of whom 32 had primary APS and 4 had secondary APS. All pregnant women received LMWH and low dose aspirin therapy. The average pregnancy lasted 37.06 ± 0.707 weeks. The treatment resulted in a high success rate (97.22%), prompting the researchers to recommend LMWH and low dose aspirin as the therapy of first choice.

A retrospective analysis[30] of 51 women with primary APS tried to determine the effect of low dose aspirin and LMWH on maternal and perinatal outcome in this cohort. Among these women, 41 (80.4%) had past pregnancy morbidity and 18 (35.3%) had experienced previous thrombotic events. Out of a total of 116 pregnancies, only 13.79% had resulted in live births. Forty four patients had positive anticardiolipin antibodies and 33 lupus anticoagulant. Treatment with low dose aspirin and LMWH resulted in 57 out of a total of 67 gestations culminating in a live

birth (85.1%). Mean (± SD) birth weight was 2837 ± 812 g and mean gestational age 37 ± 3.3 weeks. These results showed that early treatment with aspirin and LMWH, combined with close maternal-fetal surveillance, was associated with a very high chance of a successful completion of pregnancy.

A retrospective, observational study[31] was conducted to evaluate the impact of low-dose enoxaparin (20 mg) in conjunction with low-dose aspirin on the pregnancy outcome of 35 women with APS and recurrent miscarriage. The live birth rate was found to be as high as 80% against a low miscarriage rate of 20%, leading to the conclusion that low-dose enoxaparin, given along with low-dose aspirin, produced encouraging results.

Similar heartening results were obtained in a prospective clinical trial[32] on 58 pregnant Sudanese women with recurrent miscarriages associated with APS, in whom treatment with LMWH and low-dose aspirin resulted in an 81% live birth rate.

Stephenson and colleagues[33] compared the efficacy of LMWH with unfractionated heparin (UFH) in the treatment of APS in pregnancy. They randomized 28 women, who met the 1999 International Consensus Criteria for APS, to receive either prophylactic dosing of LMWH or UFH starting either pre conceptionally or early in pregnancy. All women also received low-dose aspirin, started preconceptionally.

The successful pregnancy rate in the LMWH group was more than double that in the UFH group (69% vs 31%), indicating the superiority of LMWH over UFH.

In another comparative study,[34] intravenous immunoglobulin (IVIG) was compared with LMWH plus low-dose aspirin, in women with recurrent pregnancy loss associated with antiphospholipid antibodies (aPL). Forty such women were randomized to receive either IVIG or LMW heparin plus low-dose aspirin when they became pregnant. IVIG was stopped at the 31st week of gestation, aspirin at the 34th week, and LMWH at the 37th week.

Results showed that women treated with LMWH plus low-dose aspirin had a higher rate of live births (84%) than those treated with IVIG (57%). Thus, the authors concluded, LMWH plus low-dose aspirin should be considered the standard therapy for recurrent pregnancy loss due to aPL.

Declining ovarian reserve testing and age-related increase in pregnancy loss: In a retrospective comparative analysis of 57 women presenting for RPL work-up, women with unexplained RPL were more likely to have higher basal D3 FSH testing.[7] Furthermore, the incidence of spontaneous abortion is associated with maternal age at conception. The rate of spontaneous abortion is approximately 11-13% for maternal age 29 yrs or less. The spontaneous abortion rate increases to 15% for ages 30-34, is approximately 25% for ages 35-39, 51% for ages 40-44, and peaks after age 45 over to >93%.[8]

It is now known that donor egg IVF in women with poor ovarian reserve testing has been shown associated with:

1) Increased pregnancy rates compared with autologous eggs; and.
2) Decreased rates of pregnancy loss (similar to the age-related risk of pregnancy loss of the egg donor).

Hence, in women who have RPL in the setting of poor ovarian reserve testing, or in women who are at the upper extremes of the reproductive window, donor egg IVF may be considered to improve the live birth rates.

Rationale for potential benefit of LMWH in patients with RIF and biochemical pregnancy: Mechanisms underlying the potential benefit of treatment with heparin in patients with RIF include immunomodulation, thrombo prevention, and promotion of implantation through mechanisms unknown as yet (Figure 1). There have been small retrospective studies in the past showing mixed results. A recent quasi-randomized trial[3] out of Turkey showed no benefit for patients with two or more implantation failures. There is an ongoing RCT, also in Turkey, testing whether luteal phase heparin and progesterone improve implantation rates in patients with RIF after IVF with intracytoplasmic sperm injection (ICSI). Despite the compelling and long-standing academic discussion regarding potentially beneficial mechanisms of heparin for patients with RIF, studies do not yet show overwhelming supporting evidence to the use of anticoagulates for isolated RIF. The decision to offer prophylactic anticoagulation to patients with RIF must be based on other factors which predispose to either thrombosis, or history or testing supporting antiphospholipid antibody syndrome (APS) or thrombophilia.

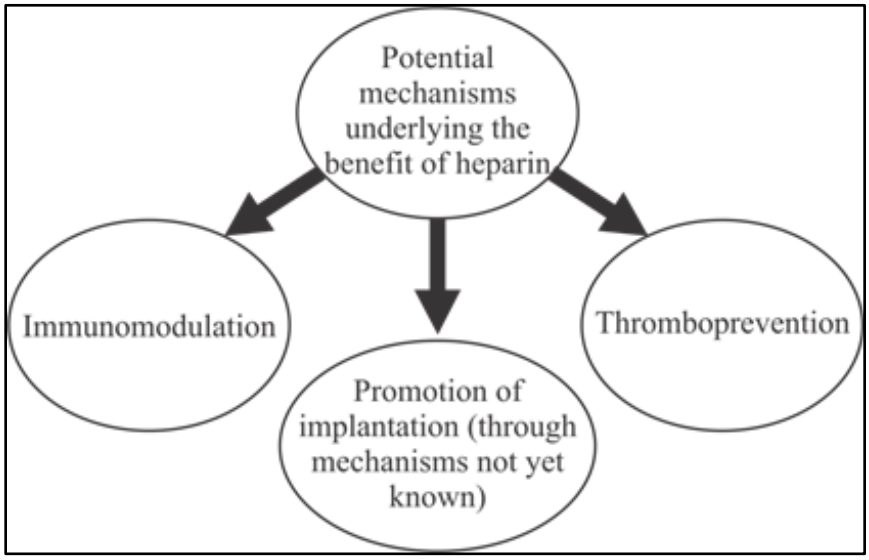

Fig. 1: Potential mechanisms underlying the benefit of heparin use in patients with RIF

In offering anticoagulation in patients with isolated RIF, it must go without saying that the patients will generally accept any treatment offered, even with potential for harm in the absence of true benefit. When offering LMWH to patients with RIF, careful counseling must provide information on the risks of treatment (including bleeding), that there is a lack of data supporting anticoagulation for primary RIF, and how other factors (such as age/uterine/unexplained factors)

may play a role in RIF. Duration of therapy may also be included in this discussion, and may be confined to the luteal phase when implantation occurs (possibly including time during gonadotropin stimulation) - essentially anticoagulation would be limited to 2 weeks after embryo transfer.

One of the causes of recurrent miscarriage is thrombosis in decidual vessels.[37,38] This is brought about by hereditary thrombophilias and passive transfer of antiphospholipid antibodies.[39-44]

Antithrombotic therapy has been used to restore hemostatic balance and improve early placentation and gestational outcome. A study[45] was conducted in Argentina to assess the efficacy of a low-molecular weight heparin (LMWH), enoxaparin, in preventing pregnancy loss in 35 women who had had a total of 105 gestations of which 89 (85%) ended in early pregnancy loss, and were subsequently diagnosed with thrombophilia. After diagnosis, 35 subsequent pregnancies were treated with enoxaparin. This resulted in 85% pregnancies culminating in live birth as compared to 15% of the pregnancies without treatment.

These results suggest that enoxaparin can be effective in the prevention of preclinical and clinical abortion in women with thrombophilia.

In another study, Brenner et al[46] evaluated the efficacy and safety of enoxaparin in 50 thrombophilic women who had had recurrent pregnancy loss (> 3 losses in 1st, > 2 losses in 2nd and > 1 loss in 3rd trimester). Enoxaparin, in the dosage of 40-80 mg/day, was used to treat 61 subsequent pregnancies throughout gestation until 4 weeks after delivery. In addition, aspirin, in the dose of 75 mg daily, was given to women with antiphospholipid syndrome.

- Whereas only 20% of untreated pregnancies prior to diagnosis of thrombophilia resulted in live births, 75% of enoxaparin-treated pregnancies did so.
- In 23 women without a single living child following 82 untreated gestations, antithrombotic therapy resulted in 84% successful deliveries.
- In 20 women with a prior living child, antithrombotic therapy improved successful delivery from 38% to 95%.

These results established the safety and efficacy of enoxaparin in preventing pregnancy loss in women with inherited and acquired thrombophilia.

Carp and colleagues[47] evaluated the effect of enoxaparin on the subsequent live birth rate in women with hereditary thrombophila. Eighty-five patients with three or more consecutive pregnancy losses and hereditary thrombophilia subsequently conceived. Of them, 37 were treated with daily subcutaneous injections of enoxaparin 40 mg, and 48 were not treated. The outcome of the subsequent pregnancy was assessed in both groups of patients in terms of live births or repeat miscarriage. Forty-seven of the 85 patients subsequently delivered, while 38 miscarried. Twenty-six of the 37 pregnancies in treated patients (70.2%) resulted in live births, compared with 21 of 48 (43.8%) in untreated patients. Primary aborters, i.e. women with no previous live births, were the main beneficiaries of the treatment (Table. 1). This treatment proved beneficial also for patients with a poor prognosis for a live birth (5 or more miscarriages), where the live birth rate increased from 18.2% to 61.6%.

REFERENCES:

1. Bad Obstetric History (BOH): Causes & Diagnosis. Available at http://www.srl.in/rd/innersense/voice81.pdf. Accessed on October 29, 2010.
2. Petrozza JC, Berin I. Recurrent Early Pregnancy Loss. Available at http://emedicine.medscape.com/article/260495. Accessed on October 29, 2010.
3. Adinolfi M. Recurrent habitual abortion, HLA sharing and deliberate immunization with partner's cells: a controversial topic. Hum Reprod. 1986; 1 (1): 45-8.
4. Shapiro AD. An overview of thrombophilia. Available at http:// www.hemophilia.org/bdi/Thrombo_article.pdf. Accessed on November 16, 2010.
5. Marik PE, Plante LA. Venous Thromboembolic Disease and Pregnancy. New England Journal of Medicine 2008; 359 (19): 2025-2033.
6. National Human Genome Research Institute. Learning About Antiphospholipid Syndrome (APS). Updated February 25, 2009.
7. Trout SW, Seifer DB. Do women with unexplained recurrent pregnancy loss have higher day 3 serum FSH and estradiol values? FertilSteril. 2000 Aug; 74 (2): 335-7.
8. Anderson FWJ, Johnson TRB. Maternal mortality at Y2K. Postgraduate Obstetrics and Gynecology 2000; 20:1.
9. Berker B,Ta§kin S, Kahraman K, et al. The role of low-molecular-weight heparin in recurrent implantation failure: a prospective, quasi-randomized, controlled study. Fertil SteriL 2011 Jun 30; 95 (8): 2499-502.
10. Belilos E, Carsons S. Antiphospholipid Syndrome. Available at: http://emedicine.medscape.com/article/333221. Accessed on October 29, 2010.
11. Djelmis J, Radoncic E, Ivanisevic M. Antiphospholipid antibody syndrome and fetal outcome. Acta Med Croatica. 2001; 55 (3): 123-30.
12. Antiphospholipid_syndrome. Available at http://en.wikipedia. org/wiki/ Antiphospholipid_syndrome. Accessed on October 29, 2010.
13. Giannakopoulos B, Passam F, Rahgozar S, Krilis SA. Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood. 15 2007; 109 (2): 422-30.
14. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004; 10 (11): 1222-6.
15. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006; 4 (2): 295-306.
16. Erkan D, Patel S, Nuzzo M, Gerosa M, Meroni PL, Tincani A, Lockshin MD. Management of the controversial aspects of the antiphospholipid syndrome pregnancies: a guide for clinicians and researchers. Rheumatology (Oxford). 2008; 47 Suppl 3: iii23-7.
17. Berg TG. Antiphospholipid Antibody Syndrome and Pregnancy. Available at http://emedicine.medscape.com/article/260495. Accessed on October 29, 2010.
18. Holzheimer RG. Low-molecular-weight heparin (LMWH) in the treatment of thrombosis. Eur J Med Res. 2004; 9 (4): 225-39.

19. Kupferminc M, Elder A, Steinman N, Many A, Bar-Am A, Jaffa A, Fait G, Lessing JB. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 340: 9-13.
20. Greer IA. Thrombophilia: implications for pregnancy outcome. Thromb Res 2003; 109:73-81.
21. Woodhams BJ, Candotti G, Shaw R, Kernoff PB. Changes in coagulation and fibrinolysis during pregnancy: evidence of activation of coagulation preceding spontaneous abortion. Thromb Res 1989; 55: 99-107.
22. Chamley LW. Action of anticardiolipin and antibodies to beta2-glycoprotein-l on trophoblast proliferation as a mechanism for fetal death. Lancet 1998; 26: 1037-1038.
23. Franklin RD, Kutteh WH. Effects of unfractionated and low molecular weight heparin on antiphospholipid antibody binding in vitro. Obstet Gynecol 2003; 101: 455-462.
24. Bose P, Black S, Kadyrov M, Bartz C, Shlebak A, Regan L, Huppertz B. Adverse effects of lupus anticoagulant positive blood sera on placental viability can be prevented by heparin in vitro. Am J Obstet Gynecol 2004; 191: 2125-2131.
25. Hills FA, Abrahams VM, Gonjalez-Timon B, Francis J, Cloke B, Hinkson L, Rai R, Mor G, Regan I, Sullivan M, et al. Heparin prevents programmed cell death in human trophoblast. Mol Hum Reprod 2006; 12: 237-243.
26. Tzafettas J, Mamopolous A, Anapliotis A, Loufopoulos A, Psarra A, Klearchou N, Mamopolous M. Thromboprophylaxis throughout pregnancy in women with previous history of recurrent miscarriages of unknown aetiology. Clin Exp Obstet Gynecol 2002; 29: 267-270
27. Frank M, Sodin-Semrl S, Rozman B, Potocnik M, Kralj-lglic V. Effects of low-molecular-weight heparin on adhesion and vesiculation of phospholipid membranes: a possible mechanism for the treatment of hypercoagulability in antiphospholipid syndrome. Ann N Y Acad 5c/1. 2009; 1173: 874-86.
28. Deruelle P, Coulon C The use of low-molecular-weight heparins in pregnancy-how safe are they? Curr Opin Obstet Gynecol. 2007; 19 (6): 573-7.
29. Glasnovic M, Bosnjak I, Vcev A, Soldo I, Kosuta M, Lenz B, Glasnovic-Horvatic E, Soldo-Butkovic S, Micunovic N. Antibody profile of pregnant women with antiphospholipid syndrome and pregnancy outcome after treatment with low dose aspirin and low-weight-molecular heparin. Coll Antropol. 2007; 31 (1): 173-7.
30. Serrano F, Nogueira I, Borges A, Branco J. Primary antiphospholipid syndrome: pregnancy outcome in a Portuguese population. Acta Reumatol Port. 2009; 34 (3): 492-7.
31. 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; 19 (2): 216-20.
32. Magid YM, Elussein EA, Omer MM, Samaan SI, A/Rahim F, Adam I. Heparin and aspirin in pregnant Sudanese women with recurrent miscarriage associated with antiphospholipid antibodies. Afr J Reprod Health. 2007; 11 (2): 95-8.
33. Stephenson MD, Ballem PJ, Tsang P, Purkiss S, Ensworth S, Houlihan E, Ensom MH. Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot

trial comparing low molecular weight heparin to unfractionated heparin. J Obstet Gynaecol Can. 2004; 26 (8): 729-34.
34. Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, Giarratano A, Licata G. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis Rheum. 2003; 48 (3): 728-31.
35. Bad Obstetric History (BOH): Causes & Diagnosis. Available at http://www.srl.in/rd/innersense/voice81.pdf. Accessed on October 29, 2010.
36. Petrozza JC, Berin I. Recurrent Early Pregnancy Loss. Available at http://emedicine.medscape.com/article/260495. Accessed on October 29, 2010.
37. Salat-Baroux J. Recurrent spontaneous miscarriages. Reprod Nutr Dev1998; 28: 1555-68.
38. Crosignani PC, Rubin BL. Recurrent spontaneous miscarriage. The recommendations of the ESHRE workshop on recurrent spontaneous miscarriage held in Anacapri on September 9-11 1990. Hum Reprod 1991; 6: 609-10.
39. Blank M, Cohen J, Toder V, Shoenfeld Y. Induction of Anti¬phospholipid syndrome in naive mice with mouse lupus monoclonal and human polyclonal anti-cardiolipin antibodies. Proc Natl Acad Sci USA 1991; 88: 3069-73.
40. Preston FE, Rosendaal FR, Walker ID, Briot E, Berntorp E, Conard J, Fontcuberta J, Makris M, Mariani G, Noteboom W, Pabinger I, Legnani C, Scharrer I, Schulman S, Van der Meer FJ. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348: 913-6.
41. Grandone E, Margaglione M, Colaizzo D, D 'Addedda M, Cappucci G, Vecchione G, Scianname N, Pavone G, Di Minno G. Factor V Leiden is associated with repeated and recurrent unexplained fetal losses. Thromb Haemost 1997; 77: 822-4.
42. Rai R, Regan L, Hadley E, Dave M, Cohen H. Second-trimester pregnancy loss is associated with activated C resistance. Br J Haematol 1996; 92: 489-90.
43. Martinelli I, Taioli E, Cetin I, Marinoni A, Gerosa S, Villa MV, Bozzo M, Mannucci PM. Mutations in coagulation factors in women with unexplained late fetal loss. N Engl J Med 2000; 343: 1015-8.
44. Tal J, Schliamser LM, Leibovitz Z, Ohel G, Attias D. A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure. Hum Reprod 1999; 14: 1624-7.
45. Sarto A, Rocha M, Geller M, Capmany C, Martinez M, Quintans C, Donaldson M, Pasqualini RS. Treatment with enoxaparin adapted to the fertility programs in women with recurrent abortion and thrombophilia. Medlcina (B Aires). 2001; 61 (4): 406-12.
46. 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 (5): 693-7.
47. Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. J Thromb Haemost. 2003; 1 (3): 433-8.

REVIEW ARTICLE

AUTHORS:

1. Champa Koppad
2. Lakshmi K. S.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of OBG, BIMS, Belgaum.
2. Assistant Professor, Department of OBG, BIMS, Belgaum.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Champa Koppad,
Department of OBG,
BIMS, Belgaum.
E-mail: champakoppad@gmail.com

Date of Submission: 30/11/2014.
Date of Peer Review: 01/12/2014.
Date of Acceptance: 04/12/2014.
Date of Publishing: 20/12/2014.