

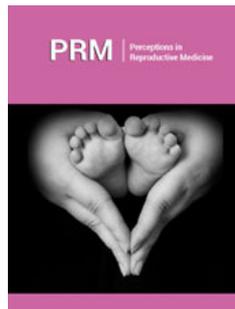
Recurrent Pregnancy Loss in Thrombophilia and Role of Anticoagulation Therapy: A Systematic Review

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Abstract

Thrombophilia also called a prothrombic state or hypercoagulability is a condition in which there is an increased tendency of the body to form clots. RPL is the most serious problem in both early and late gestation. I performed a review to establish the correlation of thrombophilia with recurrent pregnancy loss. The aim of this review was to find the association of the thrombophilia with RPL and the use of anticoagulation in preventing RPL and treatment of the hypercoagulability. Use of enoxaparin and low dose aspirin early in pregnancy with history of recurrent pregnancy loss due to acquired thrombophilia have statically significant improvement in live pregnancy. Same cannot be said about unknown cause of the recurrent pregnancy loss. The proper investigation of the cause of RPL should be carried out. A proper meta-analysis is required to prove these results by forest plot.

Introduction

Thrombophilia also called a prothrombic state or hypercoagulability is a condition in which there is an increased tendency of the body to form clots. These abnormalities can be found in about 50% of all the cases presented with thrombosis without any other risk factors [1]. Thrombophilia can be congenital or can be acquired. Congenital thrombophilia includes factor V Leiden deficiency, protein C deficiency, protein S deficiency, antithrombin III deficiency, and familial dysfibrinogenemia. Acquired thrombophilia includes antiphospholipid syndrome, Systemic lupus erythematosus, anti-cardiolipin antibodies [2]. Acquired thrombophilia is also regarded as autoimmune disease. Of all the ones antiphospholipid syndrome is most commonly associated with Recurrent Pregnancy Loss (RPL) [3]. RPL is the most serious problem in both early and late gestation. It has both social and psychological impact on the women life. It may sometime lead to divorce in third world countries. Miscarriage is common and most of its complications occur in early pregnancy before 20 weeks of gestation with a peak of about 20% occurring in the 12 weeks of gestation [4]. Data on miscarriage is not authentic and lacking because most women miscarriage before they even realize that they are pregnant.

Recurrent miscarriage also called Habitual miscarriage is defined as loss or three or more clinically evident pregnancies before 20 weeks of gestation [5]. About 1 to 2 percent of the women suffer from habitual miscarriages. RPL can be early and late depending upon whether it occur before or after 20 weeks of gestation. RPL is the most exhausting area of reproductive medicine. The etiology of RPL is not fully known and very limited options are available for the treatment. About 40-50% of all the RPL is associated with thrombophilia-the most common cause [6]. Pregnancy is the hypercoagulable state and with thrombophilia, the tendency of clot formation is high. So, both conditions occurring together impaired and worsen the blood flow to the maternal veins leading to clot formation in the placenta and deep venous thrombosis. This

leads to intrauterine growth retardation of the fetus and ultimately fetal demise [7]. The aim of this review is to find the association of thrombophilia with RPL and the use of anticoagulation in preventing RPL and treatment of hypercoagulability.

Methodology

Search for evidence: To obtain the objectives and aim of the studies, the literature search and retrieval process is conducted in four stages as guided by PRISMA guidelines. It is summarized in the Prisma chart. The initial investigation was conducted on the web browser and Google scholar search engine with suitable keywords (Figure 1).

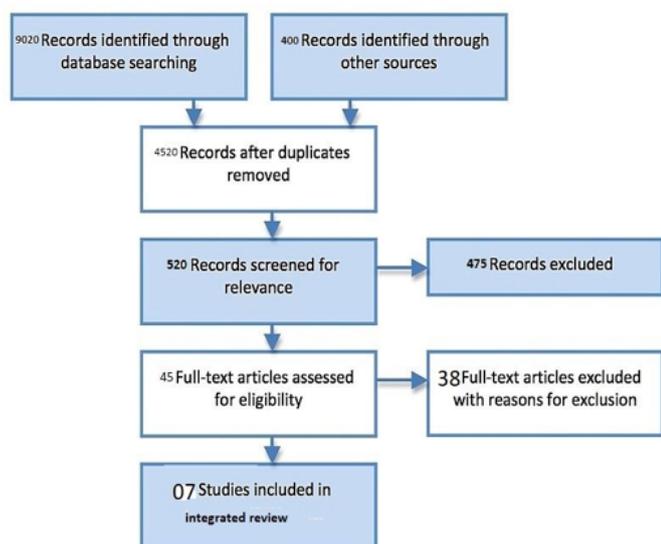


Figure 1: Prisma guideline of the literature review.

Search methodology and article selection: The purpose of it is to refine the keywords for data-based research. The current review is to establish the correlation of thrombophilia with recurrent pregnancy loss. It was extensive database research. Using the various combinations of the keywords, a search was conducted on Google Scholar, PubMed, Medline, Embase, and Wiley online library. The Google Scholar results were 9,420 the results are refined based on study design, review articles, and metaanalysis. Only those articles are selected, which are published in 2000-2021. A total of 45 citations were retrieved. The citations undergo further processing, and 38 articles were excluded. Nine because they are not in the English language and 29 because they deal with the other effects of the thrombophilia like deep venous thrombosis, stroke, cardiovascular aspects. A careful review of these articles revealed no relevancy with abortion.

Inclusion and exclusion criteria: To process the extensive preliminary and database search, a list of inclusion and exclusion criteria is developed. The purpose of the list is to determine the relevant articles that will fulfil the purpose of our literature review. The overall result showed the early use of the anticoagulation therapy in acquired thrombophilia has significant improvement in the pregnancy outcomes. The combination of therapy in APS and

ACS improves the outcomes by 75% and 55% [8-10]. Recurrent pregnancy loss treated with the combination therapy without knowing the proper diagnosis of the thrombophilia, there is no difference in the outcomes as compared to the LDA group and placebo group.

Discussion

Pregnancy is a hypercoagulable state itself. This is because of the increase in the activity of some clotting factors including factor VII, factor VIII, platelets, von Willebrand factor, and fibrinogen. D-dimers are also raised in pregnancy (Table 1). Before labelling thrombophilia as a cause of RPL, it is very important to rule out the other causes of RPL which may include diabetes, uterine malformation, immunological abnormalities, connective tissue diseases, systemic lupus erythematosus, thyroid dysfunction and chromosomal abnormalities. This is important because the treatment of RPL depends upon it. Many physicians blindly treating all kind of RPL as thrombophilia by Low Molecular Weight Heparin (LMWH) and Low Dose Aspirin (LDA). Uteroplacental insufficiency and subsequently abortion is the main pathophysiological phenomena associated with thrombophilia. Thrombosis at the maternal-fetal interface maybe arterial or venous is the underlying mechanism of inherited thrombophilia [11-14]. Deficiencies of protein S and C may lead to other clotting factors go unchecked. As a result of which more clot formation occurs and this maybe causing intrauterine growth retardation and demise of fetus. Inherited thrombophilia also causes implementation failure. This is because of microthrombi formation at causes junction resulting in implantation failure and RPL.

Table 1: Keywords used for an initial search.

Thrombophilia
Miscarriage
Recurrent pregnancy loss
Observational studies
Congenital thrombophilia
Acquired thrombophilia
Abortion
Anticoagulation therapy

On the other hand, in acquired thrombophilia antibodies are formed. Antiphospholipid syndrome APS, in which antibodies aPL formed and recognized body own phospholipids which present in the cell membrane as a foreign material and started attacking on it. 20 antibodies maybe IgG and IgM constitute the aPL. These antibodies make blood hypercoagulable. Some studies show that RPL is associated with aPL in 55% of women. Histopathology of placenta in APS shows increased number of syncytial knots and arteriopathy. Microthrombi are also present in causes vessels. In SLE, severe adverse birth outcomes are present in patients who have anticardiolipin antibodies and microthrombi formation is the main underlying mechanisms for implantation failure and RPL. Heparin is usually the drug of choice in patient with hypercoagulable

states. It acts through various mechanisms in thrombophilia. It potentiates the antithrombin effect and binds to aPL and render them ineffective. LMWH binds with these antibodies and don't let them bind to trophoblast which result in better invasion and differentiation of the cytotrophoblasts in conditions other than antiphospholipid syndrome, LMWH reduce the proinflammatory and anti-angiogenic effect of the thrombophilia (Table 2).

Table 2: Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Articles addressing the topic	Articles not meeting keywords
Observational studies	Metanalysis
Articles published in 2000-2021	Articles published before 2000
Full-text articles	No available digital copy of articles
English language	Abstract only publications
	Language other than English

Statistically significant results proved in various studies of using heparin and low-dose aspirin. Combination of heparin and LDA given in APS results in more live births than in control group. Similarly, another study concludes that LDA alone or in combination with prednisolone in patients with anti-cardiolipin syndrome results in better pregnancy outcomes and more chances of survival of fetus. Another question raised here is which form of heparin is better. LDA and LWMH have better outcomes and compliances. LMWH can be used in a single subcutaneous dose as compares to unfractionated heparin. Treating RPL by LMWH is a common practice. Several studies prove the efficiency of treating RPL by LMWH without investigating and making the diagnosis of thrombophilia as compared to placebo group. The results were statistically significant. But these studies are limited and data currently available is very limited. Few double blind and case control studies conducted in this matter and results were not the same as described earlier. The studies included in our research have many limitations. Some have allocation bias. So, it was concluded that proper investigation should be carried out to diagnose the cause of RPL and LDA and LMWH should be used in only thrombophilia not the other causes of RPL.

Conclusion

Use of enoxaparin and low dose aspirin early in pregnancy with history of recurrent pregnancy loss due to acquired thrombophilia have statically significant improvement in live pregnancy. Same

cannot be said about unknown cause of the recurrent pregnancy loss. The proper investigation of the cause of RPL should be carried out. And in case of acquired thrombophilia early treatment will benefit the patients. Studying has limitations. A proper meta-analysis is required to prove these results by forest plot.

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