Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2018/231

Original Article

Clinical Study on Prophylactic and Therapeutic Management of Thrombophilia in Adverse Pregnancy Outcome Patients

S Sooraj

Assistant Professor, Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, Kerala

Abstract

Background: There is a growing view that inherited and acquired thrombophilia may predispose to adverse pregnancy outcome (APO). APOs such as pregnancy loss, preeclampsia, and intrauterine growth retardation (IUGR) are associated with thrombotic mechanisms and thrombophilia, *vice versa*. The use of low-molecular-weight heparin (LMWH) has been studied in women with previous APO; however, the reports are inconsistent. This may be due to heterogeneity of the study groups and insufficient classification of the entire disease processes to guide the treatment guidelines. It is also due to the variation in gestational age at the start-up of LMWH treatment which is equally important. In the absence of other effective treatments and its accepted safety in pregnancy, LMWH was used in this study to analyze the results.

Aim of the Study: This study aims to evaluate the overall efficacy of LMWH and low-dose aspirin in the management of thrombophilia.

Materials and Methods: A total of 69 patients with a history of APO with thrombophilia were included to evaluate the overall efficacy of LMWH and low-dose aspirin in their management. Thrombophilic studies done: Anticardiolipin antibodies test, lupus anticoagulant test, protein C assay, protein S assay, activated protein C-resistant test, antithrombin assay, homocysteine estimation, prothrombin gene mutation test, anti-β-2 glycoprotein antibodies assay, proglobal C assay, and factor V Leiden mutation test. American College of Obstetricians and Gynecologists guidelines were applied in planning the treatment of patients consisting of dalteparin (fragmin) and low-dose aspirin. Both symptomatic (prophylaxis) and asymptomatic (therapeutic) patients with a history of previous APO were treated; dose was adjusted on regular evaluation of activated partial thromboplastin time, creatinine clearance (Cr Cl <30 mL/min), and an International Normalized Ratio 2.0–3.0. All the data were analyzed using standard statistical methods.

Observations and Results: A total of 69 patients with a history of APO were screened for inherited and acquired thrombophilia. The patients were enrolled over a period of 2 years from July 2006 to June 2008 from the OPD at the Department of Obstetrics and Gynaecology, AIIMS, New Delhi. Recurrent abortion in 32 (46.37%) patients was the most common APO in women screened for thrombophilia. Other indications were IUGR in 11 (15.94%), severe preeclampsia in 9 (13.04%), and unexplained intrauterine device in 17 (24.63%) patients. 45/69 patients were treated for thrombophilia. 2/45 patients had to undergo termination of pregnancy; hence, 43 cases were tabulated for analysis in this study. 21/43 (48.83%) were asymptomatic and 22/45 were (51.16%) symptomatic patients with active thrombophilic symptoms and signs. In asymptomatic type of thrombophilia, the live birth rate was 86.87%, and in symptomatic type, it was 90. 97% and both the results were significant statistically with *P* value of 0.010 and 0.001, respectively (P taken as significant at $P < 0.05$). Continuation of pregnancy beyond 37 weeks in asymptomatic group was 76.19% and in symptomatic group 68.18%. The results were significant with *P* values at 0.024. In the asymptomatic group, 15/21 newborns weight (71.42%) was >2.5 kg compared to 4/21 (19.045) with weight <2.5 kg and $P = 0.031$, significant. Among the newborns of symptomatic group, 14/22 (63.63%) were >2.5 kg and 7/22 (31.81%) were below, with $P = 0.040$ and significant.

Conclusions: The management of thrombophilia in the setting of pregnancy remains controversial. LMWH and aspirin provide benefit, both as prophylactic and therapeutic treatment for asymptomatic and symptomatic thrombophilia. However, prophylactic anticoagulation should be addressed on a case-by-case basis taking into account the inherited and acquired thrombophilias and history of prior pregnancies and their outcomes. Women with acquired thrombophilia are more likely to benefit from anticoagulation and should be treated according to published guidelines.

Key words: Adverse pregnancy outcome, Heparin and low-molecular-weight heparin, Pregnancy, Thrombophilia, Thrombosis

Access this article online

www.ijss-sn.com

Month of Submission : 06-2018
Month of Peer Review : 07-2018
Month of Acceptance : 08-2018
Month of Publishing : 08-2018

Corresponding Author: Dr. S Sooraj, Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, Kerala, India. E-mail: drsoorajsaiims@gmail.com

INTRODUCTION

Pregnancy is a physiological prothrombotic state. Venous thromboembolism is a leading cause of direct maternal death well described in the MBRRACE reports.[1] The various adverse pregnancy outcomes (APOs) such as recurrent abortions, intrauterine growth retardation (IUGR), preeclampsia, intrauterine death of fetus, and placental abruption collectively account to 15% of pregnancies.[2] All these conditions share similar and overlapping micro- and macro-thrombotic pathogenic processes. Recurrent abortions are defined as three or more miscarriages before 20 weeks of gestation and remain an important problem in women of reproductive age affecting approximately 1–2% of all pregnancies;[3] if they are sequential the incidence rises to 5%.[4] The association between inherited thrombophilia and recurrent abortions was first reported by Sanson *et al.*, in 1996.[5] The root cause of APO is inadequate placental perfusion due to hemostatic imbalance.[6] The causes of inherited thrombophilia are deficiency of factor V Leiden (FVL), prothrombin (PT G202I0A), methylenetetrahydrofolate reductase (MTHFR) C677T, and A1298 mutations (MTHFR), as well as protein C, protein S, and antithrombin III, whereas acquired cases of thrombophilia are due to the presence of antiphospholipid antibodies (APAs) such as lupus anticoagulant and anticardiolipin antibody.[7] Restoration of sufficient uteroplacental circulation results in saving the pregnancy and from complications. Hence, antithrombotic prophylaxis has been used in the management of thrombophilia of APO.[8] Review of one meta-analysis showed that thromboprophylaxis was helpful in antiphospholipid syndrome cases rather than inherited thrombophilia.[9] The overall effectiveness of anticoagulant prophylaxis is controversial even though it is being used widely in patients with APO and poor obstetric history. The use of low-molecular-weight heparin (LMWH) in women with thrombophilic defects and recurrent miscarriage with significant improvement in live birth rates was recorded by the studies by Brenner,[10] Tzafettas *et al.*,[11] Grandone *et al.*,[12] Brenner *et al.*[13] In a subgroup, an association between recurrent miscarriages and APAs was well established; these antibodies were shown to play a role in recurrent fetal loss by producing a thrombophilic and inflammatory effect. In such patients, the use of LMWH with low-dose aspirin was shown to be efficient and promoted as a standard care.[14] LMWH was demonstrated to have anti-inflammatory effects on the placental vasculature by preventing leukocyte activation by blocking P- and L-selectins.[15] The present study is conducted to analyze the results of final outcome in the APO patients with thrombophilia.

MATERIALS AND METHODS

A total of 69 patients with a history of APO in previous pregnancies were included in this study to evaluate the overall efficacy of LMWH and low-dose aspirin in the management of thrombophilia. Ethical committee clearance was obtained before the commencement of the study. An ethical committee approved pro forma and consent forms were used while conducting the study.

Inclusion Criteria

Patients with a history of APO in previous pregnancies such as (1) severe preeclampsia <36 weeks; (a) blood pressure more than 160/110, (b) proteinuria >5 g/day, (c) hemolysis, (d) elevated liver enzymes, (e) platelets <1 lakhs/mm^3, and (f) eclampsia; (2) placental abruption; (3) delivery of small for gestational age baby; (4) unexplained intrauterine deaths; and (5) recurrent abortions (>3) were included in the study.

Exclusion Criteria

Patients with chronic hypertension, diabetes mellitus, cardiovascular disease, renal disease, multiple pregnancies, maternal drug or alcohol abuse, intrauterine infections, suspected chromosomal abnormalities, congenital malformations detected by ultrasound, and on anticoagulation therapy, patients under progesterone therapy were excluded from the study.

Timing of Study

Patients with a history of APO fitting inclusion criteria were screened for thrombophilia in the preconception period, during pregnancy, and/or >6 weeks postpartum.

Method of Study

This was a prospective, cross-sectional, observational study. Detailed obstetric history was taken. Routine investigations such as hemogram and liver and renal function tests were done. Some special investigations such as thyroid-stimulating hormone, glucose tolerance tests with 75 g glucose, hysteroscopy, parental blood karyotyping, and TORCH screen if indicated were done to exclude other causes of APO. Various thrombophilic studies were undertaken using the blood samples of the patients. They included (1) anticardiolipin antibodies test, lupus anticoagulant test, protein C assay, protein S assay, activated protein C-resistant test, antithrombin assay, homocysteine estimation, prothrombin gene mutation test, anti-β-2 glycoprotein antibodies assay, proglobal C assay, and FVL mutation test. Based on the test results, the type of thrombophilia was diagnosed. American College of Obstetricians and Gynecologists guidelines were applied in planning the treatment of patients.[16] It consisted of administering dalteparin (fragmin) which comes in prefilled syringes of 2500 units, 5000 units, 7500 units, 10,000 units,

and 12,500 units. Among the 69 patients included 45 who were positive for thrombophilia were treated in this study irrespective of their gestational age. Allergy to heparin and/or contraindications for heparin was strictly considered, but none of the screened patients needed to be excluded from the study. Patients included did not take progesterone. In symptomatic patients, therapeutic doses of dalteparin = 200 units/kg/day were used. In asymptomatic patients with a history of previous APO, prophylactic dalteparin = 2500–5000 units/day was used. The dose was adjusted based on regular evaluation of activated partial thromboplastin time, creatinine clearance (Cr Cl <30 mL/min), and an INR 2.0–3.0 is maintained. Patients with preeclampsia were avoided treatment with dalteparin and only low-dose aspirin (150 mg/day) was used. In addition, the treatment was continued for 6 weeks in postnatal period. All the patients were kept under consultation and supervision of the institutional hematologist for modification, stoppage, or treatment of adverse effects. Patients were monitored during the antenatal period with regular ultrasound examination of abdomen and Doppler study of major vessels for evidence of complications. All the data were analyzed using standard statistical methods. Simple arithmetic mean, standard deviation, and Student's *t*-test were used to analyze the statistical significance.

OBSERVATIONS AND RESULTS

A total of 69 patients with a history of APO were screened for inherited and acquired thrombophilia. The patients were enrolled over a period of 2 years from July 2006 to June 2008 from the OPD at the Department of Obstetrics and Gynaecology, AIIMS, New Delhi. Recurrent abortion in 32 (46.37%) patients was the most common APO in women screened for thrombophilia. Other indications were IUGR in 11 (15.94%), severe preeclampsia in 9 (13.04%), and unexplained intrauterine device (IUD) in 17 (24.63%) patients [Table 1 and Figure 1].

Age distribution

The mean age of the patients in this study was 27.34 ± 3.28 with a range of 20–36 years. The mean age of patients with recurrent abortion was 27.38 ± 2.25 with a range of 22–32 years while that for the patients with intrauterine deaths it was 27.70 ± 1.99 with a range of 24–31 years, with intrauterine growth restriction it was 27.81 ± 2.92 with a range of 24–34 years and preeclampsia it was 28.66 ± 3.35 with a range of 25–36 years [Table 2].

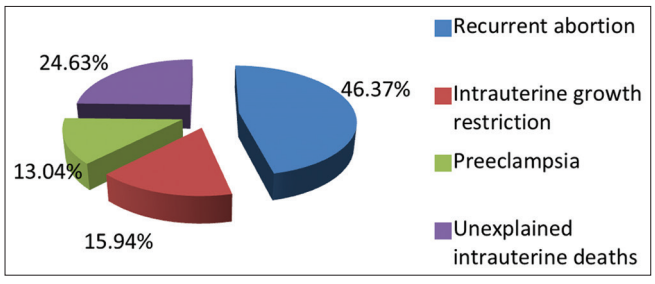

Figure 1: The incidence of adverse pregnancy outcome in the study (*n* = 69)

Distribution of Gravidity

The mean gravidity of the patients in the present study was 3.7 ± 1.25. The mean gestation of the patients with recurrent abortion was 3.81 ± 0.86, while that for patients with IUD was 3.41 ± 1.12, with IUGR it was 4 ± 0.89 and preeclampsia it was 4.33 ± 0.87 [Table 3].

Of 69 patients with APO, 45/69 (65.21%) were positive to the various thrombophilic tests. Among them, 9/45 (20%) were inherent type and 35/45 (77.77%) were acquired type of thrombophilia. 19/32 (59.37%) patients with a history of recurrent abortions were thrombophilic; among them, 3/19 (15.78%) were inherent and 16/19 (84.21%) were acquired type. Of 17 patients with IUD, 11/17 (64.70%) were thrombophilic; 2/11 (18.18%) were inherent and 10/11 (90.90%) were acquired type. Of 11 patients with IUGR, 7/11 were thrombophilic; 2/7 (28.57%) were inherent and 5/11 (45.45%) were acquired type. Among the 09 preeclampsia patients, 7/9 (77.77%) patients

Table 1: The incidence of adverse pregnancy outcome in the study (*n*=69)

Type of adverse pregnancy outcome	Number of patients *n*=69 (%)
Recurrent abortion	32 (46.37)
Intrauterine growth restriction	11 (15.94)
Preeclampsia	9 (13.04)
Unexplained intrauterine deaths	17 (24.63)

Table 2: The age distribution of patients with different adverse pregnancy outcome

Adverse pregnancy outcome	Age: Mean±SD (range in years)
All patients	27.34±3.28 (20–36)
Recurrent abortion	27.38±2.25 (22–32)
Unexplained intrauterine deaths	27.70±1.99 (24–31)
Intrauterine growth restriction	27.81±2.92 (24–34)
Preeclampsia	28.66±3.35 (25–36)

SD: Standard deviation

Table 3: The distribution of gravidity in the study group

Adverse pregnancy outcome	Mean gravidity±SD (range)
All patients	3.7±1.25 (1–8)
Recurrent abortion	3.81±0.86 (3–6)
Unexplained intrauterine deaths	3.41±1.12 (1–5)
Intrauterine growth restriction	4±0.89 (3–6)
Preeclampsia	4.33±0.87 (3–6)

SD: Standard deviation

were thrombophilic; 2/7 (28.7%) were inherent and 5/7 (71.42%) were acquired type [Table 4].

Thrombophilic tests positive in different types of APO in the present study are shown in Table 5. Anti-β-2 glycoprotein antibody was positive in 24/45 tests (53.33%). Protein C deficiency was observed in 1/45 (2.22%), (IUGR), patient. Protein S deficiency was observed in 1/45 (2.22%) (recurrent abortion) patient. Antithrombin III deficiency was observed in 2/45 (4.44%) (recurrent abortion and preeclampsia) patients, FVL mutation was observed in 4/45 (8.88%) (recurrent abortion, IUD, IUGR, and preeclampsia) patients, hyperhomocysteinemia was observed in 2/45 (4.44%) and LAC positive in 3/45 (6.66%) (two in IUD and preeclampsia) patients, and ACL test was positive in 9/45 (20%) [Table 5].

Of 45 patients, two patients had to undergo termination of pregnancy; hence, 43 cases were tabulated for analysis in this study. Among the 43 patients, 21 (48.83%) were asymptomatic and the remaining 22 (51.16%) were symptomatic patients with active thrombophilic symptoms and signs. Continuation of pregnancy beyond 37 weeks in patients with APO was considered as a good prognosis, and in the present study, the overall live birth rate following treatment was calculated. In asymptomatic type of thrombophilia, the live birth rate was 86.87%, and in symptomatic type, it was 90.97% and both the results were statistically significant with *P* value of 0.010 and 0.001, respectively (P taken as significant at $P < 0.05$). The percentage of patients with successful continuation of pregnancy beyond 37 weeks in asymptomatic group was 76.19%, and in symptomatic group, it was 68.18%. The results were significant with p values at 0.024. APGAR score and birth weight reflect the improved placental circulation in APO with thrombophilias, and in this study, in the asymptomatic group, 15/21 newborns weight (71.42%) was >2.5 kg compared to 4/21 (19.045) with weight <2.5 kg and *P* value of 0.031, significant. Among the newborns of symptomatic group, 14/22 (63.63%) were >2.5 kg and 7/22 (31.81%) were below, with *P* value of 0.040 and significant. The APGAR score of asymptomatic group was >7 in 15/21 (71.42%), and in symptomatic group, it was 63.63; *P* value was statistically significant. The overall treatment result distribution of patients depending on their obstetrical diagnosis is shown in Table 5. In this study, the overall live birth rate in patients with thrombophilia with or without symptoms and signs was 88.92%.

The overall effect of the treatment of thrombophilia in symptomatic and asymptomatic types, in terms of live birth rate, continuation of pregnancy beyond 37 weeks, birth weight, and APGAR score was to be statistically significant; $P < 0.05$ in all the parameters mentioned above.

DISCUSSION

In this study, 69 pregnant women with APOs such as recurrent abortions, IUDs, IUGRS, and preeclampsia were investigated for evidence of thrombophilias with the help of thrombophilic tests. It was observed that 45/69 was positive to thrombophilia; inherent and acquired types. The patients were treated depending on whether the symptoms and signs of thrombophilia were present or not, using American College of Obstetricians and Gynecologists guidelines.[16] Thrombophilia management during pregnancy consists of primary thromboprophylaxis in asymptomatic women, secondary prophylaxis of

Table 4: The incidence of types of thrombophilia in the study (*n*=69)

Thrombophilia patients (*n*=45)	Recurrent abortions (*n*=32)	IUD (*n*=17)	IUGR (*n*=11)	Preeclampsia (*n*=9)
Inherent (*n*=9)	3	2	2	2
Acquired (*n*=36)	16	10	5	5
Total	19	12	7	7

IUD: Intrauterine device, IUGR: Intrauterine growth retardation

Table 5: The positive thrombophilic tests in different types of APO in this study (*n*=69)

Thrombophilic tests positive (*n*=45)	Recurrent abortions (*n*=19)	IUD (*n*=12)	IUGR (*n*=7)	Preeclampsia (*n*=7)	Total *n*=45 (%)
Protein C deficiency (*n*=1)	-	-	1	-	4–8.88
Protein S deficiency (*n*=1)	1	-	-	-	1–2.22
Antithrombin III deficiency (*n*=2)	1	-	-	1	1–2.22
FVL mutation (*n*=4)	1	2	1	-	4–2.22
Hyperhomocysteinemia (*n*=2)	1	-	1	-	2–4.44
LAC (*n*=3)	-	2	-	1	2–4.44
ACL IgG (*n*=6)	3	1	1	1	6–13.33
ACL IgM (*n*=3)	3	-	-	-	3–6.66
Anti-β-2 glycoprotein antibody (n=23)	9	7	3	4	25–55.55

IUD: Intrauterine device, IUGR: Intrauterine growth retardation, APO: Adverse pregnancy outcome, FVL: Factor V Leiden

recurrences in women who have previously developed thrombosis, and the treatment of acute thrombotic episodes.[17] The absence of well-controlled trials in the management of thrombophilia in pregnancy makes it difficult to establish clear cur guidelines. Hence, recommendations regarding prophylactic and therapeutic strategies in pregnancy are largely based on clinical trials in non-pregnant populations.[18] In addition, assessing the therapeutic response to treatment is difficult as pregnancy remains a contraindication for repeated imaging procedures. Hence, the final outcome following delivery or completion of 6 weeks of postnatal period was taken in this study for therapeutic assessment. It is a well-established fact that pregnant women with previous history of fetal death, severe preeclampsia, IUGR, abruptio placenta, or recurrent miscarriage have an increased risk of recurrence in subsequent pregnancies.[19-21] It may be as high as 46% with a history of two or more adverse outcomes, even before any thrombophilia is taken into account.[22] Hence, the authors recommended prophylactic treatment which included low-dose aspirin with or without subcutaneous heparin, as well as folic acid and Vitamin B_6 supplements, according to the type of thrombophilia present as well as the nature of the previous adverse outcome. The most confirmative evidence of association between APO and pregnancy loss and thrombophilia was afforded by APAs. Women with APAs develop thrombosis, pregnancy loss, and preeclampsia.[19,20] Currently, it has been postulated that the recurrent abortions occurring especially after the week 12 of gestation may be due to interference with spiral artery remodeling during secondary trophoblastic invasion.[21] Rai *et al.*[22] using combined aspirin 75 mg and unfractionated heparin 5000 units every 12 h, in pregnant women with thrombophilia, precipitated by APAs, markedly improved the live birth rate of women to 71%. Farquharson *et al.*[23] were unable to confirm a significantly better outcome after treatment with aspirin plus heparin. Life birth rate was 78% in 51 women treated with aspirin plus heparin and 72% in women treated with aspirin alone. A recent Cochrane collaboration[24] reported a 15% reduction in the risk of preeclampsia and a 14% reduction in fetal and/or neonatal death. The combination of aspirin and heparin or LMWH was effective in recurrent fetal loss in APS syndrome and could be considered for women with inherited thrombophilias and history of severe preeclampsia, IUGR, abruptio placentae, or fetal loss, although no controlled studies on the subject are currently available. In this study, 7/9 patients with preeclampsia were positive for thrombophilia, and the final results showed a live birth rate of 100% among both the symptomatic and asymptomatic types [Table 6]. The role of LMWH and low-dose aspirin is well accepted in patients with antiphospholipids antibody-associated fetal loss. The live birth rate in these patients is about 10% if left untreated.[25] It has been demonstrated that the live birth rate can be increased to about 80% using LMWH and low-dose aspirin.[24,23,26] In the present

Table 6: Overall results of treatment with LMWH in patients with thrombophilia in the study (*n*=43)

Type of thrombophilia total (*n*=43)	Recurrent abortions (*n*=17)	IUD (*n*=12)	IUGR (*n*=7)	Preeclampsia (*n*=7)	Overall percentage	*P* value
Asymptomatic (*n*=21)	8–47.05%	5–41.66%	4–57.14%	4–57.14%		
Prophylactic treatment						
Delivered at gestation ≥37 weeks	6	4	3	3	76.19	0.024
Delivered at gestation ≤37 weeks	1	0	1	1	14.28	
Abortions ≥15 weeks gestation	1	0	0	0	04.76	
Abortions ≤15 weeks gestation	0	1	0	0	04.76	
Live birth rate	87.50%	80%	80%	100	86.87%	0.010
Birth weight ≥2.5 kg	5	4	3	3	71.42	0.031
Birth weight ≤2.5 kg	2	0	1	1	19.04	
APGAR score ≥7	6	3	3	3	71.42	0.028
APGAR score ≤7	1	1	1	1	19.04	
Postnatal DVT incidence	0	0	0	0	0	-
Symptomatic (*n*=22)	9–40.90%	7–31.81%	3–13.63%	3–13.63%		
Therapeutic treatment						
Delivered at gestation ≥37 weeks	7	5	2	1	68.18	0.024
Delivered at gestation ≤37 weeks	1	2	1	2	27.27	
Abortions ≥15 weeks gestation	1	0	0	0	04.54	
Abortions ≤15 weeks gestation	0	0	1	0	04.54	
Live birth rate	88.88%	100%	75%	100%	90.97	0.001
Birth weight ≥2.5 kg	6	5	2	1	63.63	0.040
Birth weight ≤2.5 kg	2	2	1	2	31.81	
APGAR score ≥7	6	5	2	1	63.63	0.041
APGAR score ≤7	2	2	1	2	31.81	
Postnatal DVT incidence	1	1	0	1	13.63	0.653

IUD: Intrauterine device, IUGR: Intrauterine growth retardation, DVT: Deep vein thrombosis, LMWH: Low-molecular-weight heparin

study, there were three patients with antiphospholipids antibody-associated fetal loss and following treatment [Table 6], such loss was averted. In a study by Brenner *et al.*[27] who treated 50 women with recurrent miscarriage and thrombophilia in 61 subsequent pregnancies with enoxaparin (40–120 mg/day), a 75% of live birth could be achieved compared to 20% of previously untreated pregnancies in the same women. Similar study by Carp *et al.*[28] showed 70% live births under 40 mg/day enoxaparin in 37 women with thrombophilia and recurrent abortions compared to 44% live births in 48 untreated women. A prospective multicenter study (the LIVE-ENOX study) on pregnant patients with thrombophilia and abortions compared 40 and 80 mg/day enoxaparin and found them to be equally effective resulting in live births in 81% and 77% compared to only 28% live births in previously untreated pregnancies of these women.[13] Sarto *et al.*[29] concluded from their study that live birth rate could be improved to 85% in women with recurrent abortions and thrombophilia under enoxaparin; before thrombophilia was diagnosed, only 15% of 105 untreated pregnancies of these women resulted in live births. In this study, the overall live birth rate in patients with thrombophilia with or without symptoms and signs was 88.92%. Monien *et al.*[30] from their study concluded that the overall live birth rate was 87.50%, which was far higher than the live birth rate of 16.6% recorded in the same patients in earlier pregnancies without treatment.

CONCLUSIONS

Pregnancy is a prothrombotic state in the complex underlying physiology of pregnancy, leading to an increase of procoagulant factors; physical changes lead to increased stasis and the additional contribution in cases of inherited and acquired thrombophilias. The management of thrombophilia in the setting of pregnancy remains controversial. LMWH and aspirin provide benefit, both as prophylactic and therapeutic treatment for asymptomatic and symptomatic thrombophilia. However, prophylactic anticoagulation should be addressed on a case-by-case basis taking into account the inherited and acquired thrombophilias and history of prior pregnancies and their outcomes. Women with acquired thrombophilia are more likely to benefit from anticoagulation and should be treated according to published guidelines.

REFERENCES

1. Knight M, Kenyon S, Brocklehurst P. editiors. On Behalf of MBRRACE-UK. Saving lives, Improving Mothers' Care: Lessons Learned to Inform Future Maternity Care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-12. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014, Available from: http// www.npeu.ox.ac.uk/mbrrace-uk. [Last accessed on 2018 Aug 01].
2. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, *et al.* Incidence of early loss of pregnancy. N Engl J Med 1988;319:189-94.
3. Baek KH, Lee EJ, Kim YS. Recurrent pregnancy loss: The key potential mechanisms. Trends Mol Med 2007;13:310-7.
4. Carson A, Branch W. Management of Recurrent Early Pregnancy Loss, Compendium Selected Publications. Washington, DC: American College of Obstetricians and Gynecologists; 2001. p. 372-83.
5. Sanson BJ, Friederich PW, Simioni P, Zanardi S, Hilsman MV, Girolami A, *et al.* The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost 1996;75:387-8.
6. Nadar S, Blann AD, Kamath S, Beevers DG, Lip GY. Platelet indexes in relation to target organ damage in high-risk hypertensive patients: A substudy of the anglo-scandinavian cardiac outcomes trial (ASCOT). J Am Coll Cardiol 2004;44:415-22.
7. John H. Antiphospholipid syndrome: An overview. Can Med Assoc J 2003;168:1675-82.
8. Kher A, Bauersachs R, Nielsen JD. The management of thrombosis in pregnancy: Role of low-molecular-weight heparin. Thromb Haemost 2007;97:505-13.
9. Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. Am J Obstet Gynecol 2000;183:1008-12.
10. Brenner B. Efficacy and safety of two doses of enoxaparin in pregnant women with thrombophilia and recurrent pregnancy loss. Blood 2002;100:2765-29.
11. Tzafettas J, Petropoulos P, Psarra A, Delkos D, Papaloukas C, Giannoulis H, *et al*. Early antiplatelet and antithrombotic therapy in patients with a history of recurrent miscarriages of known and unknown aetiology. Eur J Obstet Gynecol Reprod Biol 2005;120:22-6.
12. Grandone E, Brancaccio V, Colaizzo D, Sciannamé N, Pavone G, Di Minno G, *et al*. Preventing adverse obstetric outcomes in women with genetic thrombophilia. Fertil Steril 2002;78:371-5.
13. Brenner B, Hoffman R, Carp H, Dulitzky M, Younis J. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: The LIVE-ENOX study. J Thromb Haemost 2005;3:227-9.
14. Girardi G, Redecha P, Salmon J. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med 2004;10:1222-6.
15. Wang L, Brown JR, Varki A, Esko JD. Heparin's antiinflammatory effects require glucosamine 6-O-sulfation and are mediated by blockade of L- and P-selectins. J Clin Invest 2002;110:127-36.
16. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Obstet Gynecol 2013;122:1122-31.
17. Kupferminc MJ. Thrombophilia and pregnancy. Reprod Biol Endocrinol 2003;1:111.
18. Ginsberg JS, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 1998;114:524-30.
19. Paidas MJ, De-Hui WK, Arkel YS. Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome. Clin Perinatol 2004;31:783-805.
20. Infante-Rivard C, Rivard GE, Yotov WV, Génin E, Guiguet M, Weinberg C, *et al.* Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. N Engl J Med 2002;347:19-25.
21. Howley HE, Walker M, Rodger MA. A systematic review of the association between factor V Leiden or prothrombin gene variant and intrauterine growth restriction. Am J Obstet Gynecol 2005;192:694-708.
22. Rai RS, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. Hum Reprod 1995;10:3301-4.
23. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: A randomized, controlled trial of treatment. Obstet Gynecol 2002;100:408-13.
24. 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.
25. Chamley LW, Duncalf AM, Mitchell MD, Johnson PM. Action of anticardiolipin and antibodies to Beta2-glycoprotein-I on trophoblast

proliferation as a mechanism for fetal death. Lancet 1998;352:1037-8.
26. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997;314:253-7.
27. 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.
28. 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;1:433-8.
29. Sarto A, Rocha M, Geller M, Capmany C, Martínez M, Quintans C, *et al.* Treatment with enoxaparin adapted to the fertility programs in women with recurrent abortion and thrombophilia. Medicina (B Aires) 2001;61:406-12.
30. Monien S, Kadecki O, Baumgarten S, Salama A, Do¨rner T, Kiesewetter H. Use of heparin in women with early and late miscarriages with and without thrombophilia. Clin Appl Thromb/Hemost 2009;15:636-44.

How to cite this article: Sooraj S. Clinical Study on Prophylactic and Therapeutic Management of Thrombophilia in Adverse Pregnancy Outcome Patients. Int J Sci Stud 2018;6(5):105-111.

Source of Support: Nil, **Conflict of Interest:** None declared.