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Warfarin-Associated Fetal Subdural Hematoma Causing Severe Neurodevelopmental Delay: A Case Report

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Established Facts

- Warfarin use during pregnancy is associated with an increased risk of maternal and fetal adverse effects.
- Fetal subdural hematoma is a serious antenatal finding and is associated with high mortality.

Novel Insights

- Preterm infants with antenatally diagnosed subdural hematoma can survive with proper resuscitation.
- Early fetal subdural hematoma can lead to poor long-term outcomes.

Keywords
Warfarin · Subdural hematoma · Neonatology · Critical care · Case report

Abstract
Fetal subdural hematoma is an antenatal finding associated with significant morbidity and mortality. It can occur due to maternal or fetal risk factors, and its management varies based on the underlying cause and the anticipated long-term outcomes. We present a case of warfarin-associated fetal subdural hematoma resulting in a live birth and severe neurodevelopmental delay by 10 years of age. In conclusion, counseling regarding the risk of fetal intracranial hemorrhage and the potential neurodevelopmental delay is essential in women who require anticoagulation with warfarin. In addition, close antenatal follow-up with fetal sonography and strict INR monitoring are essential preventative measures.

Introduction

Subdural hematoma (SDH) occurs when the collection of blood is located between the dura mater and the arachnoid membrane. It has an incidence of 4.6–5.1%

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in autopsy studies of stillborn fetuses and accounts for 18% of antenatally diagnosed intracranial hemorrhage (ICH) [1]. It is associated with significant mortality and morbidity, with a 1-month mortality rate of 30% and 22–42% incidence of adverse neurologic outcomes among survivors [1, 2]. Fetal ICH can be caused by maternal trauma which mostly occurs in the third trimester as the fetal cranium becomes at a higher risk for direct trauma. Other reported causes include coagulation disorders such as isoimmune thrombocytopenia, arteriovenous malformation, fetal infection, and drug toxicity [3]. One of the reported drugs associated with fetal SDH is warfarin [4, 5]. Warfarin-associated SDH is rare, and the true incidence is unknown due to the scarcity of reported literature. We present a case of fetal warfarin-associated SDH causing severe neurodevelopmental delay.

Case Report

A 42-year-old, gravida 7 para 4 woman presented at 32 weeks of gestation to the emergency department complaining of reduced fetal movement with no history of trauma. The patient has mechanical mitral valve replacement, and during her pregnancy, she was taking enoxaparin 80 mg twice daily until 22 weeks and was then switched to warfarin 10 mg/day. On presentation, initial laboratories revealed an international normalized ratio (INR) of 4.7, prothrombin time of 49 s, activated partial thromboplastin time of 44 s, fibrinogen 3.4 g/L, platelets 309,000/mL, and hemoglobin 9 g/dL. Cardiotocography demonstrated instability of fetal heart rate, and an ultrasound revealed crescent hyperechoic collection measuring 8 × 1.2 cm suggestive of SDH (shown in Fig. 1). Therefore, the patient was planned for an emergency cesarean section, and warfarin was stopped 36 h prior to the surgery.

In the operating theater, the baby was born non-vigorous with no respiratory effort, pale, with a heart rate of 40 beats per minute (BPM). Initial steps of resuscitation were done without a response; then after bagging for 30 s, the heart rate increased to >100 BPM; however, there was still no breathing. The baby was intubated at 1 min of age, and oxygen saturation was 72–82% with poor perfusion and pale color. An umbilical venous catheter was inserted, and a bolus of normal saline was administered as 10 mL/kg followed by blood transfusion. The Apgar score was 2, 5, 6, and 8 at 1, 5, 10, and 15 min, respectively. Surfactant was given at a dose of 100 mg/kg, and oxygen saturation improved with a fraction of inspired oxygen of 21%. The baby was then transferred to the neonatal intensive care unit in a stable condition (heart rate 135 BPM, respiratory rate 22/min, temperature 36°C, and blood pressure 42/26 mm Hg).

The baby's birthweight was 2,010 g (<90th percentile), length was 43 cm (50th percentile), and head circumference was 31 cm (50th percentile). On physical examination, bulged anterior fontanelle and swelling in the right scrotum were noted. Capillary blood gas revealed pH 7.11, PCO_2 58 mm Hg, base excess −11.6 mmol/L, bicarbonate 18.4 mmol/L. A complete blood count with hematological profile showed hemoglobin 10.4 g/dL, platelets 119,000/mL, INR 3.7, prothrombin time 38.8 s, and activated partial thromboplastin time 71.9 s. The baby received 5 mg of vitamin K prophylaxis; as per our protocol, higher vitamin K doses are given to babies with hemorrhage.

Imaging

Brain ultrasound was done on day 1 of life (shown in Fig. 2), which showed crescent shape hypoechoic collection in the left frontoparietal region measuring 5 × 0.7 cm, suggestive of SDH with overlying echogenic area denoting layering of the hematoma. An echogenic focus of clotted blood was seen in the falx measuring 1.7 × 0.8 cm. No midline shift or ventricular dilatation was noted. Ultrasound for testes (shown in Fig. 3) showed a large turbid fluid collection in the right scrotal sac which was most probably hemorrhagic, measuring around 25 × 15 mm. Both testes had normal appearance and perfusion. In addition, computed tomography scan of the head (shown in Fig. 4) was done on the second day of life and showed significant bilateral SDH surrounding almost the whole left hemisphere with extension to the tentorium and posterior interhemispheric fissure as well as the occipital horn of the right lateral ventricle. Also, linear hyperdense lesions were seen extending along the cerebral cortical sulci, likely representing associated subarachnoid hemorrhage. Diffuse hypodense area involves both hemispheres almost entirely, suggesting diffuse brain edema with shifting of the midline structures at least 6 mm to the right.

Brain ultrasound was repeated at 20 days of life (shown in Fig. 5) and showed large subacute/chronic SDH overlying the left cerebral hemisphere with the largest pocket measuring 5.9 × 2.8 cm with midline shift to the right side. Large cystic changes involving both cerebral hemispheres suggestive of severe periventricular leukomalacia (PVL) and changes suggestive of cephalomalacia and dilated lateral ventricles were observed. At the age of 24 days, magnetic resonance imaging (MRI) (shown in Fig. 6) was done and showed large bilateral acute on subacute SDH. It also revealed features of extensive encephalomalacic changes involving the cerebral hemispheres with small areas being spared in the basal ganglionic region and in the frontotemporal area. The posterior fossa structures were also noted to be spared.

Hospital Course and Follow-Up

Over the course of the admission, the baby was managed conservatively, no seizure activity was recorded, and there was no evidence of hydrocephalus. The right scrotal hemorrhage self-resolved by 2 weeks of age. The baby also developed late onset sepsis with a urine culture positive for Klebsiella pneumoniae for which the baby receivedantibiotics for 2 weeks. The baby was discharged at 4 weeks of age (36 weeks corrected gestational age) on tube feeding and was followed up by a multidisciplinary team consisting of a neonatologist, pediatric neurologist, occupational therapist, and a physiotherapist.

As of the time of this publication, the child is 10 years old with spastic quadriplegic cerebral palsy and gross motor function classification system level 5. He has a kyphotic posture with severe global delays, no grasp, blindness, and non-recognized speech.

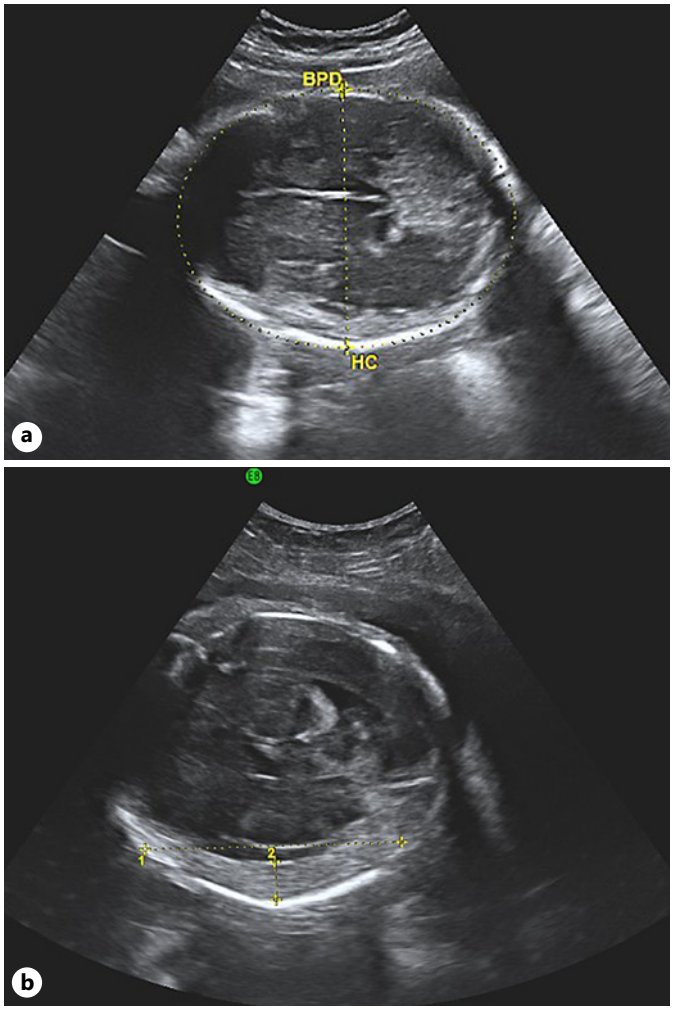

Fig. 1. a, **b** Antenatal ultrasound: antenatal ultrasound on the day of delivery showing crescent hyperechoic collection suggestive of SDH 8 × 1.2 cm (dotted lines 1 and 2).

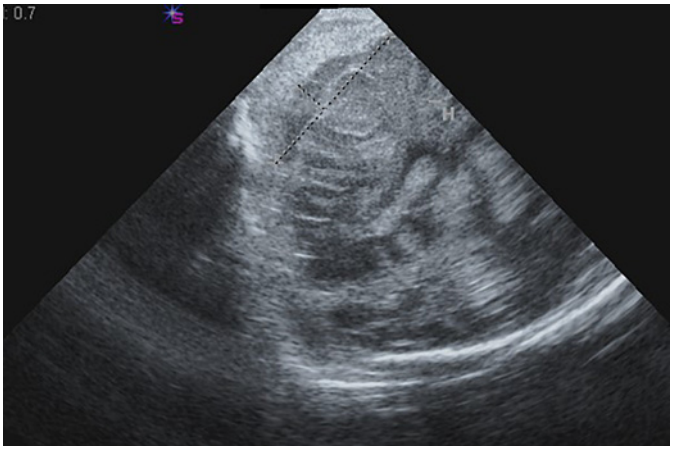

Fig. 2. First brain ultrasound: brain ultrasound on day 1 of life showing crescent shape hypoechoic collection in the left fronto-parietal region measuring 5 × 0.7 cm suggestive of SDH with overlying echogenic area probably denoting layering of the hematoma. An echogenic focus was seen in the falx measuring 1.7 × 0.8 cm which could be clotted blood. No midline shift or ventricular dilatation was noted.

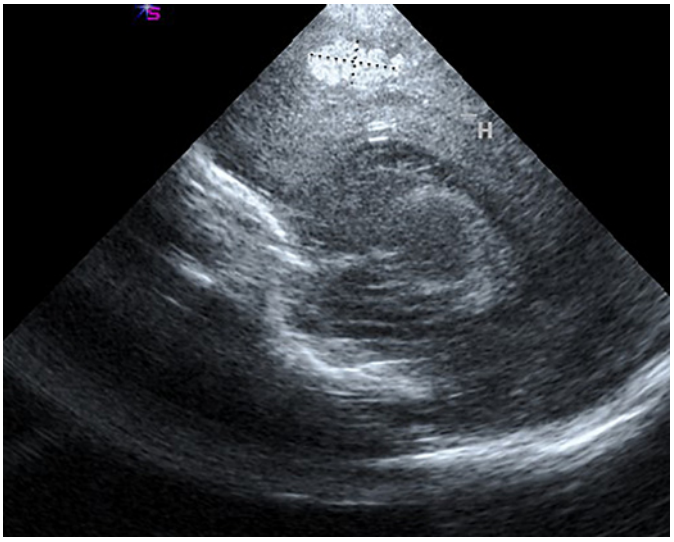

Fig. 3. Testes ultrasound: testes ultrasound on day 1 of life showing large turbid fluid collection in the right scrotal sac, most probably hemorrhagic fluid measuring around 25 × 15 mm. Normal appearance and perfusion of both testes are seen.

Discussion

Pregnant women with a mechanical mitral valve are at an increased risk for prosthetic valve thromboembolic complications, and the general recommendation is to continue anticoagulation with warfarin throughout pregnancy with close INR monitoring [6, 7]. However, low molecular weight heparin can be used during pregnancy for pregnant women who prefer to reduce the risk of fetal adverse effects [6, 7]. In our case, the use of warfarin in the third trimester has resulted in fetal SDH that was diagnosed antenatally. To our knowledge, there are 7 published cases of fetal warfarin-associated SDH, and only 2 survived the neonatal period, making our case the third.

A recent systematic review examining the diagnosis of fetal SDH reported that in 24% of the cases, ultrasonography was sufficient for the diagnosis, while 63% needed confirmation by in utero MRI [2]. Among those confirmed by in utero MRI, more than half had abnormal ultrasonographic

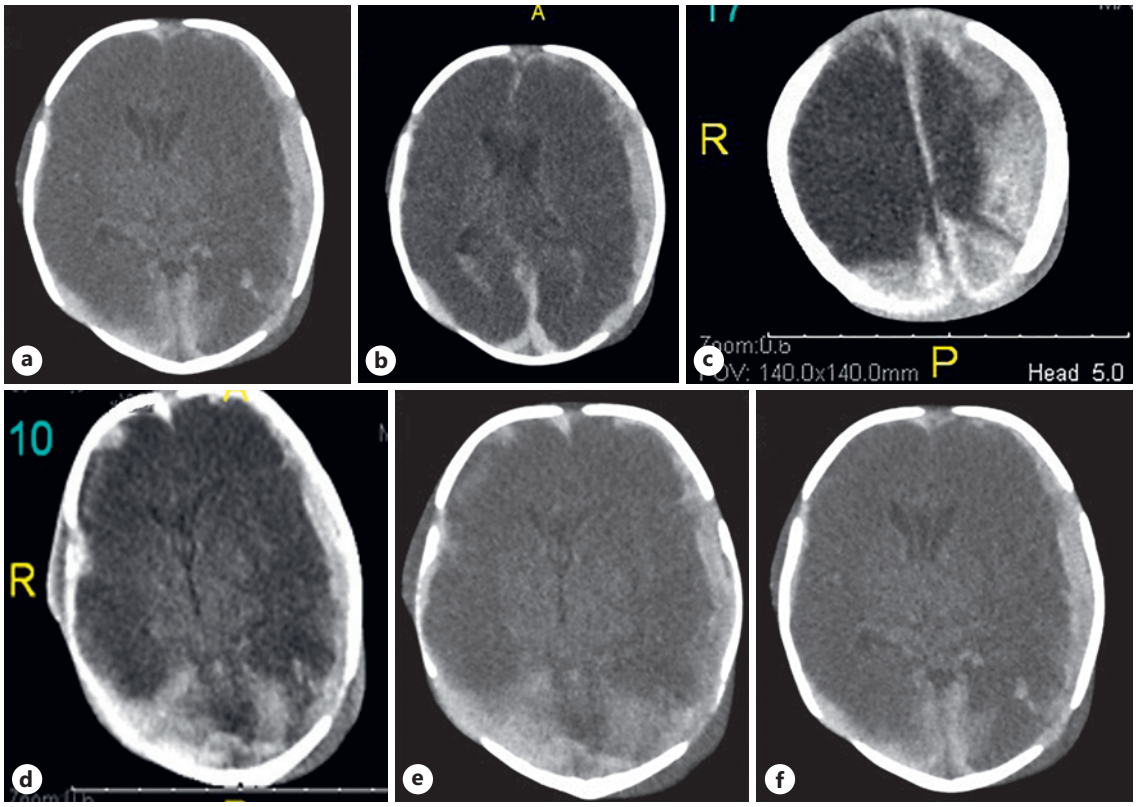

Fig. 4. a–f Head computed tomography (CT) scan: head CT on day 2 of life showing significant bilateral SDH surrounding almost the whole left hemisphere with extension to the tentorium and posterior interhemispheric fissure as well as the occipital horn of the right lateral ventricle. Also, linear hyperdense lesions are seen extending along the cerebral cortical sulci likely representing associated subarachnoid hemorrhage. Diffuse hypodense area involving both hemispheres almost entirely, suggesting diffuse brain edema with shifting of the midline structures at least 6 mm to the right.

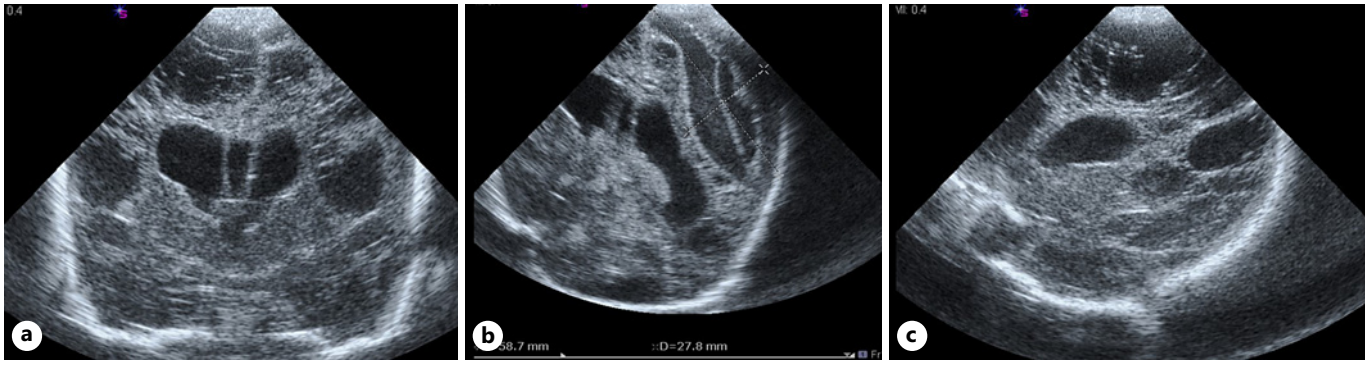

Fig. 5. a–c Brain ultrasound at 20 days of life: brain ultrasound on day 20 of life showing large subacute/chronic SDH overlying the left cerebral hemisphere with the largest pocket measuring 5.9 × 2.8 (cross dotted black lines) with midline shift to the right side. Large cystic changes involving both cerebral hemispheres suggestive of severe PVL and changes suggestive of cephalomalacia and dilated lateral ventricles were observed.

findings without suspicion of fetal SDH. The most common ultrasonographic findings were intracranial echogenicity (42%), lateral ventriculomegaly (38%), presence of an intracranial mass (31%), macrocephaly (24%), midline deviation of cerebral falx (20%), and intracranial fluid collection (11%) [2].

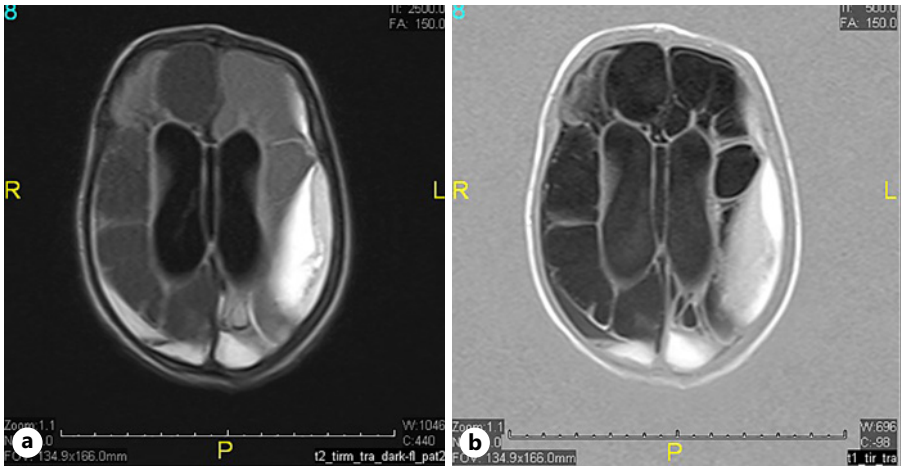

Fig. 6. a, **b** Head MRI: head MRI at day 24 of life showing large bilateral acute on subacute SDH. Features of extensive encephalomalacia changes are noted involving the cerebral hemispheres with small areas being spared in the basal ganglionic region and in the frontotemporal area. The posterior fossa structures are also noted to be spared.

PVL is a brain injury affecting the white matter and is characterized by focal periventricular necrosis and formation of cysts. Premature infants are at increased risk for PVL due to ischemic insults [8]. In a study of 433 infants with cystic PVL, 60% of the cases were first detected on ultrasound at 36 weeks corrected gestational age and the remaining 40% were detected earlier [9]. A study that assessed MRI findings of neonates with hypoxic-ischemic encephalopathy reported that cystic changes were noted as early as 1 and 2 weeks of life [10]. In our case, the combination of more than one insult during fetal life including shock, severe anemia, and acidosis was the likely reason for early detection of cystic PVL. Of note, no seizure activity was recorded in our case. This could be attributed to the location of the lesion, as seizures are mostly a result of insults to the cerebral cortex [11].

The prognosis of ICH depends on the extent and location of the lesion. In a case series assessing fetal ICH, the subdural location was associated with poor prognosis [12]. In our case, the poor outcome can be further explained by the hypoxic-ischemic insult and hemodynamic changes caused by anemia and hypoperfusion. In the 2014 American College of Obstetricians and Gynecologists' Task Force report on neonatal encephalopathy and neurologic outcome, cystic PVL was associated with cerebral palsy, visual impairment, and intellectual impairment which were all observed in our case [13].

Identification of the underlying cause of fetal SDH is essential in planning its management, which includes observation and monitoring, antenatal treatment, delivery, or termination of pregnancy [2, 14]. Termination of pregnancy might be preferred by some women given the possible adverse neurodevelopmental outcomes; however, the lack of a strong correlation between ultrasonographic findings and the prognosis of fetal SDH further increases the complexity of the decision [2].

A strength of our case report is that it is the first case report of warfarin-associated fetal SDH with long-term follow-up. However, a potential limitation is that given the early PVL changes, it is possible that there were signs or symptoms that were missed prior to the mother's presentation to the emergency room, especially that she had missed follow-up appointments just prior to the event.

In conclusion, pregnant women receiving warfarin are at an increased risk of fetal bleeding which is associated with significant morbidity and mortality. Therefore, counseling regarding the risks and benefits of warfarin use during pregnancy is of utmost importance. Finally, regular follow-up with fetal sonography and strict control of warfarin dosing with INR monitoring are essential measures to prevent intrauterine fetal complications.

Statement of Ethics

This case report was approved by the Medical Research Center, Hamad Medical Corporation, MRC-04-22-454. Written informed consent was obtained from the mother for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ibrahim Safra collected the case report data, obtained consent from mother, and contributed to manuscript writing. Shaikha Alnaimi performed literature review, wrote the manuscript, and submitted it for publication. Ashraf Gad reviewed and edited the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of patient but are available from the corresponding author [SJA].

References

1 Ghi T, Simonazzi G, Perolo A, Savelli L, Sandri F, Bernardi B, et al. Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. Ultrasound Obstet Gynecol. 2003 Aug;22(2):121–30.

2 Cheung KW, Tan LN, Seto MTY, Moholkar S, Masson G, Kilby MD. Prenatal diagnosis, management, and outcome of fetal subdural haematoma: a case report and systematic review. Fetal Diagn Ther. 2019;46(5):285–95.

3 Meagher SE, Walker SP, Choong S. Mid-trimester fetal subdural hemorrhage: prenatal diagnosis. Ultrasound Obstet Gynecol. 2002 Sep;20(3):296–8.

4 Lee HC, Cho SY, Lee HJ, Kim CJ, Park JS, Chi JG. Warfarin-associated fetal intracranial hemorrhage: a case report. J Korean Med Sci. 2003 Oct;18(5):764–7.

5 Fujiwara K, Aoki S, Kurasawa K, Okuda M, Takahashi T, Hirahara F. Warfarin-associated fetal intracranial subdural hematoma: a case report. Clin Case Rep. 2014 Jun; 2(3):108–11.

6 Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018 Nov 27;2(22):3317–59.

7 Writing Committee Members; Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, et al. 2020 ACC/AHA guideline for the management of patients with Valvular Heart disease: a report of the American College of cardiology/American heart association joint committee on clinical practice guidelines. J Am Coll Cardiol. 2021 Feb 2;77(4):e25–197.

8 Takashima S, Tanaka K. Development of cerebrovascular architecture and its relationship to periventricular leukomalacia. Arch Neurol. 1978;35(1):11–6.

9 Sarkar S, Shankaran S, Barks J, Do BT, Laptook AR, Das A, et al. Eunice kennedy shriver national institute of child health and human development neonatal Research network. Outcome of Preterm infants with transient cystic periventricular leukomalacia on serial cranial imaging up to term equivalent age. J Pediatr. 2018 Apr;195:59–65.e3.

10 Nardelli J, Thieme M, Coates R. Brain injury in neonates with hypoxic-ischemic encephalopathy: correlation of MRI findings with neurodevelopmental outcome. Pediatr Neurol. 1999.

11 Mulkey SB, du Plessis AJ. The immature autonomic nervous system, hemodynamic regulation, and brain injury in the Preterm neonate. Hemodynamics and cardiology: neonatology questions and controversies. 2018 Jun 27:111.

12 Vergani P, Strobelt N, Locatelli A, Paterlini G, Tagliabue P, Parravicini E, et al. Clinical significance of fetal intracranial hemorrhage. Am J Obstet Gynecol. 1996 Sep;175(3 Pt 1): 536–43.

13 Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on neonatal encephalopathy. Obstet Gynecol 2014; 123:896.

14 Sherer DM, Anyaegbunam A, Onyeije C. Antepartum fetal intracranial hemorrhage, predisposing factors and prenatal sonography: a review. Am J Perinatol. 1998;15(7):431–41.