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Briefly Legal: Delays in Intervention for a Spontaneous Arterial Thrombus Causes Limb Loss

Maureen E. Sims, MD; Barry Schifrin, MD

A 37-year-old G3 P0 presented to a small community hospital at 37 weeks gestation for an elective cesarean section due to cholestasis of pregnancy with bile acid levels close to 100 micromol/L. Except for the complaints of itching and the elevated bile acid values, the pregnancy, including antepartum testing, had all been normal. At delivery, the 3100-gram appropriately grown female infant received Apgar scores of 8 and 8 at 1 and 5 minutes, respectively. After cleaning, stabilization, and the intramuscular injection of vitamin K into the left anterior thigh, the baby was brought to the mother for breastfeeding. The baby showed severe irritability when placed on the breast, with an abnormal cry and a high pain score. She became dusky with obviously diminished tone in the left lower extremity. The baby was quickly placed on a warmer and given blow-by oxygen. The neonatologist was called; on examination, she encountered a dusky infant with a piercing cry and a mottled left leg with obvious bruising at the site of the earlier vitamin K injection. The left femoral pulse was normal, but the left popliteal pulse was diminished.

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The baby was admitted to the Newborn Intensive Care Unit, where the physical exam had the following: HR: 163 bpm, RR 85 bpm. The BP was normal, but the pulse oxygen saturation was only 70% on 100% inspired oxygen. The remainder of the exam was unremarkable.

A complete blood count revealed a hematocrit of 50%, a white blood count of 15.6 10^3/UL with an IT ratio of 0.327, and a platelet count of 208 10^3/ml. A capillary blood gas 1 hour of life revealed a pH of 7.13, a pC02 of 59 mmHg, a p02 of 30 mmHg, and a base excess of-11.2. A chest radiograph was normal. Prostaglandins were briefly administered while awaiting a cardiac ultrasound (which was normal). A radiograph of the left lower extremity was also found to be normal. A Doppler ultrasound of the leg showed no blood flow below the iliac artery. The baby was intubated after failing to maintain sufficient oxygenation on continuous positive airway pressure (CPAP) of +6cm H20. Four hours after birth, the neonatologist arranged for transport to a higher level of care, which, nevertheless, could not provide proper care for the obvious problem involving the blood supply to the affected leg. The transport team arrived 2 hours after the referral call (6 hours after birth).

At the referral hospital, only a faint femoral pulse was detectable in the left lower extremity; the entire left leg was mottled and had a slow capillary refill of 5 seconds. During the baby's 6-hour sojourn at this facility, various pediatrics, vascular and orthopedic surgery, and radiology specialists were consulted. However, none felt equipped to provide care and recommended that the patient be referred to the regional Children's Hospital, where a pediatric vascular surgeon would be available. The call to the children's hospital was made five and a half hours after admission. During the observation period, the leg became cold to touch, a deeper purple capillary refill was further delayed to 10 seconds, and the femoral pulse disappeared. Six hours after arriving at this facility, a helicopter transported the affected child to a children's hospital.

On arrival at the children's hospital, the baby required high-frequency oscillatory ventilation and inhaled nitric oxide because of the development of profound hypoxemic respiratory failure. She also needed dopamine and hydrocortisone for blood pressure support. Nitroglycerin paste was applied to the leg while various consultants evaluated her condition. Studies showed no Doppler flow in the leg; a magnetic resonance angiogram (MRA)_showed a thrombus in the left iliac and femoral arteries completely occluding the vessels. Recalculation procedures were found to not be possible due to the small size of the vessels. Intervention cardiology placed a catheter into the right common femoral artery traversing the patent foramen ovale and infused a thrombolytic agent, tissue plasminogen activator (t Pa, Steeplechase) and heparin in an attempt to lyse the clot. The efforts to save the leg proved futile, and a below-the-knee amputation was performed four days after admission. Extensive hematological and clotting evaluations of the baby and parents were unremarkable. The placenta was not examined. The deposition testimony of the nurse who administered the vitamin K did not reveal any circumstance or action that was considered remarkable.

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In addition, the neonatologist of the first referral hospital was sued for negligently accepting the transfer of a baby with a known ischemic leg without the resources to treat such a condition properly. Indeed, the parents consented to the transport to the first referral hospital only after they were told that a team would be waiting there to take care of their daughter upon arrival. The experts retained by the plaintiff maintained that the delays from the birth hospital cost the baby to lose her leg. The parties settled without going to trial.

As an incidental detail, the hospital the infant was initially referred to had a financial arrangement with a small community hospital.

Discussion:

Intrahepatic cholestasis of pregnancy:

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and elevated serum bile acid concentrations, typically developing in the late second or third trimester and rapidly resolving after delivery. In the United States, the incidence ranges from 0.32-5.6%. The etiology of ICP is not completely understood but likely involves a combination of genetic susceptibility, hormonal factors, and environmental factors. Transplacental gradients facilitate the fetal clearance of bile acids in normal pregnancies but are reversed in cholestatic pregnancies, which causes the accumulation of bile acids in the fetus and amniotic fluid. The accumulation of bile acids in the fetus and amniotic fluid carries a risk of fetal demise, preterm birth, meconium-stained amniotic fluid, and respiratory distress syndrome (which appears to be associated with bile acids entering the lungs). Speculation of cause for fetal death may be related to the sudden development of fetal arrhythmia or vasospasm of the placenta chorionic surface vessels induced by high levels of bile acids. Although pruritis is bothersome, ICP is not associated with other serious maternal sequelae. There are several approaches to the timing of delivery in such patients. Some favor early delivery to reduce the risk of fetal demise, especially with high bile acid levels. American Colleges of Obstetrics and Gynecology published in 2021, # 831 for patients with ICP: 1) if total bile acid levels <100 micromol/L, delivery is recommended at 36 0/7 to 39 0/7 weeks' gestation, or at diagnosis if diagnosed at >39 0/7 weeks). if total bile acid levels ≥100 micromol/L, delivery is recommended at 36 0/7 weeks or at diagnosis.

In the case discussed above, the care providers considered numerous etiological pathways connecting the ICP with the thrombus, but none were compelling. The relationship between the thrombus and the injection of Vitamin K was explored at length. No details other than the bruising at the site were documented.

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The questions about the etiology of the thrombus notwithstanding, it was generally conceded that the unconscionable delays beginning in the birthing hospital and continuing in the first referral center were directly responsible for the ultimate loss of the child's leg. Indeed, 15 hours elapsed between detecting the ischemic leg and the baby's arrival at the children's hospital.

Thrombosis in Neonates:

General:

Neonates, particularly those critically ill, have a significant risk of developing thrombosis.

The neonatal coagulation profile represents a prothrombotic state compared to children and adults. Neonates have decreased concentrations of procoagulant proteins, naturally occurring anticoagulants, and hemostatic control proteins. This prothrombotic state protects from excessive bleeding during birth but at the expense of an increased risk for thromboembolism. Although evolving, the hemostatic system in healthy fetuses and infants must be physiologic. In the face of various conditions, this balance is disrupted.

Risk factors implicated in the development of neonatal thrombosis	
Maternal-Fetal risk factors:	
	Pre-eclampsia, autoimmune disorders, oligohydramnios, twin-to-twin transfusion, drug abuse (cocaine), and infertility and its treatment
Intrapartum risk factors:	
	Difficult deliveries (especially assisted by instrumentation), emergency cesarean sections, fetal heart rate abnormalities, and asphyxia
Neonatal risk factors:	
	Intravascular catheters, infection, congenital heart disease, polycythemia, extracorporeal membrane oxygenation, dehydration, and hypoglycemia

Inherited or acquired prothrombotic conditions:

Rare, including factor V Leiden and prothrombin gene mutation; deficiencies of protein C, protein S, and antithrombin; elevated factor VIII, lipoprotein (a) and homocysteine; and antiphospholipid antibodies. In determining the etiology of a neonatal thrombus, the physiologic levels of many coagulation proteins in neonates are low, thereby inviting the diagnosis of some inherited and acquired hemostatic problems.

Over the last 30 years, the incidence of thromboembolic issues, especially for premature babies, have increased, with ranges reported up to 5.1 per 100,00 live births and 2.4 per 1000 NICU admissions, with 45% to 55% of these events affecting preterm infants. In a prospective Canadian registry study, 61% of thromboembolism cases were venous, 31% were arterial thrombotic events, and 4% had both venous and arterial thrombosis.

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Neonatal Arterial Thrombosis:

Iatrogenic thrombosis:

Umbilical arterial catheters:

An indwelling arterial catheter causes most cases of arterial thrombosis in the newborn infant. Umbilical artery catheters (UAC) remain the basic means of arterial sampling and blood

pressure monitoring in critically ill neonates. The most common visible problem from a UAC is blanching or cyanosis of part or all of a distal extremity or the buttock area. This complication may be reduced by high placement, with the catheter tip at the level of T7 or T8, as opposed to lower placement at L3 or L4 just above the aortic bifurcation. Small amounts of heparin added to the continuous infusion appear to reduce the risk of arterial thrombi. Hypertension can result if a renal artery is involved.

A thrombus can form when the catheter tip causes mechanical injury to the vascular endothelium exposing subendothelial tissue and collagen to circulating blood, causing adherence and aggregation of platelets, thereby releasing adenosine diphosphate (ADP) and thromboxane A2 (a platelet stimulator and potent vasoconstrictor). Initially, vasospasm occurs around the catheter, then vessel occlusion, tissue ischemia, and clot formation.

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The UAC should be securely anchored to avoid any movement of the catheter to keep it in the intended place, avoiding or minimally creating mechanical injury to the intima of the aorta and the development of thrombi. The position of the catheter should be documented and regularly checked to ensure that it does not move. Multiple attempts to insert a UAC also create arterial intima harm, which is a perfect nidus for thrombus development and should be avoided. If the sterile field is broken after the UAC has been placed, the catheter should never be advanced to avoid inserting organisms into the vessel and avoiding endothelial injury. Once the catheter is removed, another should not be inserted. Studies have shown that UACs in place for even one day are associated with a 16% incidence of aortic thrombosis, with an incidence of 32% at seven days.

Most UAC-associated thromboses are asymptomatic, and 50% disappear by discharge. Long-term consequences of UAC-associated thromboembolisms have been linked to mesenteric ischemia, hypertension, renal dysfunction, sepsis, loss of an extremity, and death. In long-term follow-up studies, leg length discrepancy has been found. The potential short and long-term morbidities underscore the need to use UACs only when indicated, to monitor their placement carefully, and to remove them timely. Optimally, umbilical artery catheters should not be left in place for >5 days.

Peripheral arterial line (PAL):

The radial artery is the primary site for the cannulation of a peripheral artery. The overall risk of ischemic injury to this site is approximately 5%. Because of the potential risk of ischemic injury to the entire hand or arm, the most distal location of the radial artery is generally the preferred site, and only if insertion is unsuccessful should alternative sites be tried. The posterior tibial artery is a reasonable alternative to the radial artery and has been shown to be viable when inserted under ultrasound guidance. The ulnar, brachial, and axillary arteries are used infrequently because of the risk of harm. Proper care requires the demonstration of collateral circulation in the hand by the Allen Test before the radial artery is catheterized. Further, monitoring the tips of the fingers for signs of vascular compromise is crucial. Documentation by the nurses in the medical record needs to be done hourly, and the physician needs to be called immediately if blanching, duskiness, or any evidence of decreased perfusion occurs.

Rescuing ischemic tissue - Catheter removal is the first step:

When the clinician faces a neonate with any evidence of ischemia in an extremity, digit or of any anatomical ischemic region, the catheter must be removed immediately. If skin color and pulse do not return, this is a medical emergency, and consultation and referral immediately to a facility with the complete resources to evaluate and treat the patient, potentially with anticoagulation, thrombolysis, or clot removal. There is much truth in the adage that "Time = tissue."

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Other treatments may include 2% nitroglycerin as a topical ointment when vasospasm is suspected while waiting for the various consults to provide input or while transporting to a specialized center. Nitroglycerin may directly affect vascular smooth muscle producing arterial and venous dilatation. Acute vascular dilatation relieves vasospasm permitting blood flow around the microthrombi, thereby improving collateral circulation to the affected areas.

Indeed, occasional success has come from placing the ointment on a contralateral area resulting in increased blood flow to the ischemic area.

Perinatal Arterial Ischemic Stroke (PAIS):

The risk of stroke is highest during the perinatal period. The incidence of PAIS ranges from 17.8/100,000 to 35/100,000. The incidence estimates have increased over time, but whether this is due to a true increase or improved detection is unclear. PAIS represents 71% of all perinatal strokes and has a male predominance. While multiple pathophysiological mechanisms have been suggested, Martinez-Biarge, Gomez, and their colleagues have underscored common intrapartum risk factors for HIE and PAIS. Thrombophilia is an uncommon finding in these patients. A popular medico-legal theory suggests that the thrombi from the placental circulation pass through the patent foramen ovale to the cerebral arterial vasculature. This theory still requires validation.

PAIS affects both preterm and term infants, mainly occurring in the left hemisphere with the middle cerebral artery distribution. Maternal factors linked to PAIS include pre-eclampsia, premature prolonged rupture of membranes, prolonged 2nd stage of labor, difficult deliveries, especially those involving instrumentation, fetal distress, and asphyxia. Factors linked to PAIS after birth include

the need for resuscitation with 5-minute Apgar <7, hypoglycemia, congenital heart disease, and infection. The babies often present with seizures, but other neurological symptoms of lethargy, hypotonia, apnea, and feeding difficulties have been identified. The management of the infant with NAIS should begin with careful attention to fluid, electrolyte, and glucose status and supportive measures related to cardiorespiratory function and prompt treatment of seizures. Thrombolytic therapy is not a practical consideration because the initiating lesion's timing is generally unknown and is generally many hours before diagnosis.

It is essential to understand that PAIS may not induce immediate signs and symptoms in neonates but manifest problems weeks to months after birth. This has been termed "Presumed perinatal stroke."

Spontaneous Arterial Thrombosis:

Spontaneous arterial thromboses are rare. Timely assessment of the location and extent of the thrombus and evaluation for a prothrombotic disorder is necessary. A referral center with a full complement of resources is essential. Treatment depends on the findings similar to the approach with catheter-related ischemia.

Neonatal Venous Thrombosis:

Central venous catheter-related thrombosis:

Umbilical venous catheters (UVC) and peripherally inserted central catheters (PICC) are routinely used in the NICU. Occlusion and infection remain the most commonly encountered problems. Clinical manifestations may include catheter dysfunction, limb, face or chest, or groin swelling, discoloration of the skin and/or distension of the superficial veins, persistent chylous effusion, pleural effusion, and superior vena cava syndrome. Sometimes the baby is asymptomatic, and the thrombus is only incidentally identified. For thrombosis involving the upper central venous system (proximal subclavian vein, brachiocephalic vein, superior vena cava), Doppler ultrasound has low sensitivity; magnetic resonance, computed tomography or conventional venography or echocardiography may be required to make the diagnosis in this location. Intervention depends on the location and extent of the resulting pathology. Studies have found that 20% of babies with UVCs have thrombus formation in the inferior vena cava or portal vein. Twenty to 65% have evidence of thromboembolism on autopsy. The Centers for Disease Control and Prevention currently recommend that the use of UVCs be limited to 14 days. Long-term complications of venous thromboembolism include chronic venous obstruction, chylothorax, portal hypertension, and post-thrombotic syndrome.

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Suspicion or confirmation of a venous thrombus warrants prompt catheter removal due to the risk of emboli. However, based on limited data, some have advocated delaying the removal after 3 to 5 days of anticoagulant therapy. No clinical evidence at this point supports this practice in neonates. Management of venous thromboembolism in the newborn period varies depending on the location and extent of the thrombus and the risk for acute embolic complications and later vascular compromise. Therapeutic decisions are guided by practitioners' experience, published case reports and case series, several large registries, and extrapolation from the results of clinical trials in adults with thromboembolic disease. Whether management includes expectant (observation) or intervention with anticoagulants, thrombolytics, or surgical removal of a clot, the baby needs to be at a center with the full array of resources for diagnosis and potential interventions. Multicenter, prospective, controlled clinical trials in this important patient population are needed to provide evidence-based data to inform optimal management.

Neonatal Portal Vein Thrombosis:

"Whether management includes expectant (observation) or intervention with anticoagulants, thrombolytics, or surgical removal of a clot, the baby needs to be at a center with the full array of resources for diagnosis and potential interventions."

Neonatal portal vein thrombosis (PVT) is an under-recognized thrombotic event that is most commonly encountered in association with UVC placement, especially mal-positioned catheters (low or intrahepatic), and prolonged catheterization. The reported incidence of UVC-related PVT is highly variable, ranging from 1.3% to 43%. A large, single-center retrospective study reported an estimated incidence of at least 3.6 per 1000 NICU admissions. Besides malposition of the UVC, other risk factors include transfusion through the UVC and patient-related factors, including low birth weight, low-flow state, hypoxia, infection, sepsis, congenital malformations, and gestational diabetes mellitus. Portal vein thrombosis is often associated with subtle, nonspecific, or absent clinical and laboratory signs. Unexplained thrombocytopenia may be an initial manifestation. Diagnosis is usually established by Doppler ultrasound. Management is similar to DVT with any central venous line, although it is unclear if anticoagulation improves outcome. Long-term complications of PVT include portal hypertension and hepatic lobar atrophy, which is usually asymptomatic. As such, PVT is the primary cause of childhood extrahepatic portal hypertension and gastrointestinal bleeding.

Neonatal Renal Vein Thrombosis:

Neonatal renal vein thrombosis (RVT) is the most prevalent non-catheter-related thrombotic event during the neonatal period, accounting for up to 20% of all thrombotic events in newborns. Risk factors include a history of perinatal asphyxia, gestational diabetes mellitus, prematurity, dehydration, infection, and congenital heart disease. Involvement of renal veins may also be seen in the context of central venous line-related thrombosis of the inferior vena cava. Males are more commonly affected than females, representing 67.2% of cases. Approximately 70% of neonatal RVT cases are unilateral, with a left-sided predominance. Most neonates with RVT will manifest one or more of the three cardinal clinical features of macroscopic (or microscopic) hematuria, palpable flank mass, and thrombocytopenia. Doppler ultrasonography confirms the diagnosis. Acute complications of RVT include adrenal hemorrhage and distant embolization. Long-term complications include chronic renal insufficiency and hypertension.

Cerebral Sinovenous Thrombosis (CSVT):

Cerebral sinovenous thrombosis accounts for 20% of neonatal strokes and is more common than previously expected in the era before MR imaging. Pre-eclampsia, which involves a hypercoagulable state, is a common maternal risk factor. Other maternal factors include gestational diabetes and chorioamnionitis. Peripartum complications include hypoxia, acidosis, meconium-stained fluid, and the need for newborn resuscitation. In a report of 52 well-studied neonates with CSVT from the Netherlands, 60% experienced a complicated delivery, including vacuum or forceps delivery. This finding underscores the possibility that pressure on the cranium during delivery creates venous sinus obstruction: congenital heart disease, dehydration, sepsis/meningitis. Seizures are often the presenting sign, with the onset usually in the first 48 hours after birth. Lethargy, poor feeding, apnea, hypotonia, irritability, or respiratory distress may precede the seizures. The acute therapy of CSVT is similar to that noted for NAIS, namely careful attention to fluid, electrolyte, and glucose status and supportive measures related to cardiorespiratory function and prompt treatment of seizures. Thrombolytic therapy is not a practical consideration because the initiating lesion's timing is generally unknown and is generally many hours before diagnosis. In CSVT, such comorbidities as sepsis, meningitis, and dehydration require exceptionally prompt treatment.

Intracardiac Thrombosis:

Intracardiac thrombosis is associated with central venous lines placed incorrectly into the right atrium instead of at the junction of the right atrium with the superior or inferior vena cava. Not only does a catheter in this position carry the risk of perforation of the right atrium, which is wet-paper thin, but intracardiac thrombi may form. This is a life-threatening condition due to the risk of dissemination of emboli into the lungs or obstruction of the right pulmonary artery. Neonates with congenital heart disease, especially those undergoing cardiac surgery, are at high risk for thrombosis. Blood flow disturbances due to hypoplastic ventricles with limited inflow/outflow, dilated atria, arterial or femoral venous catheters, and surgically placed shunts create an environment conducive to thrombus formation. Other risk factors include cardiac surgery with platelet dysfunction/activation, inflammation, and blood hypercoagulability.

Conclusion:

Some avenues exist for clinicians to minimize the risk and prevent arterial or venous thromboses in several situations. Antenatal management of pre-eclampsia and twin pregnancies to optimize fetal well-being, avoidance of hypoxia, and mechanical trauma will likely minimize the risk or potentially avoid the problem.

Better outcomes beget less need for invasive procedures that appear to increase the risk of thrombosis. When catheterization is deemed necessary, they should be inserted using impeccable technique, carefully monitoring the insertion depth, observing for early signs of tissue compromise (ischemia, swelling, or organ involvement), and timely removal will likely reduce the risk of complications. Once a thrombus (ischemia) is suspected, it must be considered a medical emergency, and timely recruitment of experienced resources capable of dealing with the problem is required. Every neonatology service must have already identified such services.

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Suggested reading:

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Corresponding Author:

Maureen E. Sims, M.D.
Professor of Pediatrics
Geffen School of Medicine,
University of California, Los Angeles
Los Angeles, California
email: mes@g.ucla.edu

Barry Schifrin, M.D,
Western University of Health Sciences, Pomona, California
Formerly, Professor of Obstetrics & Gynecology
Keck School of Medicine, University of Southern California
Los Angeles, California