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Effect of Hypoxia and Acidosis on Fetal Outcomes

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Abstract:

Hypoxia is a normal and essential part of embryonic development. However, this state may leave the embryo vulnerable to damage when oxygen supply is disturbed. Embryofetal response to hypoxia is dependent on duration and depth of hypoxia, as well as developmental stage. Early postimplantation rat embryos were resilient to hypoxia, with many surviving up to 1.5 hr of uterine clamping, while most mid-gestation embryos were dead after 1 hour of clamping. Survivors were small and many had a range of defects, principally terminal transverse limb reduction defects. Similar patterns of malformations occurred when embryonic hypoxia was induced by maternal hypoxia, interruption of uteroplacental flow, or perfusion and embryonic bradycardia. There is good evidence that high altitude pregnancies are associated with smaller babies and increased risk of some malformations, but these results are complicated by increased risk of pre-eclampsia. Early onset pre-eclampsia itself is associated with small for dates and increased risk of atrio-ventricular septal defects. Limb defects have clearly been associated with chorionic villus sampling, cocaine, and misoprostol use. Similar defects are also observed with increased frequency among fetuses who are homozygous for thalassemia. Drugs that block the potassium current, whether as the prime site of action or as a side effect, are highly teratogenic in experimental animals. They induce embryonic bradycardia, hypoxia, hemorrhage, and blisters, leading to transverse limb defects as well as craniofacial and cardiovascular defects. While evidence linking these drugs to birth defects in humans is not compelling, the reason may be methodological rather than biological.

Keywords: Hypoxia, Acidosis, Fetal Outcomes

Introduction:

Perinatal asphyxia is caused by a lack of oxygen to organ systems due to a hypoxic or ischemic insult that occurs within close temporal proximity to labor (peripartum) and delivery (intrapartum). In the neonate, the lack of oxygen may lead to multi-organ failure with brain involvement as the major organ of concern (hypoxic-ischemic encephalopathy [HIE]). In most cases of HIE, injury to other major organ systems occurs, including the heart, kidney, lung, and liver [1].

The American College of Obstetricians and Gynecologists published an executive summary that outlines neonatal signs and contributing factors used to establish acute hypoxic-ischemic events in term and late preterm infants (gestational age [GA] ≥ 35 weeks) that would likely result in hypoxic-ischemic encephalopathy (HIE). Neonatal signs consistent with an acute perinatal hypoxic-ischemic event include: [2].

- 1) Apgar score of <5 at 5 minutes and 10 minutes
- 2) Fetal umbilical artery pH <7.0 , or base deficit ≥ 12 mmol/L, or both
- 3) Brain injury seen on brain magnetic resonance imaging (MRI) or MR spectroscopy consistent with acute hypoxia-ischemia
- 4) Presence of multisystem organ failure consistent with hypoxic-ischemic encephalopathy (HIE) [2].

Contributing factors (type and timing) consistent with an acute perinatal event include:

- A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery, such as ruptured uterus or severe abruptio placentae [3].
- Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event (eg, conversion of category I fetal heart rate [normal pattern] to a category III pattern [absent variability with recurrent late or variable decelerations or bradycardia or sinusoidal pattern]) [4]
- The timing and type of brain injury patterns based on imaging studies that are typical of hypoxic-ischemic injury in the term and late preterm newborn. [5]
- No evidence of other proximal or distal factors that could be contributing to encephalopathy [6].

EPIDEMIOLOGY:

The incidence of perinatal asphyxia depends on the definition used, the ability to accurately make the diagnosis, and the quality of obstetrical care. In a Swiss study that recoded 622 clinically diagnosed cases of intrauterine or birth asphyxia based on ICD-10 codes (mean gestational age [GA] 37 5/7 weeks), the incidence of perinatal asphyxia (defined as fulfilling three of the following criteria: five-minute Apgar score ≤ 5 , pH ≤ 7 , base deficit ≥ 16 mmol/L, or lactate ≥ 12 mmol/L) ranged from 5 to 8 per 1000 live births over the study period of time from 2004 to 2014. The incidence of hypoxic-ischemic encephalopathy (HIE) was approximately 1 per 1000 live births. The risk of perinatal asphyxia is higher in resource-limited countries and is one of the main causes of infant mortality and morbidity [7]

Clinical Manifestations of Initial Perinatal Asphyxia Insult:

Data regarding the direct effects of perinatal asphyxia on major organ systems are limited and based on observations of infants with hypoxic-ischemic encephalopathy (HIE) prior to the routine use of hypothermia. In most infants with moderate to severe HIE, there is evidence of dysfunction in at least one other organ system. However, systemic effects of perinatal asphyxia may be present even in the absence of encephalopathy [8].

The brain is the major organ of concern following a perinatal hypoxic-ischemic event. Hypoxia-ischemia initially causes energy failure and loss of mitochondrial function. This is accompanied by membrane depolarization, brain edema, an increase of neurotransmitter release and inhibition of uptake, and an increase of intracellular calcium that sets off additional pathologic cascades. These include oxidative stress, with the production of reactive oxygen species and interaction with nitric oxide pathway to produce reactive nitrogen species and finally cellular injury and death [9].

Respiratory findings:

Although severe respiratory insufficiency is frequently seen in infants with severe perinatal asphyxia, it is commonly the result of an underlying or concomitant disorder such as sepsis, pneumonia, or meconium aspiration syndrome (MAS). However, perinatal asphyxia is associated with persistent pulmonary hypertension of the newborn (PPHN), which occurs when pulmonary vascular resistance (PVR) remains elevated after birth, resulting in right-to-left (R to L) shunting of blood through the fetal circulatory pathways that leads to hypoxia [10].

Following perinatal asphyxia, apnea or hypoventilation may occur due to HIE and seizures. In severe cases, death may occur with terminal apnea if the infant is not successfully resuscitated. A chest radiograph, pulse oximetry, and capillary blood gases are generally sufficient to assess the pulmonary status of the infant with perinatal asphyxia and to determine underlying etiologies for respiratory distress (eg, pneumonia, MAS, pulmonary congestion, and PPHN). However, echocardiography may be helpful in making the diagnosis of PPHN. Infants with respiratory failure require intubation and mechanical ventilation during the first hours of life [11].

Cardiovascular manifestations:

After a significant hypoxic-ischemic insult, reduced cardiac output and hypotension are commonly observed due to impaired myocardial contractility secondary to myocardial ischemia. The ischemic effects on the cardiovascular system are detected by blood pressure measurement (hypotension) and assessment of myocardial function: [12].

- Functional cardiac echocardiography is useful in demonstrating ventricular dysfunction due to myocardial ischemia. Echocardiography can also identify infants with PPHN, which is

associated with perinatal asphyxia, and can also assess volume status to guide volume therapy to restore blood pressure and avoid fluid overload [13].

- ECG changes demonstrating myocardial ischemia may include ST depression and T-wave inversion [14].

Cardiac markers are used to assess myocardial damage, but they are not specific to injury caused by perinatal asphyxia.

- Cardiac troponins as a marker of myocardial injury appear in the blood two to four hours after perinatal asphyxia. They remain detectable for up to 21 days. [15].
- Creatine kinase-MB (CK-MB) levels are elevated in newborns after perinatal asphyxia, but this elevation is not specific for only cardiac injury due to perinatal asphyxia [16].
- Serum B-type natriuretic peptide (BNP) is used as a biomarker in the diagnosis and management of pulmonary hypertension (PH), and changes in BNP levels have been used to monitor treatment of PPHN [17].

Renal manifestations:

Oliguria as a manifestation of kidney dysfunction is common after perinatal asphyxia. It is due to either reduced cardiac output or acute kidney injury secondary to tubular necrosis. Impaired kidney function is detected by an elevation in serum creatinine (SCr). Serial measurements of SCr and electrolytes and ongoing accurate monitoring of urine output are required to assess and follow the effect of asphyxia on renal function. Depending on the degree of kidney impairment further management, including adjusting fluid and electrolyte management and drug dosing for medications that are renally excreted [13].

Hepatic findings:

Elevation of liver enzymes defined as serum alanine transaminase level >100 units/L is common in infants with perinatal asphyxia. Decreased liver function may contribute to hyperbilirubinemia, hypoalbuminemia, reduced production of coagulation factors, and affect pharmacokinetics of drugs that rely on hepatic metabolism or biliary excretion [8].

Gastrointestinal tract effects:

Due to the redistribution of blood flow away from the splanchnic circulation to vital organs such as the brain. Therefore, either no or only minimal enteral feeding is provided to infants with perinatal asphyxia, particularly during therapeutic hypothermia. In addition, perinatal asphyxia carries an increased risk of necrotizing enterocolitis in the term and near-term infants [18].

Hematologic manifestations:

● **Impaired coagulation and thrombocytopenia** are common after a severe asphyxial event due to several factors:

- Disseminated intravascular coagulation occurs after perinatal asphyxia resulting in ongoing consumption of clotting factors and platelets
- Bone marrow suppression contributing to thrombocytopenia.
- Impaired hepatic production of clotting factors due to hepatic injury.

Perinatal asphyxia has also been reported to be associated with increases in bleeding time and endothelial dysfunction [19].

● **Acute blood loss:** Severe antenatal or peripartum/intrapartum blood loss due to hemolysis, massive feto-maternal transfusion, or blood loss during placental abruption may be the cause of perinatal asphyxia. Severe anemia at birth needs immediate treatment [20].

Glucose metabolism: In neonates with perinatal asphyxia, there is an initial stress-induced hyperglycemia that is followed by a sharp drop in blood glucose levels due to increased glucose consumption. Hypoglycemia is also more common in infants with severe liver damage due to inadequate glycolysis.

INITIAL STEPS Of Clinical stabilization:

Goal: The goal of a concurrent initial evaluation during stabilization is to determine the presence and extent of end-organ damage, identify a possible etiology or concomitant condition that require specific therapy, the need for therapeutic hypothermia, and to obtain a baseline to compare changes in organ function over time.

General assessment: General assessment consists of an evaluation of the neonate's respiratory status (evidence of respiratory distress [labored breathing/tachypnea] and need for respiratory support), cardiac status (eg, hypotension or need for inotropic blood pressure support), neurologic status (hypotonia and the presence of seizures), and basic laboratory evaluation. Urinary output is also monitored [21].

Basic laboratory tests include:

● **Blood gas analysis:** Arterial or venous blood gases are obtained to assess gas exchange (oxygenation and ventilation) and acid-base disturbances. Indication for therapeutic hypothermia is based on a sample of umbilical cord blood or any blood obtained within the first hour after birth and after resuscitation with a pH of ≤ 7.0 or a base deficit of ≥ 16 mmol/L along with evidence of hypoxic-ischemic encephalopathy [22].

- **Complete blood count (CBC):** anemia may contribute to asphyxia, thrombocytopenia (increased risk of bleeding), and/or elevated white count (suggestive of infection). It has been suggested that elevated nucleated red blood cell (NRBC) counts in cord blood is a marker of fetal hypoxia and perinatal brain injury [23].
- **Glucose:** Infants with perinatal asphyxia are at-risk for abnormal glucose levels (hypoglycemia and hyperglycemia). [24].
- **Kidney function studies:** Initial testing for kidney function includes serum creatinine (SCr), BUN, and electrolytes to identify infants with acute kidney injury (decrease in glomerular filtration rate), which may result in electrolyte abnormalities due to renal dysfunction and fluid overload [25].
- **Liver function studies:** Initial hepatic testing includes measuring total and conjugated bilirubin, serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) [26].
- **Cardiac evaluation:** Electrocardiography is performed to detect myocardial ischemia.
- **Infectious disease evaluation:**
 - Blood and surface cultures are performed in all infants with perinatal asphyxia because serious infections (eg, sepsis) is a major complication.
 - C-reactive protein (CRP) is obtained, as an elevated level is a nonspecific marker for bacterial infection.
- **Cranial ultrasound:** Cranial ultrasound is performed to exclude subdural or intraventricular hemorrhage. Daily imaging with cranial ultrasound is performed after birth to detect ischemic lesions in particular to the deep grey matter, which may not be seen earlier than 24 hours after the insult [27].

Additional testing: Based on the clinical status of the infants and initial evaluation, additional testing may be performed:

- **Chest radiography:** For infants with respiratory distress, chest radiography is performed to identify other concomitant conditions (eg, pneumonia, meconium aspiration syndrome, pulmonary congestion, or persistent pulmonary hypertension of the newborn) [28].
- **Abdominal ultrasound:** For patients with severe anemia, abdominal ultrasound is performed to detect any evidence of hepatic injury or adrenal hemorrhage. In addition, for neonates with persistent thrombocytopenia, ultrasound evaluation of major vessels may be helpful in detecting an underlying thrombosis [29].

- Cardiac evaluation:** For infants with evidence of cardiac injury (hypotension, administration of inotropic drugs, or respiratory distress), functional cardiac echocardiography is performed, and cardiac troponins and serum B-type natriuretic peptide (BNP) are obtained [20].
- Coagulation studies:** For infants with evidence of multiorgan dysfunction with liver involvement or with massive bleeding, coagulation tests including PT (prothrombin time) and aPTT (activated partial thromboplastin time) are obtained [30].

Management:

Therapeutic hypothermia:

Therapeutic hypothermia is the only proven neuroprotection intervention for hypoxic-ischemic encephalopathy (HIE) and perinatal asphyxia in term and late preterm infants. It is initiated for infants with pH of ≤ 7 or a base deficit of ≥ 16 mmol/L. If hypothermia is not available at the birth center, it is imperative that infants who meet the criteria for hypothermia are transferred immediately, as hypothermia needs to be initiated within the first six hours after delivery. Because cooling needs to be started within the first six hours after delivery to be neuroprotective, it has clinical effects on all the other major organ systems. Reducing the body temperature to the therapeutic hypothermic range of 33 to 34°C from the optimal temperature of 37°C alters all organ function [31].

- Respiratory effects:** Smits et al. [32] States that partial pressure of carbon dioxide (pCO_2) decreases by 3 to 4 percent for every 1°C drop in temperature below 37°C. This is due to reduced CO_2 production as metabolism declines and increasing of CO_2 in blood as body temperature is lowered. In blood gas samples, there is a concomitant increase in pH with the lower pCO_2 . It remains uncertain what the optimal target ranges should be for pCO_2 and pH during therapeutic hypothermia. In their center, pCO_2 levels are set for 50 mmHg (6.7 kPa) to avoid hypocapnia.
- Cardiovascular effects:** Cardiac output falls due to a reduction in heart rate (sinus bradycardia) and stroke volume. However, there appears to be no significant change in the risk of hypotension due to the initial perinatal asphyxia. This is most likely due to peripheral vasoconstriction that occurs with cooling. A systematic review suggested that therapeutic hypothermia provides a cardioprotective effect [33].
- Coagulopathy and thrombocytopenia:** cooling is associated with an increased risk of thrombocytopenia. However, coagulopathy requiring intervention remains a common occurrence during therapeutic hypothermia so that ongoing monitoring of clotting factors (eg, plasma fibrinogen) and liver function is needed [34].
- Intestinal function:** Hypothermia does not appear to increase the risk of necrotizing enterocolitis and may provide potential benefit for preventing additional ischemic intestinal

injury. However, the mandatory administration of morphine for sedation/analgesia during therapeutic hypothermia may further reduce intestinal motility. As a result, full enteric feeding is avoided during therapeutic hypothermia, but "minimal enteral feeding" is provided [35].

Monitoring:

Clinical monitoring: in experienced neonatal intensive care units (NICUs) equipped to care for infants with perinatal asphyxia, including therapeutic hypothermia, routine monitoring at the bedside consists of (amplitude-integrated, continuous) electroencephalography (EEG or aEEG) and ongoing measurements of heart rate, blood pressure, respiratory rate, and oxygen saturation using pulse oximetry. In dedicated level III NICUs, near-infrared spectroscopy is also used to assess cerebral oxygenation. Blood gas analysis, glucose, and CBCs are obtained several times during the first three days after resuscitation and daily until therapeutic hypothermia is discontinued. For infants who do not qualify for therapeutic hypothermia, most abnormalities will have normalized by the third day. However, we continue to monitor these laboratory studies until values have returned to normal ranges, especially in infants who receive parenteral nutrition and/or have multiorgan failure [36].

- Daily testing includes SCr, total and conjugated bilirubin, liver enzyme studies (ALT and AST), and CRP. In addition, coagulation testing is monitored for infants who have multiorgan failure with liver involvement and massive bleeding. Daily cranial ultrasound is performed to assess the presence of hemorrhage or hypoxic-ischemia alterations [37].

Supportive care based on organ system:

Respiratory support: The goal of supportive care is to maintain adequate oxygenation and ventilation, especially during sedation needed for hypothermia, and avoid episodes of hyperoxia, hypoxia, hypercapnia, and hypocapnia. In their center, temperature-corrected target ranges of arterial partial pressure of oxygen (pO_2) are 60 to 80 mmHg (8 to 10.7 kPa) and for partial pressure of carbon dioxide (pCO_2) 35 to 45 mmHg (4.7 to 6 kPa). Most infants receiving therapeutic hypothermia will need intubation and mechanical ventilation for optimal respiratory support as the mandatory need for sedation (eg, with morphine) during cooling impairs the respiratory drive of the neonate. However, some patients may only require nasal continuous positive airway pressure (nCPAP) [10].

Cardiovascular support:

For infants with evidence of myocardial failure, inotropic agents may be used to support cardiac function. Sympathomimetic stimulation by catecholamine agents such as dobutamine and dopamine improves myocardial contractility and may have an additional beneficial effect on peripheral vascular beds [38].

Fluid and electrolyte management:

Infants with perinatal asphyxia are at-risk for fluid and electrolyte abnormalities due to acute kidney injury and the syndrome of inappropriate antidiuretic hormone (SIADH). Electrolyte levels should be maintained in the normal range during cooling by adjusting fluid therapy [39].

Nutrition:

Full enteral feeding is withheld during the period of therapeutic hypothermia, and "minimal enteral feeding" is only provided due to concern of reduced intestinal function and metabolism. Total parenteral nutrition (TPN) is used to provide adequate nutrition. The amount and composition of intravenous fluids may need to be adjusted based on changes in the monitored levels of electrolytes, triglycerides, and glucose. Clearance of intravenous lipids from TPN may be reduced due to hepatic impairment [40].

Hemostatic management:

- **Coagulation deficiency:** For infants with significant coagulation disorders (eg, severely prolonged aPTT and PT times) or overt bleeding, fresh frozen plasma is given to replace clotting factors that may be either consumed (disseminated intravascular coagulation) or below due to impaired hepatic function [41].
- **Thrombocytopenia:** platelets are transfused when the platelet count falls below 50,000/microL. However, new evidence suggest that a lower threshold of 20,000/microL may be used [42].
- **Acute blood loss:** Neonates with significant acute blood loss require immediate fluid resuscitation, but may not require a red blood cell (RBC) transfusion. Indications after volume resuscitation include >20 percent blood loss, 10 to 20 percent blood loss with evidence of inadequate oxygen delivery (eg, persistent acidosis), and/or ongoing hemorrhage [43].
- **Infectious disease management:** Because patients are at-risk for serious infection, empirical antibiotics are administered until culture results are known. Antibiotic dosing should be adjusted [44].
- **Renal management:** Small trials have reported that the administration of theophylline reduced or prevented acute kidney injury, but further studies are needed to test the safety and efficacy of this intervention especially during therapeutic hypothermia as renal clearance is significantly reduced. In rare cases, kidney replacement therapy may be needed [45].

Outcome:

The outcome of perinatal asphyxia is primarily based on the likelihood and extent of brain damage. Mortality and long-term development outcome for infants with perinatal asphyxia

have improved with the advent of therapeutic hypothermia. It remains uncertain whether therapeutic hypothermia has similar benefit for other organ systems (eg, heart, kidney, and liver) [46].

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