

COMPLICATIONS OF THE USE OF WARFARIN DURING PREGNANCY AND FETAL WARFARIN SYNDROME: SCIENTIFIC REVIEW

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Abstract: Thromboembolism represents a significant cause of maternal morbidity and mortality during pregnancy, leading to the need for anticoagulant interventions in specific cases. Warfarin, a widely used oral anticoagulant, carries substantial risks when administered during pregnancy, including teratogenicity and the induction of fetal warfarin syndrome. This study aims to deepen the understanding of complications associated with the use of warfarin in pregnant women and explore the clinical characteristics of fetal warfarin syndrome through a comprehensive systematic review. Case reports and observational studies published between 2017 and 2022 were analyzed, selected from reliable databases, focusing on pregnant women exposed to warfarin and outcomes related to the fetus. The results indicate that exposure to warfarin, especially during the first trimester of pregnancy, is significantly associated with congenital malformations, highlighting nasal, neurological and skeletal abnormalities as the most common manifestations of fetal warfarin syndrome. This study reinforces the need for careful management strategies for women of reproductive age who require anticoagulation, highlighting the importance of safer therapeutic alternatives during pregnancy. Multidisciplinary collaboration is essential to optimize care and minimize risks, both for the mother and the fetus, given the complexity of anticoagulant management in this critical period.

Keywords: Warfarin, Pregnancy, Fetal Warfarin Syndrome, Teratogenicity, Anticoagulation in Pregnancy

INTRODUCTION

During pregnancy, the risk of thromboembolic diseases has been considered one of the main causes of maternal morbidity and mortality, since pulmonary thromboembolism occurs in 15 to 25% of

cases of untreated deep vein thrombosis (DVT), being responsible for the maternal mortality rate. from 12 to 15% (JUNQUEIRA, 2024). Thus, during pregnancy, risk factors become preponderant regarding the possible development of thromboembolism, factors such as extensive hypercoagulability due to the increase in procoagulants during this period, such as significant venous stasis due to the increase in vascular compression by the pregnant uterus and such as endothelial injury due to a possible cesarean section or an operative vaginal birth (FOCHESATTO FILHO, L.; BARROS, E., 2013). Thus, these factors constitute Virchow's Triad, revealing the changes that occur in hemostasis and coagulability in pregnant women. (FOCHESATTO FILHO, L.; BARROS, E., 2013)

From this perspective, the use of anticoagulant drugs to treat this disorder must be widely evaluated regarding the need and carefully researched regarding the risks, since the use of this pharmacological class, such as warfarin, a vitamin K antagonist, during pregnancy can cause numerous complications and abnormalities in both the fetus and the mother (Genetic and Rare Diseases Information Center (GARD) - National Center for Advancing Translational Sciences (NCATS), 2017). Therefore, warfarin, better known as Marfarin in the usual nomenclature, is classified as risk). Warfarin, if administered in the first trimester of pregnancy, is capable of causing fetal warfarin syndrome, a set of fetal anomalies, such as dotted bone irregularities, known as Chondrodysplasia Punctata, facial abnormalities and CNS deformities, also developing after administration in the second and third quarters (SILVEIRA, P. R. M., 2002).

Furthermore, in addition to revealing the intense complications generated to the fetus, it is also worth evaluating the pathogenesis that triggered the use of warfarin as a therapeutic

form, since due to some extreme need some pregnant women use this medication both in the pre-gestational period and during pregnancy. pregnancy and the postpartum period. The pathologies mentioned are found, in the case reports studied, related to heart problems with thrombotic risks, such as mechanical valve prostheses, in which care must be intensified and preventive measures in the face of the main complications for pregnant women must be part of the protocol in risk maternity hospitals (Brazilian Society of Cardiology, May 2020). Furthermore, the decision on the type of delivery must be precisely assessed with regard to a high-risk pregnancy, requiring the assessment of the risks, the health status of the pregnant woman, the medications used before and during pregnancy (DOMINGUES, R. M. S. M. et al., ago .2014).

Therefore, the objective of the study was to carry out a systematic review of the possible adverse reactions and complications caused by the use of warfarin during pregnancy, highlighting the main clinical characteristics arising from case reports, revealing different side effects caused to the fetus and relevant cases regarding the indispensability of warfarin in specific reports of pregnant women.

METHODOLOGY

The methodology used was based on a bibliographical review of the complications of warfarin use during pregnancy and fetal warfarin syndrome, in addition to trying to correlate possible coexisting variables related to this topic. As a basis for the development of the highlighted review, case reports were used, explored in databases such as: Online Scientific Electronic Library (SCIELO), United States National Library of Medicine (PubMed), The Virtual Health Library (VHL), Repository of USP Production.

Furthermore, it is important to highlight

that the search for descriptors used for the purpose of this study was carried out on the DEC's website (Descriptors in Health Sciences). In the research, the descriptors in Portuguese were considered: "Warfarin", "Pregnancy" and the Boolean operator "AND" to correlate the descriptors and terms used to find the appropriate publications for the "case report" study.

To select the case reports, it was necessary to determine the inclusion criteria, which covered articles in the Portuguese language, associated with publication time, with those from 2017 to 2022 being selected. In this sense, after selecting the articles, the variables were chosen: age of the pregnant woman, age of the child/fetus, length of time using warfarin, pathologies triggered by the use of warfarin by the pregnant woman, main complications in the fetus/child.

Finally, this bibliographic review did not need to be submitted to the ethics committee, as it is a study based on publicly accessible data, as case reports have already been published, following what is stated in the Ordinance of the Regional Health Council /MS-CNS, Resolution 510/2016, adopting basic ethical principles.

RESULTS

During the electronic data collection stage carried out in the databases chosen as a pillar for this research, a total of 579 references were identified related to warfarin complications in pregnancy and fetal warfarin syndrome, using the following descriptors: "Warfarin", "Pregnancy Complications", "Pregnancy Complications. 98.27% (569) were found from the VHL, 1.5% (9) from PUBMED and 0.33% (1) from the USP production repository.

And when the inclusion and exclusion criteria were applied, the numbers suffered significant drops. In the VHL, of the 569 total results, only 32 were published in the

period between 2017 and 2022 and, of these, 29 were published in Portuguese and English. On the PUBMED platform, of the total of 9 publications related to the topic studied, 3 fell within the stipulated period. In the USP Production Repository, only 1 was identified with the theme being in Portuguese and belonging to the period of 5 years from the date of publication. Finally, articles that presented case reports were selected, leaving six for analysis (shown in table 1).

After formatting and inspecting the analyzed references, it was possible to select the variables: “age of the pregnant woman”, “age of the child/fetus”, “time of warfarin use”, “pathologies that triggered the use of warfarin by the pregnant woman” and “main complications in the fetus/child”. The table below shows the articles that portrayed case reports included in the requirements displayed.

DISCUSSION

When starting the discussion about the anticoagulant warfarin, it is worth gaining knowledge about the phases of coagulation: initiation, amplification, propagation and completion, in which the adhesion and aggregation of platelets occur to form a plug, the activation of coagulation factors and finally, the limitation of the hemostatic process, fibrinolysis (BONATE, P. L. et al., 2016). These hemostasis processes include the presence of some aids, such as Ca^{+2} salts and vitamin K, which activate coagulation factors II, VII, IX and X (NUTRITOTAL, Aug. 26, 2019).

Thus, warfarin is in the pharmacological class of anticoagulants, more specifically as an enzyme blocker that uses vitamin K to activate the production of clotting factors in the liver, thus interrupting the clotting mechanism and prolonging the processes of hemostasis, such use tends to reduce the

propensity of clotting and does not completely cease hemostasis (BRUNETTO, M., 2024). Therefore, the administration of this drug must be monitored, through the analysis of the Prothrombin Time and the International Normalized Index, both capable of measuring in seconds the time required for the formation of a clot (CAGNOLATI, D. et al., 2017).

Thus, warfarin is one of the most commonly used oral anticoagulants in current pharmacology, used clinically in the prevention and treatment of problems such as deep vein thrombosis (DVT), pulmonary embolism, coronary ischemia and, consequently, considered a drug that has the side effects an increased risk of bleeding. Therefore, with regard to warfarin recommendations, the most contraindicated target audience is the pregnant population, since the medicine in vogue has a low safety margin, increasing the risk of miscarriages and increasing the tendency of fetal anomalies (COLET, C. F.; AMADOR, T. A.; HEINECK, I., 2017).

From this perspective, the use of warfarin during pregnancy is a widely discussed topic in neonatology, given that this medication crosses the placental barrier and is teratogenic, particularly between the 6th and 9th week of pregnancy, causing 1 to 3% of congenital malformations, and favors spontaneous abortion in around 10 to 33%, according to the Brazilian Society of Speech Therapy, thus, the high tendency to miscarriage among pregnant women who use this drug is notorious (RIBEIRO, C. C.; LAMÔNICA, D. A. C., 2017). Therefore, fetuses exposed to warfarin become susceptible to the development of a pathology known as fetal warfarin syndrome, which is quite common among fetuses from mothers who used warfarin during pregnancy for specific reasons (SOUSA, A. R.; BARREIRA, R.; SANTOS, E., 2018).

In this systematic review, case reports

| First Author/ year | Age of the pregnant woman | Age of the child/fetus | Warfarin use time | Pathology that triggered the use of warfarin by the pregnant woman | Main complications in the fetus/child |
|-----------------------|---------------------------|----------------------------|--|--|--|
| Shah SSH (2022) | ---- | Evaluated 2 months ago | Used for 3 years prior to pregnancy and during | Mechanical heart valve valve replacement | Nasal anomalies - nasal hypoplasia |
| Asaph Ziruma (2017) | 28 years | 20 weeks | Used after the 2nd trimester of pregnancy – the most advanced stage of pregnancy | Mechanical mitral valve | Neurological abnormalities -hydranencephaly; Abortion induction |
| Songmen S (2017) | 27 years | 37 weeks | Used during 2nd and 3rd trimesters of pregnancy | Heart valve prostheses | Nasal and bone anomalies - facial dysmorphism in the form of a depressed nasal bridge - dotted epiphyses |
| Ana R Sousa (2017) | ----- | Evaluated 12 months | Used during the 1st trimester of pregnancy | Mitral and aortic mechanical heart valves | Bone abnormalities – bone stippling; Interventricular communication |
| Rahul M (2022) | ---- | Assessed at 8 years of age | Used during the 1st trimester of pregnancy | Prevention of thromboembolic events associated with heart valve prosthesis | Nasal and dentofacial abnormalities |
| Schapkaitz E (2020) | --- | Review ed at 11 weeks | Used before and during pregnancy – time not specified | Mitral mechanical heart valves; Rheumatic Heart Disease | Neurological abnormalities – fetal central nervous system anomaly – meningocele with hemorrhage |
| Ribeiro C da C (2017) | ---- | Evaluated after 9 months | Used during the 2nd and 3rd trimesters of pregnancy | ---- | Neurological and nasal anomalies – speech-language disorders |

Table 1: Complications associated with the use of Warfarin during pregnancy and outcomes in fetal warfarin syndrome

were presented in Table 1 regarding pregnant women who used warfarin during pregnancy. Regarding the age of the women studied, very significant information was not obtained, as in some cases the mother's age was not revealed, however, given the ages reported, 100% of pregnant women were aged between 27-28 years. This data reveals a beneficial age for pregnancy, however, it does not say much about the tendency of thrombotic events and future complications generated by the fetus/child.

VARIABLE 2:

Regarding the variable age of the child/fetus, it is important to initially highlight that the studies chosen for the research in question address both babies and children already born, as well as fetuses in the gestational period, leading to a good overview of the topic. Thus, evaluating all the variables together, it is possible to conclude that even if the child is still being evaluated during the gestational period or after birth, there are no noticeable changes regarding the complications triggered by them, on the other hand, when the time of use with complications is put into focus, it is

It is clear that the period in which warfarin was administered during pregnancy greatly influences the severity of the consequences. It is often mentioned in several studies that the risks occur, mainly, if warfarin is administered between the 6th and 12th weeks of pregnancy, and are practically eliminated if warfarin is stopped before the 6th week (RAMOS, Afonso Carvalho, 2020).

Furthermore, even though the age at which the child/fetus was evaluated does not present significant importance in this research, it is undeniable that any and all monitoring of cases with high risks such as the one described in this study are capable of predicting and trying to put together strategies that can reduce damage and improve the quality of life of those affected. These follow-ups must be carried out both prenatally and in pediatric consultations, after birth, to improve the children's outlook on life.

With regard to the variable of time of use of warfarin, it is clear that individuals who used it first before pregnancy and later concomitantly, the babies they gestated presented nasal and neurological abnormalities, hallmark characteristics of Warfarin Syndrome. Fetal (*``Núcleo de Telessaúde Rio Grande do Sul``*, 20 Aug. 2009) and a fact that corroborates its title of class X (Gui de Remédios 2014, 12th ed., São Paulo: *``Editora Scala``*, 2014). Pregnant women who used the medication in the 1st trimester exhibited nasal, dentofacial and bone abnormalities, represented by the deformed tip or bridge of the nose and calcifications speckled in the final part of the bone (Genetic and Rare Diseases Information Center (GARD) - National Center for Advancing Translational Sciences (NCATS), 2017). However, what stands out most during this period is the risk of miscarriage, fetal death and embryopathy (SALINAS, P. et al., 2006).

In the same analysis, it was noticed that

users of the drug who used it during the 2nd and 3rd trimester had children who showed a prevalence of associations with abnormalities of the nervous system (Núcleo de Telessaúde Rio Grande do Sul, 20 Aug. 2009). However, this factor does not seem to be strictly related to the gestational period in which it was used (SALINAS, P. et al., 2006).

Regarding the pathologies that triggered the use of warfarin by pregnant women, it is possible to verify the prevalence of valvular heart disease as a motivating factor for the administration of this medication. Therefore, the use of cardiac valve prostheses by pregnant women is observed, particularly mechanical ones, as an aspect responsible for adversities in newborns. This occurs because, after performing valve replacement, therapeutic anticoagulation becomes an indispensable measure to minimize the risks of thromboembolic events (GÜNER, A. et al., 2020).

From this perspective, because pregnancy is a pro-thrombotic state, in which there is an increase in coagulation factors and favoring blood stasis, when associated with the presence of cardiac prostheses, it substantially increases the risk of hypercoagulability and the occurrence of thrombotic processes. Thus, the consumption of warfarin, as it is highly used in clinical practice and has numerous studies that prove its effectiveness, appears as prophylaxis against prosthetic thrombogenicity (DAUGHETY, M. M. et al., 2020).

Finally, data on the main complications generated in the fetus/child by the use of warfarin by pregnant women are the most preponderant variable in the clinical cases studied, since the side effects generated in the fetus constitute the limiting factor in the use of this anticoagulant during pregnancy (MELLO, T. T., 2018). This drug, if administered in the first trimester of

pregnancy, can cause fetal warfarin syndrome, characterized by nasal hypoplasia, dysplasia of the bony epiphyses, limb deformities and respiratory problems, in addition to being associated with abnormalities of the central nervous system, when used in the second trimester. gestation and the child may present meningeal hemorrhages due to compression of the fetal cephalic pole (RIBEIRO, C. C.; LAMÔNICA, D. A. C., 2017).

Thus, among the seven reports presented, 57% of the cases reveal nasal anomalies in the fetus/child as a consequence of the mother's use of warfarin, in which some are signaled by nasal hypoplasia, a characteristic sign of fetal warfarin syndrome, demonstrated through anteverted nostrils, depressed nasal bridge and short nose, revealing facial dysmorphism in the fetus (MAZZONI JÚNIOR, G. T., 2009). These nasal deformities constitute an incomplete fetal development of the nasal regions, being associated with genetic anomalies linked to a trisomy of chromosome 21 (COSSI, P. S. et al., 2008). Thus, when evaluating the case reports, it is clear that nasal deformities in the fetal period are significant complications when using warfarin during pregnancy and can, therefore, make an effective quality of life for the child unfeasible (FetalMed.net, 12 Sept. 2014).

Furthermore, in addition to nasal disorders, it is also worth discussing skeletal anomalies generated by the use of the anticoagulant in question, expressed in 43% of cases, through stippling of vertebrae or bone epiphyses, a delay in the endochondral ossification process, characteristic of skeletal dysplasias, such as Chondrodysplasia Punctata, discussed in one of the research cases (FIGUEIRÊDO, S. D. S. et al., Feb. 2007). Therefore, skeletal dysplasias may be associated with different metabolic, teratogenic and chromosomal disorders, constituting one of the complications caused by the use of warfarin in the fetus, in which,

if the mother uses the drug, we find changes in shape, size and constitution. of bones or cartilage (FetalMed.net, September 12, 2014). Therefore, to obtain the diagnosis, ultrasound is used as an exam, which becomes evident, in most cases, only in the second or third trimesters of pregnancy (FetalMed.net, September 12, 2014).

When evaluating case reports, the side effects of warfarin on the fetus and the ways in which its teratogenicity affects fetal life and the baby's development, neurological anomalies are also found as a complication of the use of this drug, especially when the drug is administered between the second and third trimester, such anomalies are expressed in 43% of the cases studied, through abnormalities of the central nervous system (*``Núcleo de Tele saúde Rio Grande do Sul``*, Aug. 20, 2009). These abnormalities are evidenced in the cases evaluated, through voice changes (dysphonia), speech changes (dysarthria), language changes, dysacusis and even facial paralysis, such complications are triggered by a disorder of the central nervous system (SILVA, G. P. da et al., Dec. 2020).

In addition to these disorders, still within the neurological alterations, there is also among the clinical reports, a case of hydranencephaly as one of the fetal warfarin complications, a congenital anomaly characterized by the absence of cerebral hemispheres and the replacement of such space by cerebrospinal fluid, being diagnosed by a translumination exam (PETITTO, C. E., 2022). Furthermore, among the clinical cases evaluated, a case of meningocele with hemorrhage, a congenital defect associated with spina bifida, in which the bones of the spine do not form completely, occurring when the spinal cord and nervous tissue do not project to the inside the sac linked to some type of hemorrhage in the case in question (FetalMed.net, Aug. 10, 2018).

Therefore, in addition to the nasal-facial,

bone and neurological anomalies found in the seven case reports evaluated in this scientific review, it is necessary to evaluate that in one of the cases there is an induction of abortion, this problem is closely associated with the administration of warfarin by the pregnant woman during periods advanced stages of pregnancy, since warfarin generates a greater risk of maternal mortality and a greater risk of anomalies in the fetal central nervous system when used by pregnant women in the 3rd trimester (ZIRUMA, A. et al., 2017).

CONCLUSION

In conclusion, this systematic review highlights the complexity and severity of complications associated with the use of warfarin during pregnancy, especially highlighting the induction of fetal warfarin syndrome, which is characterized by a series of fetal malformations and abnormalities (SOUSA, A. R.; BARREIRA, R.; SANTOS, E., 2018). The data collected highlights that, despite the need for anticoagulation for certain maternal health conditions, the use of warfarin represents a substantial risk for both the fetus and the mother, which emphasizes the importance of seeking safer therapeutic alternatives during this critical period. (RIBEIRO, C. C.; LAMÔNICA, D. A. C., 2017).

Careful administration of warfarin, with a rigorous assessment of risks and benefits, is crucial, especially during gestational periods most vulnerable to teratogenicity (GÜNER, A. et al., 2020). Furthermore, the prevalence of valvular heart disease as the main reason for prescribing this medication highlights the need for adaptive clinical protocols that prioritize fetal safety without compromising maternal health (DAUGHETY, M. M. et al., 2020).

This study also highlights the importance of close monitoring and adaptive clinical

management for women requiring anticoagulation during pregnancy, including consideration of alternatives to warfarin whenever possible (MELLO, T. T., 2018). Multidisciplinary collaboration between obstetricians, cardiologists and hematologists is essential to optimize results and minimize the risks associated with anticoagulation (Brazilian Society of Cardiology, May 2020).

Thus, this review contributes significantly to knowledge about the challenges and complications of warfarin use in pregnancy, serving as a critical reminder of the need for vigilance, continued research, and development of management strategies that ensure the safety of both mother and fetus. It is imperative that future research focuses on expanding safe anticoagulant treatment options during pregnancy and deepening understanding of the long-term implications of fetal exposure to warfarin (RAMOS, Afonso Carvalho, 2020).

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