

Indiscriminate use of antithrombotics and their side effects in prophylactic treatment in postpartum women

RESUMO | Objetivo: Abordar os efeitos adversos relacionados a utilização indiscriminada de antitrombóticos no tratamento profilático em puérperas. Método: Revisão integrativa da literatura realizada entre fevereiro e abril de 2022 nas bases: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scientific Electronic Library Online (SciELO), SciVerse Scopus (SCOPUS) e Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed). Foram selecionados para essa revisão 10 artigos, publicadas entre 2012 e abril de 2022 (10 anos). Resultados: Os resultados evidenciam que a minimização de eventos tromboembólicos no puerpério é indispensável o acompanhamento desde a gestação, dessa forma se identificará precocemente os riscos e assim será possível tomar as devidas medidas preventivas eficazes na redução das consequências manifestadas pela doença. Conclusão: Evidencia-se que não há um procedimento específico com alto nível de evidência científica quando se trata de envolvimento do paciente sem risco iminente, em razão à escassez de estudos disponíveis acerca da temática.

Descritores: Período pós-parto; Terapêutica; Trombose.

ABSTRACT | Objective: To address the adverse effects related to the indiscriminate use of antithrombotics in the prophylactic treatment of postpartum women. Method: Integrative literature review carried out between February and April 2022 in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), SciVerse Scopus (SCOPUS) and Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed). Ten articles were selected for this review, published between 2012 and April 2022 (10 years). Results: The results show that the minimization of thromboembolic events in the puerperium is essential to follow up since pregnancy, in this way the risks will be identified early and thus it will be possible to take the appropriate preventive measures effective in reducing the consequences manifested by the disease. Conclusion: It is evident that there is no specific procedure with a high level of scientific evidence when it comes to patient involvement without imminent risk, due to the scarcity of available studies on the subject.

Keywords: Postpartum Period; Therapeutics; Thrombosis.

RESUMEN | Objetivo: Abordar los efectos adversos relacionados con el uso indiscriminado de antitrombóticos en el tratamiento profilático de la puérpera. Método: Revisión integrativa de la literatura realizada entre febrero y abril de 2022 en las siguientes bases de datos: Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), Scientific Electronic Library Online (SciELO), SciVerse Scopus (SCOPUS) y Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed). Se seleccionaron diez artículos para esta revisión, publicados entre 2012 y abril de 2022 (10 años). Resultados: Los resultados muestran que la minimización de los eventos tromboembólicos en el puerperio es fundamental para el seguimiento desde el embarazo, de esta forma se identificarán tempranamente los riesgos y así se podrán tomar las medidas preventivas oportunas efectivas en la reducción de las consecuencias manifestadas por la enfermedad. Conclusión: Se evidencia que no existe un procedimiento específico con alto nivel de evidencia científica cuando se trata de involucramiento del paciente sin riesgo inminente, debido a la escasez de estudios disponibles sobre el tema.

Palabras claves: Período posparto; Terapia; Trombosis.

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INTRODUÇÃO

Deep Vein Thrombosis (DVT) is characterized by the formation of thrombi in the deep venous blood vessels, being more common in the lower limbs. ⁽¹⁾ Its main complication is Pulmonary Embolism (PE), the main cause of preventable death in hospital beds and an important factor of morbidity and mortality. In turn, regarding the clinical picture, only 50% of the cases are related to the disease, which is why the isolated symptomatology does not confirm or rule out the diagnosis of DVT, in which the most common symptoms are: pain, erythema, edema, temperature increase, muscle swelling, cyanosis and pain on palpation. ⁽²⁾

Thrombus development is dependent on changes that were described in the 19th century by Virchow, such as venous stasis, hypercoagulability, and vascular or endothelial wall injury. ⁽³⁾ It is also noteworthy that DVT in the lower limbs is divided according to its location: proximal, when it affects the iliac, popliteal and/or femoral veins; distal when it affects the veins located below the popliteal. ⁽¹⁾

The incidence of this pathology, according to some studies, is demonstrated in the general population as 5 cases per 10,000 individuals annually, and in Brazil around 0.6 per 1000 inhabitants

annually. Proximal type DVT evolves to pulmonary embolism in 46% of cases, and if left untreated, it can progress to death in 4% of cases. In Europe, rates reach 600,000 cases of deep vein thrombosis and pulmonary embolism annually. In the United States of America, 300,000 cases of thrombosis are registered per year, with DVT being the third most common cause among cardiovascular pathologies. In Brazil, studies show 122,096 hospitalizations for thrombosis, recorded in 2014, and a decrease in this rate to 113,817 in 2015. ⁽⁴⁾

During pregnancy, a woman may present the signs that characterize Virchow's Triad, which corresponds to three categories of factors that contribute to DVT, namely, venous stasis, due to compression of the veins by the gravid uterus, hypercoagulability, due to changes in factors such as fibrinogen, and endothelial injury, present in implantation, in endovascular remodeling of uterospiral arteries and in delivery. ⁽⁵⁾ Thus, during pregnancy, the risk of developing thromboembolic disease, especially in the second trimester, is greatly increased due to these physiological events of an adaptive nature that aim to maintain the pregnancy and the viability of the fetus. ⁽⁶⁾

In view of this, such changes presumably represent an evolutionary response, with the aim of reducing bleeding complications, especially in the prepartum and postpartum period. Endothelial damage is a consequence of vascular damage during labor and delivery (vaginal or cesarean). ⁽⁷⁾ Thus, there are protocols that support and guide the initiation of antithrombotics, drugs that act to prevent the formation of blood clots in the postpartum period in a prophylactic way. However, there is no gold standard, with a diversity of protocols that differ in many aspects. Therefore, the decision for or against pharmacological thromboprophylaxis must be made individually, considering the risk of VTE and also the side and adverse effects of indiscriminately using the medication for all pregnant

women. ⁽⁸⁾

Given the above, the present aims to address the adverse effects related to the indiscriminate use of antithrombotics in the prophylactic treatment of postpartum women.

METHOD

This is an Integrative Literature Review (ILR). The elaboration of a study of this nature consists of the fulfillment of the steps: identification of the problem, literature search, evaluation, analysis and interpretation of data and presentation of the integrative review. ⁽⁹⁾

The guiding question was elaborated with the help of the PICO strategy: P= puerperal women; I= Indiscriminate use of antithrombotics; Co= Prophylactic treatment. Therefore, the following guiding question was arrived at: What are the adverse effects of the indiscriminate use of antithrombotics in prophylactic treatment in postpartum women?

The search and analysis of the data collected in the studies were carried out between February and April 2022, through the following electronic databases: Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), SciVerse Scopus (SCOPUS) and Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed). The inclusion criteria of the defined articles were: articles published in Portuguese, English and Spanish, available in full, published between 2012 and April 2022 (last 10 years).

The uni-terms present in the Health Sciences Descriptors (DeCS) were used: Período pós-parto; Profilaxia; Trombose, and articles indexed by descriptors registered in the Medical Subject Headings (MeSH): Postpartum Period, Therapeutics e Thrombosis, combined with each other through the Boolean operators "AND" and "OR", in the researched bases. Duplicate and literature review articles (secondary data source) were excluded.

Through this search parameter, 193

studies were identified. After applying the filters based on the inclusion criteria, 81 publications were obtained. After reading the titles and abstracts, 53 were excluded for not relating to the topic of this review and 5 for not providing the full text. After this step, 23 studies were selected for full reading, of which 13 articles were excluded, which, when read in full, fit the search exclusion criteria. Thus, resulting in 10 studies selected for the composition of that study. Figure 1 details the flowchart of the searches performed.

RESULTS

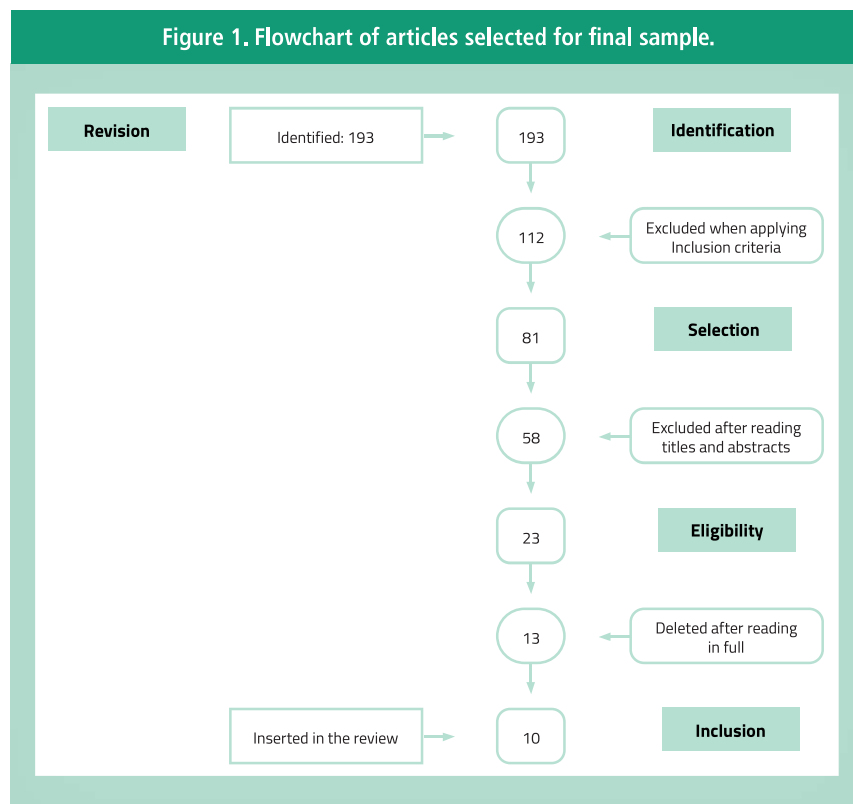
From the adaptation of an extraction instrument⁽¹⁰⁾, a synthesis of the included articles was made. Data extraction captured the following information: title; year of publication; authors; published journal and main findings, described in table 1.

DISCUSSION

The puerperal period is characterized by the gradual and physiological retreat of the maternal body, requiring care and information. Thus, the importance of early diagnosis and adequate treatment of VTE, aims to prevent complications such as pulmonary embolism, with high mortality in the puerperal period, and prophylactic and preventive treatment must be carried out properly.⁽¹¹⁾

The analyzed studies show that there is no recommendation considered gold standard about the prophylactic treatment for thrombosis in patients during the pregnancy-puerperal period. In view of this statement, the verification of the adverse effects of the indiscriminate use of antithrombotic drugs in the prophylactic treatment of puerperal women is a complex activity, as there are not enough clinical trials carried out with pregnant women in which these adversities are evaluated.⁽¹¹⁾

For the purposes of optimal thromboprophylaxis, a peculiar analysis of the risk for VTE is advised, however, to carry out



Source: Elaborated by the authors, (2022).

the evaluation, there are no ratified devices that help the sedimentation of risks and indicate the excellent time to start anticoagulation, in addition to observing the general effects of the drugs.⁽¹²⁾ Although there are difficulties, some recommendations could be extracted from the studies included in that work.

In one study, a possible hemorrhage linked to the use of LMWH and four cases of urticarial reactions at the drug administration sites are analyzed. However, it is noteworthy that in this study, despite the literature, no cases of osteoporosis and thrombocytopenia were diagnosed as an adverse response to the application of heparin. In addition, it is also pointed out that other harmful consequences of the indiscriminate use of antithrombotics in the prophylaxis of women in the puerperal period: of 810, 3% were examined and cared for according to a German scale and who had considerable bleeding

associated with the careless use of antithrombotics.⁽¹³⁾

Skeith L.⁽¹⁴⁾ discussed in his study that for patients using antithrombotics, recommendations were indicated regarding the prevention of thromboembolic events during pregnancy and in the puerperium, as well as: use of compression stockings, avoid long periods of rest, make lymphatic drainage to reduce the swelling of the legs, go for walks and physical exercises that stimulate the circulation. In summary, it is evident that there is no clinical benefit of prophylaxis when the risk of VTE in the prenatal or postpartum period is less than 1%, but when it is greater than 3%. From another perspective, it is concluded that these data are only consistent with the front line and that the decision measure encompasses other aspects in addition to the patient's family background and preferences.

Due to the higher risk of VTE in wo-

Table 1. Distribution of articles according to title, year of publication, authors, published journal and main findings. Coroaá, Maranhão, Brazil – 2022.

| TITLE | YEAR OF PUBLICATION | AUTHORS | JOURNAL | MAIN FINDINGS |
|---|---------------------|--|---|--|
| Prophylaxis and Therapy of Venous Thrombotic Events (VTE) in Pregnancy and the Postpartum Period ⁽¹¹⁾ | 2020 | Sucker C. | Geburtshilfe Frauenheilkd. | Low molecular weight heparins (LMWH) are the standard medication for the prophylaxis and treatment of thrombotic events in pregnancy and postpartum. Medical thrombosis prophylaxis initiated during pregnancy is usually continued for about six weeks postpartum because of the risk of thrombosis that peaks during the postpartum period. |
| Renal vein thrombosis in the puerperium: case report. (Trombose na veia renal no puerpério: relato de caso.) ⁽¹²⁾ | 2015 | Hillman BR, Steffens SM, Trapani Junior A. | Rev. Bras. Ginecol. Obstet. | Patients with RVT are more likely to have hereditary thrombophilia and should be treated with an oral anticoagulant for three to six months and have all screening tests done for hereditary thrombophilia |
| Personalized thromboprophylaxis using a risk score for the management of pregnancies with high risk of thrombosis: a prospective clinical study ⁽¹³⁾ | 2017 | Dargaud Y, et al. | J Thromb Haemost. | In the antepartum period, prophylaxis with low molecular weight heparin (LMWH) was prescribed for 64.5% of patients at high risk of VTE. Among them, 34.4% were treated only in the third trimester and 30.1% were treated throughout pregnancy. During the postpartum period, all patients received LMWH for at least 6 weeks. |
| Preventing venous thromboembolism during pregnancy and postpartum: crossing the threshold ⁽¹⁴⁾ | 2017 | Skeith L. | Hematology Am Soc Hematol Educ Program. | The article explores the concept of risk threshold from a clinical and patient perspective in providing guidance for the use of pre- and postpartum LMWH prophylaxis in women with known thrombophilia or previous VTE. Advising for management the use of LMWH prophylaxis around labor and delivery is also reviewed. |
| Society for Maternal-Fetal Medicine Consult Series #51: Thromboembolism prophylaxis for cesarean delivery ⁽¹⁵⁾ | 2020 | Pacheco L, Saade G, Metz TD. | Am J Obstet Gynecol. | It is suggested that women with a previous personal history of deep vein thrombosis or pulmonary embolism undergoing cesarean section should receive mechanical prophylaxis (starting preoperatively and continuing to the outpatient clinic) and pharmacological (for 6 weeks postoperatively) with the use of low-molecular-weight heparin as the preferred thromboprophylactic agent in pregnancy and puerperium. |
| Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium ⁽¹⁶⁾ | 2015 | Green-top G. | Royal College of Obstetricians and Gynaecologists | The study reports that the relative risk of VTE in pregnancy increases even more in the postpartum period, being 9 to 11 times greater. |
| Missed opportunities for venous thromboembolism prophylaxis during pregnancy and the postpartum period: evidence from mainland China in 2019 ⁽¹⁷⁾ | 2019 | Zhao Z, Zhou Q, Li X. | BMC Pregnancy Childbirth. | It is pointed out that the lack of treatment with anticoagulants in the puerperal period causes complications for women. Thus, efforts from patients, health agencies and health professionals are essential to improve the implementation of preventive strategies. |
| Deep vein thrombosis in pregnancy and puerperium (Trombose venosa profunda na gestação e puerpério) ⁽¹⁸⁾ | 2016 | Sarno MAC, et al. | Rep. Uni. Federal da Bahia | The study cites that the prophylactic treatment of thrombosis in low-risk patients should be cautious as there are risks of harmful consequences of thromboprophylaxis. |
| Pregnancy-related venous thromboembolism: Risk and the effect of thromboprophylaxis ⁽¹⁹⁾ | 2012 | Lussana F, et al, 2012 | Thrombosis Research | It is evident that VTE is considered potentially preventable with the prophylactic administration of anticoagulants, but there are no high-quality randomized clinical trials comparing different thromboprophylaxis strategies in pregnant women, and the absolute risk of VTE must be balanced against the risks of exposure to anticoagulants. |
| Thromboprophylaxis in Pregnancy ⁽²⁰⁾ | 2018 | Kolettis D, Craigio S. | Obstet Gynecol Clin North Am. | All guidelines require clinicians to think critically about each patient's risk factors during pregnancy and the postpartum period. |

Source: Elaborated by the authors, (2022).



men with cesarean delivery, they should receive mechanical prophylaxis with compression devices during the preoperative period until their recovery, according to the American College of Obstetricians and Gynecologists (ACOG). This is a low-cost and highly effective alternative for all pregnant women undergoing cesarean section, unlike pharmacological prophylaxis, which can be combined individually according to risk. However, all institutions must implement a safety policy for these women, with a view to reducing maternal morbidity and mortality.⁽¹⁵⁾

In summary, it is supported that the risk for VTE during the gestational period increases even more the chances of its development when compared to the puerperal period, where the chances are 9 to 11 times greater. Although the literature discusses risk factors and recommends the use of thromboprophylaxis in certain situations, there is clearly not enough scientific evidence to support these recommendations, as they are quite restricted in the scientific field.⁽¹⁶⁾

VTE prophylaxis in postpartum women is performed according to specific protocols established by each institution, and there is no general standard for its implementation. However, it is guided by the realization of risk layers, with several factors involved, such as: personal, family and genetic background, changes in the environment and mode of delivery.⁽¹⁷⁾

In view of this situation, mechanical prophylaxis can be used, with the use of compression devices, recommended in some cases, for example, by cesarean section; as well as pharmacological prophylaxis, and should be used when the risk outweighs the harm, in accordance with organizational procedures.⁽¹⁸⁾

LMWH and unfractionated heparin (UFH) are the pharmacological agents used in the prevention of VTE, the former being represented by enoxaparin, the drug of choice, and the latter being more rigorously used. Enoxaparin is eliminated by the kidneys, therefore, they are not appropriate in postpartum wo-

men with significant renal dysfunction; On the other hand, UFH is preferentially excreted by the reticuloendothelial system, constituting an alternative for these patients. It is worth noting that the use of new oral anticoagulants in the puerperium is not recommended due to the scarcity of research that recommends their use.⁽¹⁵⁾

As previously mentioned, the use of thromboprophylaxis is guided by organized and systematic procedures, where pregnant women perform a screening according to the risk aspects they present.

One of the several protocols that fall under the topic is the Lyon VTE Score in institutions, like the classification of patients at increased risk for VTE, an individualized management is recommended. This protocol was analyzed in a survey for its effectiveness and support, taking into account an analysis of 455 pregnant women with a history of VTE within 10 years of its development. This tool classifies the risk of VTE in pregnant women, who receive a predetermined prophylactic schedule: medium risk (receiving 6 points: prophylactic dose of LMWH since the beginning of pregnancy) and was created to collaborate in this type of evaluation, due to lack of reference guides.⁽¹³⁾

In view of this, suggestions for conduct, such as those discussed, are indispensable, however, because for adequate stratification and management, the variables used to classify medium, high and very high risk must be standardized. On the Lyon scale, the variables analyzed were: history of VTE, thrombophilic pregnant woman, over 35 years old, body mass index (BMI) > 30kg/m², at rest or immobilization, and twin pregnancy.⁽¹⁶⁾

In addition to these variables, other general medical conditions such as varicose veins, certain hematological diseases and inflammatory disorders were also considered risk factors in other institutional protocols. Due to the lack of randomized controlled trials comparing different thromboprophylaxis strategies, approaches are based on the balance

between the risk of VTE and the adverse effects of thromboprophylaxis. However, all pregnant women should be informed about the signs and symptoms of VTE and, if the benefit/risk balance is uncertain, the pregnant woman's preferences may also be taken into account.⁽¹⁷⁾

With this in mind, research has shown that patients at high risk, that is, with a history of VTE, hormonal arousal, genetic mutations, late pregnancy, severe obesity or comorbidities, may benefit from drug prophylaxis. In fact, generating potential benefits can outweigh potential side effects. However, this practice is not suggestive for low-risk patients, because the risk of adverse consequences of thromboprophylaxis, such as bleeding, osteoporosis, urticaria and thrombocytopenia, are greater in relation to the risk of developing VTE.⁽¹⁸⁾

Other studies point to other medical conditions that profile risk factors for thromboembolic events in postpartum women and require special attention, such as advanced age, black skin color, heart disease, sickle cell anemia, diabetes, smoking, systemic lupus, multiple pregnancy and cesarean delivery. This last factor, according to an analytical research that analyzed the risk of VTE, concluded that it is 6 times greater in relation to normal delivery.⁽¹⁹⁾

In summary, it is important to mention that the relatively low VTE situation makes prospective research difficult. Otherwise, practical suggestions are largely based on minimal retrospective studies, epidemiological research, and expert opinion.⁽²⁰⁾ Therefore, the potential benefit of thromboprophylaxis should be weighed against the possible adverse effects in postpartum women and its indiscriminate use should be avoided.

For the minimization of thromboembolic events in the puerperium, monitoring from pregnancy is essential, in this way the risks will be identified early and thus it will be possible to take the necessary effective preventive measures to reduce the consequences manifested by the

disease. ⁽²⁰⁾

CONCLUSION

This study showed that the adverse effects of indiscriminate use of antithrombotics in postpartum women bring harm to their health, in addition to pointing out that patients with high thrombotic risk have compensatory risks and benefits in preventive treatment. Otherwise, there is

no specific procedure with a high level of scientific evidence when it comes to patient involvement without imminent risk, due to the scarcity of available studies on the subject.

This finding provides evidence of applicability to clinical practice, as it highlights the heterogeneity and limitations of studies regarding indications for pharmacological management in patients at low to moderate risk for VTE, as its in-

discriminate use can cause considerable complications for the puerperal woman.

In view of this, it is recommended that further research be carried out, with the aim of adding better and more scientific evidence for the management of these patients. In addition, it is essential to encourage the planning of effective and standardized interventions to provide the best behavior for the puerperal woman. 🐦

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