Antenatal anticoagulant therapy and neonatal hemorrhagic syndrome. Case report.

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Case Report

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Abstract

Neonatal hemorrhagic syndrome, which affects several principal organs during the early neonatal period, denotes a deficiency of vitamin K and coagulation factors, respectively.

This article presents the case of a patient that gave birth at term, who had congenital heart disease and required several prior surgical interventions including corrected transposition of the great vessels via ventricular septal defect (VSD) repair, atrial septal defect (in childhood) and tricuspid valve replacement (6 years ago), mitral regurgitation (MR), grade I pulmonary regurgitation (PR), grade II mitral and tricuspid valve regurgitation, and grade II heart failure based on the New York Health Association (NYHA) classification. Throughout the pregnancy the patient administered large doses of anticoagulant, specifically Acenocumarolum, until the moment she gave birth. The vaginal delivery was spontaneous, contrary to the recommendations given to the pregnant woman in a secondary healthcare institution. At birth, the newborn was in satisfactory condition, with 8/9 on the Apgar score. However, the newborn's condition worsened over time, suspected of having neonatal hemorrhagic syndrome caused by medications administered by the mother. Forty-eight hours after birth the newborn died.

Anticoagulant therapy cannot be considered absolutely safe during pregnancy because it presents risks for the development of hemodynamic disorders, not only for the mother, but also for the newborn. In such cases, it is recommended that a multidisciplinary team work together to inform the mother about possible complications, collaboratively establish the duration of treatment with vitamin K antagonists (VKAs), establish a plan for monitoring the pregnancy and determining in which institution the mother and newborn can benefit from qualified medical assistance, taking into consideration the higher incidence of perinatal mortality in such cases (10-30%).

Introduction

Bleeding caused by vitamin K deficiency in newborns can occur early and later following birth. Early forms usually appear in the first 24 hours of life; anticoagulantsand maternal malnutrition (vitamin K deficiency) are direct risk factors. The scientific literature lists carbamazepine, phenobarbital, phenylhydantoin, rifampicin, cephalosporins, and VKAs (coumarins, warfarin) asmedications that interfere with vitamin K metabolism in newborns when administered 15 days before birth. The clinical case presented in this article demonstrates circumstances in the development of neonatal hemorrhagic syndrome because of bleeding caused by vitamin K deficiency. Vitamin K deficiency bleeding usually occurs after 24 hours after birth but may present as late as the first week of life. Vitamin K deficiency bleeding is observed in infants who have not received prophylactic vitamin K at birth, with an incidence ranging from 0.25 to 1.7 cases per 100 births[1].

After regimens for prophylaxis were introduced vitamin K deficiency bleeding has fallen from 4.4–7.2 cases per 100,000 births to 1.4–6.4 cases per 100,000 births in reports from Asia and Europe. In India

and China mandatory vitamin K prophylaxis is required, considering the high burden of neonatal deaths, to reduce the long-term morbidity and mortality related to vitamin K deficiency bleeding [2, 3, 4].

Neonatal hemorrhagic syndrome, which affects several principal organs during the early neonatal period, denotes a deficiency of vitamin K and some coagulation factors, respectively. A Cochrane systematic review entitled “Vitamin K supplementation during pregnancy for improving outcomes” synthesizes existing evidence related to this problem. Vitamin K deficiency can be a serious risk for the pregnant woman and the newborn. Bleeding is caused by reduced levels of prothrombin, an important element of the blood that is dependent on vitamin K, which disrupts the blood clotting process and can lead to excessive maternal or neonatal bleeding [5, 6].

Exposure of women to vitamin K anticoagulants during pregnancy may affect the fetus in utero by the formation of coumarin embryopathy (CE) [7]. Approximately 6% of newborns exposed to the consumption of coumarin during pregnancy develop CE, and skeletal abnormalities (midfacial hypoplasia, epiphyseal calcifications) are recorded in 80% of these children. Central nervous system malformations (e.g., midline structural defects) have been detected in 45% of children diagnosed with CE. Signs of intracranial hemorrhage have been observed in 10% ofnewborns. Since coumarins cross the placenta, affecting fetal coagulation, they increase the risk of intracranial hemorrhage before birth [8].

Moreover, the immaturity of the fetal liver is a major cause of slow metabolism of warfarin and a low level of coagulation factor in the fetus, thus the anticoagulant effect is significantly higher than in the mother.In addition, there is an increased risk of bleeding in newborns during birth, sometimes with a possible fatal outcome [9]. This hypothesis is also supported by Shearer (2009), who mentions that insufficient vitamin K levels can lead to intracranial hemorrhage shortly after birth. Babies are born with lower levels of vitamin K and do not receive adequate amounts of breast milk due to the lower rate of placental transfer [7]. The medication taken by the mother affects the metabolism of vitamin K and can oftentimes increase the incidence of disease in infants. A mortality rate of 20% has been estimated in neonates with severe bleeding disorders, including intracranial hemorrhage (50%) and neurological impairment[5]. Hetzel (2006) suggests that the administration of vitamin K antagonists should be under strict control during anticoagulant treatment in pregnant women with mechanical heart valves [7].

Case Presentation

Patient A, a 20-year-old, first time pregnant woman with a history of congenital heart disease (CHD), corrected transposition of the great vessels via VSD repair, ASD (in childhood), tricuspid valve replacement (6 years ago), MR, grade I PR, grade II mitral and tricuspid valve regurgitation, and grade II heart failure based on the NYHA classification, was registered under the surveillance of her primary care physician at 12 weeks pregnancy. The pregnancy was planned and wanted.

Over the course of the pregnancy the patient was monitored by her family doctor and consulted by obstetric, cardiology, and heart surgery specialists. Taking into consideration preexisting heart problems and previous surgical interventions, the patient was recommended a treatment with anticoagulants, VKAs

(Acenocoumarol) during pregnancy. The heart surgeon recommended maintaining international normalized ratio (INR) values between 2.5 and 3. Thus, throughout the pregnancy the prescribed dose of anticoagulants varied between 6 and 7mg of Acenocoumarol. In addition, at every antenatal visit coagulation testing was carried out for monitoring the effectiveness of the anticoagulant treatment necessary for patients with anamnesis of heart valve replacement. During the pregnancy, the patient had two echocardiograms, the results of which demonstrated satisfactory functioning of the heart.

Patient A was supervised during the antenatal period by her family doctor, showing up for all planned medical visits. Five ultrasound exams were conducted over the course of the pregnancy, at 13, 15, 21, 28, and 34 weeks. In all cases, development and the intrauterine condition of the fetus was assessed as satisfactory. At 28 weeks pregnancy, the patient was urgently hospitalized in a tertiary healthcare institution with the following diagnosis:primigravida, primipara, imminent premature birth, CHD, corrected transposition of the great vessels via VSD repair, ASD, tricuspid valve replacement, MR, grade I PR, grade II mitral and tricuspid valve regurgitation, and grade II heart failure based on the NYHA classification. Monitoring and consultation from a cardiologist took place and the dose of administered cardiometabolic medication (2mg Acenocoumarol- 3 times) was corrected.

Even though delivery was recommended to take place in atertiary level maternity hospital following leaking of amniotic fluid and the onset of regular uterine contractions, the patient urgently went to a primary level maternity unit in her place of residence. The following diagnostics were recorded: 39-weeks pregnant, primipara, premature rupture of membranes (PROM), longitudinal position of the fetus, cranial presentation, anterior variety, position II.

The first period (4 hours 30minutes) and the second (30minutes) of birth took place physiologically, without signs of fetal suffering, and without the utilization of fetal vacuum extraction and forceps. At birth, the newborn was in a satisfactory conditionwith 8/9 on the Apgar score, had clean, pale skin and mucous membranes. The neurological status of the newborn was assessed as satisfactory. There were no pathological ocular symptoms. The head was in a dolichocephalic form, and a 3x3cm cephalohematoma wasobserved in the occipital region.

The postpartum period was complicated on the second day following birth with the appearance of a hematoma in the region of the external genital organs, as well as hemodynamic disorders. The patient was transferred to a tertiary level healthcare facility, where the following diagnostics were established: day four postpartum, condition following natural childbirth, hematoma in the region of the internal and external genital organs, grade II iron deficiency anemia, CHD, corrected transposition of the great vessels via VSD repair, ASD, tricuspid valve replacement, MR, grade I PR, grade II mitral and tricuspid valve regurgitation, and grade II heart failure based on the NYHA classification. Laboratory readings indicated low prothrombin – 36%, but the level of fibrinogen could not be detected. During her stay in the intensive care unit, she was prescribed an anticoagulant treatment and a blood transfusion. On the sixth day following her admittance, she was discharged in a satisfactory condition.

Twenty-two hours after birth, the newborn was in an aggravated condition;it suddenly became restless, refused to suck, and had a painful scream and moan. The newborn's skin turned paler, muscle hypertonia was observed, breathing was difficult, and it had a SaO2 of88-90%.

Twenty-four hours after birth, the newborn's condition became extremely critical. It was very pale. Regarding its neurologic condition, it had a week reaction to physical examination. The newborn went into a coma and began to convulse. Its head grew in volume with a cranial circumference of 39.4cm (4.4cm greater than at birth) and at the level of the occipital bones a fluctuatingcollection of fluidwas observed.SpO2 was not determined, frequency of heart contractions was 110 per minute, respiratory rate was 38–40 per minute, and capillary recovery time was > 3 seconds. A complete blood count (CBC) showed the following: hemoglobin – 87g/L, erythrocytes – $2.9x10^{12}$cells/L, hematocrit – 32%, leukocytes (WBC) – $28.8x10^{3}$/microL, metamyelocytes – 2%, unsegmented – 10%, segmented – 50%, eosinophils – 0%, lymphocytes – 36%, monocytes – 2%. The newborn was given vitamin K – 2mg, volume expansion with 0.9% NaCl – 10ml/kg, dopamine – 10mcg/kg/min increased to 15mcg/kg/min, packed red blood cells (PRBCs) (A (II) Rhnegative)-10ml/kg,and fresh frozen plasm (FFP) – 10ml/kg. The child's condition stabilized, SaO2 increased to 97–98% and frequency of heart contractions grew to 115–120 per minute. The skin grew pinker.

The newborn was transferred to an intensive care unit in a tertiary healthcare facility, where its condition was assessed as profoundly serious. It was moaning.SaO2 without the administration of O2 was73-74%, thus requiring artificial ventilation of the lungs with fraction of inspired O2 at 30%. SpO2 increased to91-93%. The skin was pale, capillary recovery time was > 3 second, and arterial blood pressure was 25/16/20. A fluctuating collection of fluid localized in the parieto-occipital sulcus spreading to the cervical region was observed. The newborn exhibited slow photoreaction of pupils, hypotonia, hyporeflexia, and hypodynamic heart function. Hemoglobin was 110g/L, erythrocytes – $3.4x10^{12}$cells/L, hematocrit – 33%, WBC- 45 $x8x10^{3}$/microL, absolute neutrophil count(ANC) 35100, immature-to-total ratio – 0.25, platelets – 170 x 10^{3}/microL, acid-base balance - pH 7.04, pCO2 16.8, pO2–54.8, plasma bicarbonate – 7.6, base deficit – 24.4. Prothrombin time (PT) was 38 seconds, activated partial thromboplastin time (APTT) – 1 minute 54 seconds, fibrinogen – 1.8gm/l, prothrombin – 46%. The newborn received volume expansion therapy with 0.9% NaCl – 10ml/kg, cardiotonic dopamine therapy-15mcg/kg/min, homeostatic therapy with vitamin K – 2mg intravenously (IV), correction of posthemorrhagic anemia withPRBCs- 15ml/kg. Following the transfusion, hemoglobin increased to 145, erythrocytes – 4.5, and hematocrit – 0.44, respectively.

Forty-three hours after birth, clonicseizureswere registered, bloody content was eliminated from the gastronomy tube. Macrohematuria, melena, hematemesis, and anuria were observed. Cranial circumference was registered at 40cm (at birth it was 35cm). The newborn suffered a profound cerebral coma. It was in an agonal state. The CBC showed hemoglobin levels of 105g/L and platelets – 128 x 10^{3}/microL. PT was 49 seconds, APTT – 1 minute 54 seconds, acid-base balance – pH 7.11, pCO2–28.2,

pO2–39.2, plasma bicarbonate – 10. The newborn was given PRBCs(A (II) Rh negative)- 15ml/kg, FFP A(II) – 20ml/kg and vitamin k IV – 2mg. Forty-eight hours after birth the newborn died.

The cause of death based on the autopsy was determined to be neonatal hemorrhagic syndrome. Acute bleeding disorders, rectal bleeding and per diapedesis in the epicranial aponeurosis, at the level of the leptomeninges, brain, thymus, lungs, diaphragm, stomach, intestines, and kidneys were observed. Collection of blood occurred at the level of the leptomeninges and diaphragm. The amount of blood accumulated in the right lung was 10ml and in the stomach- 100ml.

Discussion

The advantages and disadvantages of different anticoagulant regimens should be discussed at length before pregnancy. The mother must understand that the use of VKAs is the most effective regimen for preventing valvular thrombosis, and therefore the safest regimen for her, though these risks for the mother alsoput the child in danger. At the same time, it is important for the mother to be compliant regardless of the chosen regimen. Subsequently, continuation of VKA administration may be considered in pregnant women after fully informed consent. The pregnant woman in the clinical case received treatment with VKAs throughout her pregnancy.When a higher dose of VKAs is required, the treatment may be discontinued between 6 and 12 weeks and replaced with an adjusted dose of unfractionated heparin (UFH) or low-molecular-weight heparins(LMWH) IVtwice daily, with dose adjustment according to maximum anti-factor Xa levels.

One of the important issues is to determine when it is appropriate to stop treatment with anticoagulants. Thus, according to the 2012 American College of Chest Physicians (ACCP) Guidelines, VKAs should be discontinued three weeks before the expected date of birth [11].The 2014 American College of Cardiology and the American Heart Association (ACC/AHA) guide recommends discontinuing VKAs at 36 weeks pregnancy and initiating UFH IV therapy, which should be stopped approximately 4–8 hours before the expected birth with resumption of treatment 4–6 hours after birth in the absence of bleeding. VKA treatment can be resumed 24 hours after birth [12].

The European Society of Cardiology (ESC) guide “Guidelines for the management of cardiovascular diseases during pregnancy” (2018) proposes dose adjustment depending on INR values and factor Xa. The authors also mention that vaginal birth while the mother is administering VKAs is contraindicated due to the risk of fetal intracranial bleeding and hemorrhagic complications in the mother, which can occur regardless of the chosen regimen. The incidence of such complications is lower when administering VKAs during pregnancy than when LMWH or UFH is administered during pregnancy. Patients administering VKAsare recommended caesarean section when labor begins [13].

The guide recommends stopping VKA treatment at 36 weeks of gestation and replacing it with UFH or LMWH IV until 36 hours before birth. At that point, LMWH should be replaced withUFH IV [13]. The ACCP guide recommends that pregnant women at remarkably high risk of thromboembolism (older generation mitral valves and previous thromboembolism) should continue to take warfarin as close to birth as

possible, generally 48 hours before the expected time of birth, when VKA therapy should be replaced by UFH or LMWH [11].

In the case of an unexpected birth, before the scheduled date when the patient should receive oral anticoagulant therapy, cesarean section is recommended due to the risk of fetal intracranial hemorrhage. Panduranga et al. recommend stopping the UFH IV 4–6 hours before birth and resuming it 4–6 hours after birth [15].Montavon et al. consider that UFH or LMWH should be administered 12 hours after cesarean section or 6 hours after vaginal birth in combination with VKAs the next day until therapeutic INR values are reached [9].

Analyzing the characteristics of the presented clinical case, the patient had a history ofCHD, namely - corrected transposition of the great vessels, condition following VSD repair, ASD (in childhood), tricuspid valve replacement (6 years ago), which from the beginning warranted the patient's inclusion in the risk group for hemodynamic disorders during pregnancy, as well as during childbirth and postpartum. Pregnancy is a risk for such patients, so it requires supervision at a tertiary level medical facility. Pregnant women with this cardiac disease must be monitored as rigorously as possibledue to changes in coagulation and increases in the volume of blood circulating during pregnancy.

At present, there is no national protocol available that clearly outlines the doses of anticoagulants that can be administered during pregnancy, be it that they are recommended for pregnant women with a severe heart disease or following heart surgery. Patients that have had cardiac procedures and surgeriesrequiring anticoagulants in relatively high doses are presented as unique cases, and the doses are recommended on an individual basis depending on the type of procedure, blood parameters, and the general condition of the patient.

During pregnancy, the dose of anticoagulant administered has been correlated with the INR index, in accordance with existing guidelines, which recommend maintaining the mean values of this indicator between 2.5 and 3.5. At the same time, it is known that utilization of coumarins, which cross the placental barrier, may cause neonatal hemorrhagic syndrome, which is probably what occurred in the presented case.

The presence of an advanced heart disease indicates the need for delivery to take place in a tertiary level maternity hospital so that parturition can be appropriately monitored and supervised. Coagulation testing should take place at the moment the patient is admitted to the hospital, availability of blood products should be verified, and a multidisciplinary team should be established in casethe patient's condition worsens or shebegins to hemorrhage. Likewise, the newborn requires a more rigorous examination in the neonatal period; additional investigations are available at tertiary level facilities and the newborn thus benefits from qualified medical care in terms of diagnosis and treatment.

From an obstetrical point of few there is no relationship between consequences to the fetusand the obstetrical conduct of delivery. The autopsy report showing the presence of neonatal hemorrhagic syndromewas indicated by acute circulatory bleeding disorders and accumulation of blood in the right

lung and stomach. Considering the presence ofdesquamative interstitial bronchopneumonia, residual aspiration syndrome, and preexisting heart problems, we consider that the bleeding experienced by the newborn was not caused by the labor itself, but by the long-term administration of coumarin anticoagulants (Acenocoumarol) by the mother during pregnancy and up until labor. The administration of this medication led to vitamin K deficiency in the pregnant woman and, consequently, in the newborn, causing acute circulatory bleeding disorders and accumulation of blood, which were determined to be the cause of death.Also, the administration of vitamin K in the period immediately following childbirth was indispensable. Coagulation disorders in the fetus during the neonatal period were a consequence of the mother's condition, which, during childbirth, was also complicated by coagulation disorders (hypoprothrombinemia), requiringqualified medical assistance, including blood transfusion.

Another case of coumarin embryopathy after in utero (throughout intra uterine life) exposure to Acenocoumarol was described in 2018 by Ankur Singh, however the neonate showed all features of coumarin embryopathy (flat facial profile, depressed nasal bridge, short columella, skeletal stippling, short distal phalanges in hand) and cephalhaematoma in addition. The authors conclude that doses causing embryopathy remained unexplored field, and that coumarins act as double edge sword as fetus is unnecessarily exposed to teratogenic effect of drug[16].

In another case report, K. Stefanidis describes an uneventful course of pregnancy and delivery in a pregnant patient with a mechanical heart valve receiving anticoagulation treatmentbecause of mitral valve replacement at the age of 16 due to rheumatic disease. The antithrombotic regimen used was acenocoumarol 2 mg/day throughout the 2nd and 3rd trimesters of pregnancy with replacement of acenocoumarol by enoxaparin sodium 60 mg twice daily (low-molecular-weight heparin - LMWH) in the 1st trimester during weeks 7–12. International normalization ratio (INR) values were kept above 2.5. At 36 weeks of gestation, acenocoumarol was substituted with unfractionated heparin and 2 days later the patient entered spontaneous premature labor and was emergently delivered via cesarean section (INR = 1.4).No coumarin embryopathy or neonatal bleeding was revealed and the postoperative course of the mother was uneventful.Possibly the case was a success due to optimum replacements of coumarins[17].

Vitamin K metabolism can also be disrupted by maternal medication in the 15 days before birth, which requires the administration of antenatal vitamin K (10-20mg/day orally). If this treatment has been omitted, the intramuscular (IM) administration of 10mg intrapartum vitamin K to the mother is recommended at the beginning of birth [14].Therefore, immediate postnatal administration of vitamin K is considered optimal for vitamin K deficiency prophylaxis for this group of children. According to the recommendations provided byMihatsch (2016), all newborns should receive prophylactic vitamin K.The administration of prophylactic vitamin K should be documented. Parental refusal of prophylactic vitamin K after being adequately informed should be documented, particularly considering therisk of late vitamin K deficiency bleeding (VKDB) [16].Healthy newborns should receive either 1mg vitamin K1 by IM injection at birth or 3mg vitamin K1 twice orally after birth, at 4–6 days and 4–6 weeks, or 2 mg vitamin K1 orally at birth and a weekly dose of 1mg orally for 3 months.The success of oral administration depends on compliance with the chosen protocol, which can vary between populations and environments. If the

infant vomits or regurgitates within 1 hour of administration, the oral dose may be repeated.The oral route is not suitable for premature infants and newborns who are ill, have cholestasis or impaired intestinal absorption, are unable to take oral vitamin K, or for those whose mothers have taken medicines that interfere with vitamin K metabolism [18, 21].

Dose-ranging studies suggest that current recommended doses of vitamin K for premature infants lead to supraphysiological levels. A randomized study showed that administration of 0.2mg vitamin K IM at birth resulted in adequate serum levels, whereas 0.5mg IM and 0.2mg IVresulted in high levels of vitamin Kepoxide, demonstrating hepatic overaccumulation [19].Thus, an initial dose of prophylactic vitamin K1 of 0.2mg IM should maintain adequate levels of vitamin K in premature infants bornbefore the 32nd week of pregnancy until at least the fourth week following birth. This should occur without causing hepatic overaccumulation of vitamin K1, which isrecycledduring the first week of life [20].

Treatment of hemorrhagic syndrome caused by vitamin K deficiency is focused on strict monitoring of coagulation tests:PT, platelets, fibrinogen, APTT. If VKDB is suspected,an IV of 1-2mg vitamin K should be administered parenterally, slowly, for 10-15minutes or subcutaneously (in case of lack of venous access) as soon as possible.This will reduce the duration of bleeding in a few hours. After 4–6 hours it is necessary to repeat PT. If PT remains prolonged and APTT is normal in a clinically stable child, a repeated dose of 1mg vitamin K IVshould be administered. Coagulation tests should be repeated every 4–6 hours. If PT and APTT remain prolonged, 10-20ml/kg FFP should be administered for 30–60 minutes.In the presence of major bleeding, 10-20ml/kg FFPor prothrombin complex concentrates (factors involved in the “extrinsic” and common coagulation pathway: VII-proconvertin; Stuart-Prower factor; V-proaccelerin; II –Prothrombin and I-fibrinogen) should be administered. If signs of anemia and/or hypovolemic shock are present (pale skin, increased capillary recovery time,increased frequency of heart contractions,normal or decreased arterial blood pressure) PRBCs – 15-20ml/kg should be administered.

Postpartum vitamin K prophylaxis is critical for reducing VKDB morbidity and mortality in newborns. Based on 2017 World Health Organization (WHO) recommendations, prophylactic vitamin K administration should be characterized by the following:

- After birth, all newborns should be given 1mg of vitamin K IM after the first hour of life (the time when the baby should be in skin-to-skin contact with the mother and breastfeeding should be initiated) (III B).
- Newborns that require surgical procedures or experience trauma during birth, premature newborns, and those exposed antenatally to drugs that interfere with vitamin K uptakehave a high risk of bleeding and require administration of 1mg vitamin K IM early after birth (III B) [22].

Doses and timing of vitamin K depending on birth weight were reviewed and proposed by the French Society of Neonatology in 2017 [23].

- Healthy full-term babies: 1mg (0.1ml) IM after the first hour following birth (preferably as soon as possible, up to 3–6 hours after birth)

- Premature babies weighing ≥ 1.5 kg: 1mg (0.1ml) IM after the first hour following birth (preferably as soon as possible, up to 3–6 hours after birth), then weekly 1 mg until corrected gestational age of 40 weeks. [19]
- Premature babies weighing ≤ 1.5 kg: 0.5mg (0.05ml) IM, preferably IV, slowly, for 10–15 minutes, after the first hour following birth (preferably as soon as possible, up to 3–6 hours after birth), weekly until the baby weighs ≥ 1.5 kg. Then weekly 1mg until the corrected gestational age of 40 weeks. [23].

Conclusion

Anticoagulant therapy is indicated during pregnancy in women with mechanical heart valve prostheses, with a history of or current venous thrombosis and thromboembolism, as well as in the presence of a thrombus in the cardiac chambers, atrial fibrillation with a high thromboembolic risk, pulmonary hypertension causedby a severe form of thrombophilia, or if the mother has a recurrent history of miscarriage. In addition to thrombophilia with recurrent miscarriages, anticoagulant therapy is also considered in cases of stagnant pregnancy/antenatal death of the fetus, preeclampsia, post-thrombotic syndrome, ovarian hyperstimulation syndrome, which is associated with states of hypercoagulability. In these cases, it is necessary to follow a standardized/national clinical protocol that outlines recommended doses, modes of administration, the type of anticoagulant and the term of pregnancy when administration of the drug will be discontinued.Better surveillance during pregnancy and careful medical evaluation of neonate after delivery are essential.

Anticoagulant therapy during pregnancy cannot be considered absolutely safe, as it presents risks of hemodynamic disorders for both the mother and the newborn, but it is necessary to select the least offensive options at different stages of pregnancy (preconception, first trimester of pregnancy, birth, postpartum) depending on maternal risk factors, and existing comorbidities, evaluating benefits and risks of the treatment. These pregnant women must be closely monitored by their family doctor, gynecologist, cardiologist and/or cardiac surgeon, with hospitalization in a tertiary level maternity hospital. The birth must be overseenby a multidisciplinary team (obstetrician-gynecologist, neonatologist, anesthesiologist) that is familiar with the patient's history, with close monitoring of coagulation tests, and early administration of vitamin Kas necessary and with the availability of blood products.

Declarations

Author's contribution I.S., D.R.: study conception and design; I.S., R.D.: acquisition of data; I.S., O.C., D.R.: analysisand interpretation of data; I.S., D.R.,: drafting of manuscript; I.S., D.R.,O.C.: critical revision.

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