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Influence of anticoagulant medications on gestational thrombophilia: a systematic review

Influência de medicamentos anticoagulantes na trombofilia gestacional: uma revisão sistemática

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ABSTRACT
Objective: To address the effectiveness of anticoagulants as a prophylactic treatment in cases of gestational thrombophilia, exploring their relationship in the control of thromboembolic complications, especially in recurrent pregnancy loss. Method: The PRISMA method was used, which was adapted in 5 steps, with a systematic literature search in electronic databases for articles between 2018 and 2022. Results: 11 articles were aligned with the research question: "Is the use of anticoagulants effective in pregnant women with thrombophilia?" Given this, the articles point out that thrombophilic pregnant women are at greater risk of recurrent miscarriages, hence the use of anticoagulants has become an option for prevention. Conclusion: The articles disagree on points addressed in this review, therefore, future research should refine clinical possibilities, to compose more concise and personalized protocols, providing even safer and more effective obstetric care, despite many positive outcomes with the use of medications.

Keywords: Anticoagulants; Pregnancy; Thrombophilia.

RESUMO
Objetivo: Abordar a eficácia de anticoagulantes como um tratamento profilático em casos de trombofilia gestacional, explorando sua relação no controle de complicações tromboembólicas principalmente na perda gestacional recorrente. Método: Utilizado o método PRISMA, adaptado em 5 etapas, com busca sistemática na literatura de bases de dados eletrônicas, incluindo artigos entre 2018-2022. Resultados: Incluídos 11 artigos alinhados à pergunta desta pesquisa: *"O uso de anticoagulantes é eficaz em gestantes com trombofilia?*". Diante disso, os artigos apontam que gestantes trombofílicas apresentam mais riscos de perdas gestacionais recorrentes, portanto o uso de anticoagulantes se tornou uma opção para a prevenção. Conclusão: Os artigos discordam em pontos abordados nesta revisão, logo, pesquisas futuras devem aprimorar as possibilidades clínicas, de modo a compor protocolos mais concisos e personalizados, proporcionando um cuidado obstétrico ainda mais seguro e eficaz, apesar de muitos resultados positivos com o uso dos medicamentos.

Palavras-chave: Anticoagulantes; Gravidez; Trombofilia.

INTRODUCTION

Pregnancy is a prothrombotic condition caused by the high level of estrogen and, as a result, the consequences of gestational thrombophilia are varied and can lead to early or late fetal loss. Given this panorama, there is a need to analyze the available studies on the possible prophylactic measures, especially anticoagulants, to deeply understand the recurrence of cases of pregnancy losses related to the condition.

Pre-eclampsia, placental abruption, intrauterine growth restriction (IUGR), recurrent pregnancy loss (RPL), and venous thromboembolism (VTE) are the most serious complications in pregnancies with disorders associated with coagulation, such as thrombophilia[1].

The disease is linked to a predisposition to develop thrombosis, which encompasses multiple pathophysiological factors and can be classified as hereditary or acquired. Hereditary thrombophilia is related to genetic factors, such as deficiency of protein C, antithrombin III, and protein S, which are closely associated with blood clotting. It is also possible to relate variations that affect coagulation, such as the mutation in factor V Leiden and the prothrombin gene (G20210A). Acquired thrombophilia, on the other hand, is associated with external and immune factors that influence blood clotting, such as some metabolic syndromes, prolonged immobilization, hormone replacement, and immune disorders; the most common is antiphospholipid syndrome (APS), which is related to lupus antibodies and anticardiolipin antibodies.

Therefore, pregnancy loss usually occurs in the first months of pregnancy, as the clots formed by thrombophilia impair the blood flow to the placenta. Thus, microthrombi impede blood flow to the fetus, which no longer receives the necessary amount of nutrients, which harms fetal development and, in some cases, leads to pregnancy loss.

Regarding the occurrence of cases, there are reports of 0.5 to three cases of VTE for every 1,000 pregnancies[2]. Thus, the association of thrombophilia with the hypercoagulable state during pregnancy leads to gestational thrombosis, substantially increasing maternal and fetal morbidity and mortality. As these conditions are subject to research aimed at prevention, the importance of studies in the area is demonstrated at an international level.

Therefore, the prevention and treatment of thrombosis in pregnancy are extremely relevant, highlighting that important data related to the use of anticoagulants can prevent pregnancy loss due to their antithrombotic action. An example is low molecular weight heparins (LMWH), such as enoxaparin, which are generally pharmacological options used for thrombosis prophylaxis, as they do not cross the uteroplacental barrier, presenting a low risk of fetal exposure, in addition to having longer bioavailability, long half-life, and more predictable response, and can be administered once or twice a day. Currently, International Guidelines support the use of LMWH as prophylaxis after appropriate assessment of risk factors.

Although there is no concrete evidence to suggest the use of LMWH in women with thrombophilia, women with two or more successive pregnancy losses are prescribed heparin due to the lack of studies and effective treatments for recurrent pregnancy losses. Due to these immense controversies, detailed research is necessary to relate the effectiveness of anticoagulants during pregnancy, in women with thrombophilia, to prevent recurrent miscarriages. Prevention and health promotion in gestational thrombophilia are essential to reduce maternal and fetal risks, emphasizing the importance of strict medical monitoring and adoption of appropriate preventive measures during pregnancy, such as the prophylactic use of anticoagulants.

This context evidences the importance of the present study, which aims to answer the following question: "What is the influence of the use of anticoagulants on gestational thrombophilia?". From this, we sought to evaluate the effectiveness of prophylaxis with anticoagulants in women diagnosed with thrombophilia and who have a history of recurrent pregnancy losses.

METHODOLOGY

This systematic review was carried out in 5 steps, following the methodological rigor that ensures the reproducibility of the information found. The steps are listed in Figure 1, following the guidelines of PRISMA[3]. Therefore, articles published by the journal "Saúde em Debate" were not included due to the application of the Boolean search string, so a consistent review method was possible.

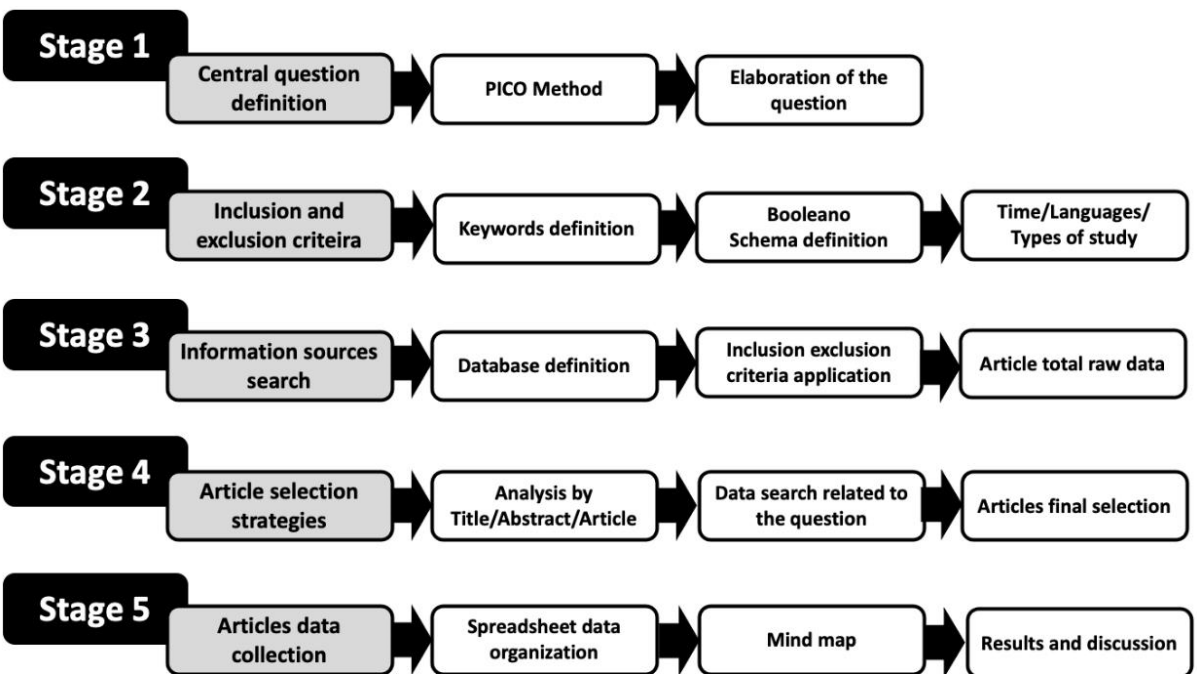

Figure 1. Research method used and its 5 investigation steps based on PRISMA.
Source: adapted from Page et al (2022)

The steps of this research are described below:

Step I included the definition of the research question, obtained via the PICO[4] method.

Once the research question was defined, the keywords to compose the research were then defined.

Step II consisted of defining a Boolean search string to solve the research problem, as well as article eligibility criteria, such as time, and availability in Portuguese and English, and having been developed based on the question obtained by the PICO method. Furthermore, they should present a direct relationship with the object of study and its guiding question, have no conflicts of interest, and have been published for a maximum of 5 years.

Step III corresponded to the activity of defining the search sites, using the PubMed and Scielo databases.

Step IV was the selection of articles found on the databases, in which the following analysis was carried out: initially by the title and then the abstract, and thus those of interest were separated for analysis to answer the research problem.

Step V was the analysis of the results using spreadsheets containing information from the PICO question and the variables chosen for the study, aiming to ultimately generate the results and discussions of the article.

RESULTS

Considering the terms required in the research question[4], the items were established according to Box 1.

Box 1. Preparation of the research question.

	P	I	C	O
Acronym Definition	Population	Intervention [or exposure]	Comparison [relativize]	Outcome
Question Components	Pregnant women with thrombophilia	Use of anticoagulants as prophylaxis	Use and non-use of prophylaxis in the treatment of thrombophilia	Anticoagulants will or will not be effective in the consequences of thrombophilia

Source: Prepared by the authors (2023)

The result of the question was expressed as follows: *Is the use of anticoagulants effective in pregnant women with thrombophilia?*

Thus, the Boolean search string was defined to search for articles linked to the question, using "*thrombophilia AND pregnant women OR abortion*" in the databases cited in the method. As a second complementary method, for theoretical complementation, other articles were used outside the main Boolean search string.

A total of 954 articles were retrieved by the Boolean search strategy, of which 5 met the research selection criteria to find propositions that answered the research question of the work. In addition to a second Boolean strategy, due to a lack of information, where a total of 3 articles were used to complement the research, and 3 works were added outside the Boolean search string for theoretical complementation; as illustrated in Figure 2.

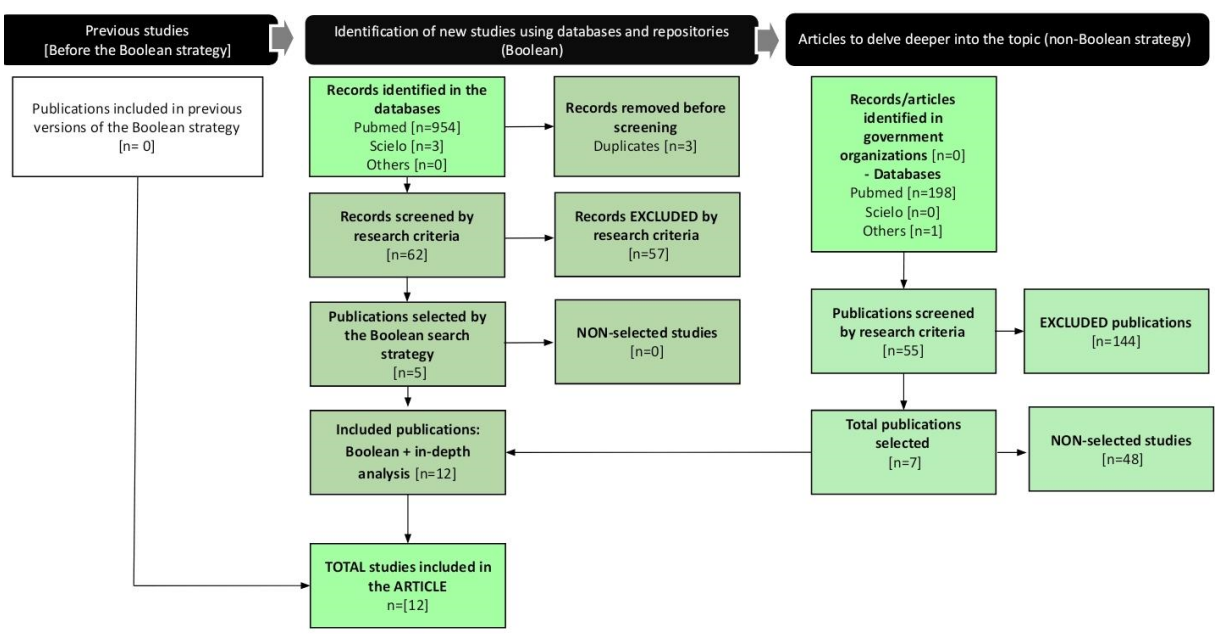

Figure 2. Results of article screening.
Source: Prepared by the authors (2023)

DISCUSSION

INFLUENCE OF MEDICATIONS ON THROMBOPHILIA

Thrombophilia is a genetic or acquired disease that affects approximately 0.16 to 0.21% of the general population[5], and is characterized as a defect in coagulation due to the reduced activity of protein S, protein C, antithrombin III, factor V Leiden, or mutation in the G20210A gene, and may also be related to antiphospholipid syndrome (APS). During pregnancy, women with the disease have a greater chance of developing venous thromboembolism (VTE) and recurrent pregnancy losses (RPL). By gathering information about the use of low molecular weight heparin (LMWH), we notice a reduction in recurrent pregnancy loss, as little is observed in studies on this positive result[6].

The studies reveal that the indication of antecedents can be the starting point for the thrombophilia test and the availability of anticoagulants for treatment in these pregnant women, as the disease is still frequently neglected by health professionals. Current guidelines recommend testing patients who have had previous cases of VTE, RPL, or cases of high risk of thrombophilia in the first-degree family, as the procoagulant state can increase 6 to 7 times more in pregnant women, because the body is preparing for blood loss at the time of birth, mainly due to the increase in the hormone estrogen[7].

Therefore, the disease, generally genetic, in addition to acquired conditions of this population causes an increased risk of recurrent pregnancy loss, with the possibility of more recurrent thrombotic events. Hereditary thrombophilia is associated with spontaneous microthrombotic events in the blood vessels of the placenta[7]. With this, the general overview of the state these women are in and the treatment using anticoagulants can be a key point in reducing these incidents[7].

ANTICOAGULANTS AND THEIR USE IN TREATMENT

Considering the various factors that generate hereditary thrombophilia, the increased risk of recurrent pregnancy loss associated with protein S deficiency was one of the first truly integrated methods to reach a conclusion, despite the limited number of studies[8]. As a result, research was intensified to understand the best time for the detection test and when to begin treatment with anticoagulants to avoid these acquired conditions[8].

Therefore, the use of anticoagulants has not been effectively proven but represents one of the treatments that has shown the most results in hereditary thrombophilia[8]. Today, it is believed that the authors, despite disagreements due to the lack of effective randomized studies, agree that the use of low molecular weight heparin (LMWH) combined with acetylsalicylic acid (ASA) tends to have much more effective results than the separate use of each one[9].

Thus, three types of doses were established: prophylactic, intermediate, and therapeutic, described according to American and European guidelines.

According to Meng Yin and Xiaosong Qin[9], there is a study in which 822 patients with acute venous thromboembolism after treatment with LMWH had a lower risk of bleeding or recurrent pregnancy losses, highlighting that the rates were much better in pregnant women on LMWH combined with ASA. Heparin alone can also induce thrombocytopenia, a condition characterized by low platelet levels in the blood, caused by an association of platelets mediated by antibodies, which may increase the risk of thrombosis. When LMWH is used with low doses of ASA, platelets are reduced, causing less risk, as well as inhibiting thrombin.

However, women with heart valves cannot use the medication; in addition, ASA can cause gastrointestinal problems, liver damage, and kidney bleeding[9]. Therefore, there are limitations and the use of anticoagulants can be effective, but appropriate randomized studies must highlight the importance of protecting these women and fetuses in these situations.

Table 2 lists the main articles used in this systematic review, which were used to encourage discussion, being divided into: author/year, objective, sample size, study design, intervention, and instrument. The characteristics relating to the

subject researched are observed in this table. Thus, it is possible to analyze common points and divergences in the prophylactic use of anticoagulants in thrombophilia and which methods each author used in their research.

Box 2. Main articles selected for the systematic review that support the discussion.

Author/ year	Objective of the study	Sample size	Study design	Intervention/ instrument	Outcome/ Conclusion
Nahas et al., 2018	Check the influence of using LMWH, like enoxaparin and aspirin, on treatment.	490 thrombophilic pregnant women, of whom 488 matched the study profile.	Retrospective clinical trial, with control group.	Between 2004 and 2010 in northern Israel.	With the use of enoxaparin, the rate of recurrent pregnancy loss decreased.
Garmi et al.,2018	Examine the occurrence of placental vascular lesions in thrombophilic women treated with LMWH with a dose adjusted according to anti-factor Xa, compared with a fixed dose.	144 women were in the trial, but only 88 placentas were analyzed.	Cross-sectional randomized controlled clinical trial.	Between October 2009 and January 2015 at a university teaching hospital and three specialized community clinics.	The adjusted dose of enoxaparin according to anti-factor Xa levels compared with a fixed dose did not affect placental vascular lesions in thrombophilic women.
Trasca et al., 2019	Relate treatment with anticoagulants to hereditary thrombophilia in pregnant women.	The search was carried out on PubMed, between April 1981 and November 2018.	Cross-sectional literature review.	Database.	The use of any anticoagulant depends on thrombotic factors, degree of risk, and family history.
Liu et al., 2021	Determine the factors that generate an increased risk of recurrent pregnancy loss associated with hereditary thrombophilia.	The search was carried out on PubMed, Web of Science, and EMBASE.	Cross-sectional systematic review.	Database.	The use of anticoagulants is currently not beneficial, due to the inconsistency of studies.
Meng Yin and Xiaosong Qin, 2023	Analyze the influence of using LMWH combined with low doses of aspirin on pregnant women with thrombophilia.	487 relevant articles were retrieved and only 14 were effectively used.	Meta-analysis and cross-sectional systematic review.	Databases such as PubMed, Web of Science, Embase and China National Knowledge Infrastructure and Wanfang	Low molecular weight heparin combined with aspirin reduces VTE and recurrent pregnancy losses.

Source: Prepared by the authors (2023)

EFFECTIVENESS AND ITS ADVANTAGES AND DISADVANTAGES

When analyzing the problem affecting pregnant women around the world - thrombophilia - acquired conditions are very present. For example, RPL impacts pregnant women to a high degree, given that this disease involves the interaction between genetic and environmental factors. Despite all the studies, more than 50% of the factors remain unexplained[8], since the authors are unable to associate concrete evidence that relates thrombophilia and RPL because the studies are

inconclusive and do not present a separation of possible influencing factors, such as the ethnicity and geographic region of these patients. Although research shows that the geographic region can directly influence thrombophilia and recurrent pregnancy loss[8], there is still a high heterogeneity of studies related to the subject, which becomes an obstacle, and the majority do not consider criteria such as ethnicity and age.

According to the meta-analysis carried out by Meng Yin and Xiaosong Qin[9], 6 articles reported notably prolonged thrombin time in patients who ingested LMWH with low doses of ASA, than only aspirin or LMWH separately[9], correcting the function of coagulation in pregnant women and improving adverse effects. However, there is controversy, as ASA can cause gastrointestinal reactions, liver damage, and kidney bleeding, which can lead to major postpartum hemorrhages, as the guidelines do not provide specific guidance on the choice of anticoagulants in the treatment of patients with venous thromboembolism resulting from hereditary or acquired thrombophilia.

A retrospective cohort study carried out between 2004 and 2010 in northern Israel[10] examined 490 thrombophilic pregnant women; the parameters analyzed were the use of enoxaparin - a type of LMWH - and aspirin, or the two in combination. Of these women, 488 had a thrombophilia profile, after being tested for PCR, factor V Leiden, and mutation in the G20210A gene (as the test was not free of charge, not all pregnant women were able to take it). As a result, 431 took the anticoagulant, 320 had thrombophilia, 301 were then treated with enoxaparin alone, 17 with enoxaparin and ASA, and 2 with ASA alone.

Of pregnant women with thrombophilia treated with enoxaparin, a rate of 72.9% of live births was obtained[9]. In conclusion, the study[10] addressed that the use of enoxaparin at 40 mg once a day is a possible measure of prophylaxis for women with recurrent pregnancy losses who may or may not have thrombophilia. Importantly, the study does not have a control group, and involved women with and without thrombophilia, it has limitations because the participants did not carry out all the exams, for financial and geographical reasons. Another limitation found is the lack of specification of the combined dosages of LMWH + ASA, or ASA alone, used in the study.

Furthermore, in Israel, a study[11] monitored the anti-factor Xa present in enoxaparin, which acts directly on Factor X in the coagulation cascade, and reported no significant differences in placental lesions between pregnant women treated with fixed doses of 40 mg of enoxaparin and those treated with the same medication, but with doses adjusted according to anti-factor Xa levels. Fetal placental lesions included the presence of thrombi in subchorionic blood vessels, thrombi in stem villi blood vessels, and thrombi in large fetal vessels. However, based on previous clinical trials, subsequent pregnancies are believed to show some difference, thus demonstrating a potential starting point for anticoagulant treatment. A comparison of the use of medication and its consequences on the risks of placenta-mediated pregnancy complications (PMPCs) is listed in Box 3, below.

Box 3. Comparison of medication use and its consequences on PMPCs.

Authors	Used medications	Live births	Authors' remarks
Jiang et al., 2021	LMWH	86% improvement in the systematic review carried out.	Despite the studies, variations in dosages were noted for patients according to weight and types of LMWH during pregnancy.
Allison A Eubanks, Shad H Deering, Lisa M Thiel, 2018	LMWH	Use of anticoagulants in prepartum and post-partum, as in the first 6 weeks after delivery, there is a greater risk of thrombosis.	LMWH has a long half-life when considering its concentration, therefore, it requires greater planning during treatment
Jacobson et al., 2019	LMWH (enoxaparin monotherapy)	Reduction in the chances of RPL by 58% compared to the control group (significant heterogeneity)	The use of enoxaparin is relatively safe with few adverse effects, however, its effectiveness requires further studies, considering social and geographic factors.
	LMWH + ASA	Reduction in the chances of RPL by 42% compared to the isolated use of ASA.	Observational study with women with a history of thromboembolic obstetric events, cases of malformation were reported in patients who received enoxaparin + ASA in the first trimester or ASA alone. No cases were observed with the use of enoxaparin + ASA in the second trimester.

Source: Prepared by the authors (2023)

In conclusion, low molecular weight heparin (LMWH) has a shorter half-life and lower peak when considering the concentration time, which is why in pregnant women the dosage tends to be higher, and the use of LMWH is recommended as it causes less bruising, fewer skin reactions, fewer allergic reactions and less risk of osteopenia and thrombocytopenia induced by unfractionated heparin (UFH)[12]. As there is still a high risk of thrombosis in the first 6 weeks postpartum, prophylactic treatment must continue, as all pregnant women, from uncomplicated to high risk, and those with thrombophilia that have greater chances of VTE must be treated with anticoagulants in the prepartum and post-partum period[12].

In addition, the vascular damage that occurs during births, mainly in cesarean sections and operative deliveries, is added to other factors that can increase the risk, such as obesity, hypertension, and smoking, emphasizing the importance of ethnic and geographic identification of this patient.

RISKS AND GAPS MUST BE STUDIED

Currently, in the medical-scientific context, the options for prophylactic measures for thrombophilic pregnant women are scarce due to the high maternal-fetal risk, which limits research. Therefore, the use of an anticoagulant that has the advantage of not crossing the placenta and presenting a low fetal risk provided researchers with a great treatment opportunity.

According to the discussion reported, the use of LMWH is the best option according to the authors to reduce recurrent pregnancy loss and VTE[13]. Therefore, there are variants of LMWH, such as enoxaparin[13], which have been mentioned, and a possible association with ASA to improve the effectiveness of these treatments. It is worth highlighting that the drug's side effects were small compared to the risk of recurrent

pregnancy loss, since the prophylactic use of LMWH significantly increases the number of live births in women who have recurrent pregnancy losses, an important effect for these women who wish a safe birth, both for the mother and the fetus, as enoxaparin, according to the study, proved safe in terms of adverse effects[13].

The most likely hypothesis is that the use of LMWH alone or combined with ASA, in a certain dosage throughout the prepartum and postpartum period, prevents recurrent pregnancy loss and also the course of venous thromboembolism. The ideal dosage cannot yet be specified, as further studies are needed that consider external and internal factors related to blood clotting such as women with heart valves, immunity, weight (kg), and social issues (diet, ethnicity, and physical activity), since care in the prenatal period with its nutritional requirements and dietary care, aimed at health promotion and disease prevention in these women[14], generates different consequences throughout pregnancy.

Therefore, delving deeper into this hypothesis is of great importance, as it will be possible to analyze pregnant women according to their various particularities, such as ethnicity, geographic region, and genetic mutations intrinsic to each patient. The limitations of the study make it impossible to legitimately prove the efficacy and safety of treatment in thrombophilic women with anticoagulants. Nevertheless, current guidelines indicate that the only current measure to prevent these fetal losses is the use of LMWH alone or combined with ASA.

THE USE OF ANTICOAGULANTS IS EFFECTIVE, BUT THERE ARE CONTROVERSIES

In search of an answer to the research question “Is the use of anticoagulants effective in pregnant women with thrombophilia?”, it is concluded that yes, the use of anticoagulants is effective, however, there are limitations, exposed throughout the review. One of them is the low number of randomized clinical trials, and the inconclusive result of several systematic reviews, mainly due to the lack of data, justified by the ethical limitations of the research, as it covers pregnant women as a population.

However, despite the fear surrounding research with pregnant women, there are already some dosage parameters for anticoagulants - mainly LMWH - such as those established by American and European guidelines[7], which represents an alternative treatment for women who suffer from recurrent miscarriages and have difficulty getting pregnant due to thrombophilia and its aggravating factors.

ASPECTS RELATED TO HEALTH PROMOTION AND PREVENTION

The importance of the preventive use of anticoagulants concerning maternal-fetal complications is well known. This systematic review highlights the importance of anticoagulants for health promotion and disease prevention in pregnant women with a history of recurrent pregnancy losses or at risk of thrombosis. Studies related to thrombophilia, described by the predisposition to develop thrombosis, significantly increase the risks during pregnancy. Therefore, early diagnosis of thrombophilia is essential to prevent severe complications. Pre-conception testing or testing at the beginning of pregnancy allows the identification of women at risk, enabling immediate interventions[6]. Therefore, intensive prenatal care is a key element in preventing complications associated with gestational thrombophilia. Because of this, personalized dosing of low molecular weight heparin (LMWH) and constant monitoring are essential to ensure effective and safe treatment[7].

Furthermore, educating pregnant women about warning signs of thromboembolic complications is also extremely important so that through education and awareness, effective management of gestational thrombophilia can occur. Informing these women about the risks, symptoms and the importance of treatment can improve adherence to preventive interventions, thus promoting better health promotion and disease prevention for these patients and their unborn children.

PRACTICAL IMPLICATIONS OF THE STUDY

The practical and relevant implications of this study are of great importance for professionals who deal with pregnant women at risk of developing thrombophilia. The central

purpose of this article is to provide an updated knowledge base for physicians and other health professionals, enabling them to scientifically base their decisions regarding prophylaxis and treatment with anticoagulants in thrombophilic pregnant women, aiming to improve clinical practices, making them safer and more effective.

Therefore, according to the data collected by the study, LMWH presents good treatment results[12]. Regarding its use, both LMWH and LMWH combined with ASA can be prescribed after investigating the disease and taking into account the criteria that prevent its use in some women, such as those with heart valves. This treatment produces few side effects compared to recurrent pregnancy loss, and it will be possible to increase the chance of live births promoting an improvement in health promotion and disease prevention for the population.

This systematic review can serve as a basis for developing and updating clinical guidelines on the management of thrombophilia in pregnant women. Since scientifically well-founded protocols are essential to improve the quality of gestational care.

CONCLUSION

Based on the studies found in the current scientific literature, the main findings point to a promising use of anticoagulants as prophylaxis of obstetric complications in thrombophilic pregnant women. Preventive use in pregnant women at risk of thrombosis or with a history of recurrent miscarriages is crucial for promoting maternal-fetal health. LMWH and ASA stand out as an effective treatment in reducing thromboembolic events and spontaneous abortions[9]. Early diagnosis and intensive prenatal care, combined with education for pregnant women, are essential for the safe and effective management of thrombophilia during pregnancy. Therefore, with the use of anticoagulants, research is essential to improve clinical protocols and determine the long-term effectiveness of this intervention.

Healthcare professionals must identify the essential requirements for testing for thrombophilia considering the patient's history, genetic factors, and quality of life during pregnancy. Therefore, multidisciplinary collaboration between health professionals and qualified listening to the patient is essential to ensure comprehensive and integrated monitoring, safeguarding maternal-fetal health even if the results of the treatment are still uncertain.

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