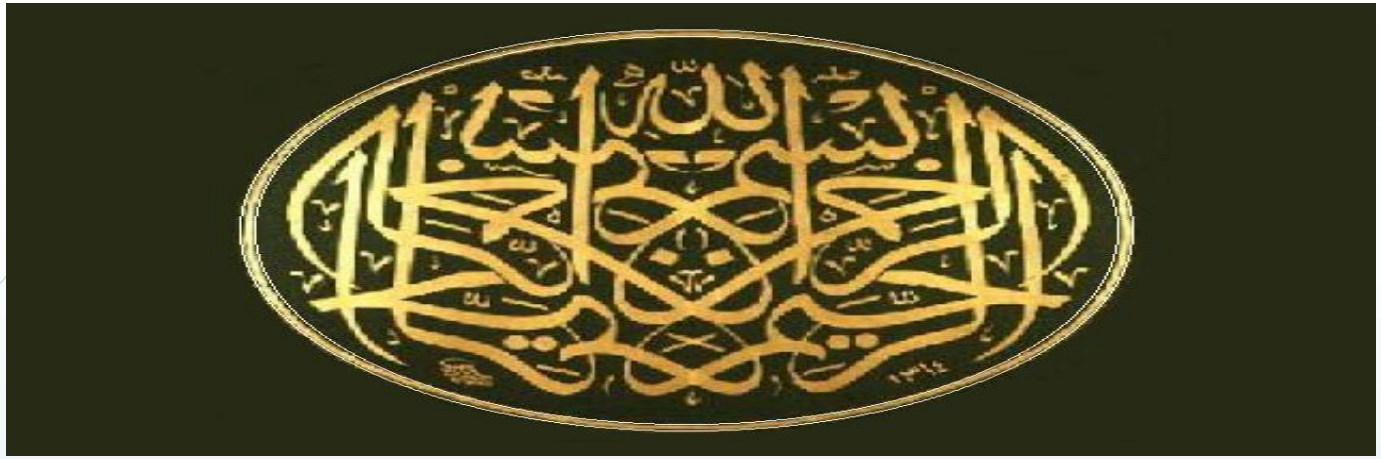

Multiorgan Dysfunction After Birth Asphyxia

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Birth asphyxia causes:

- hypoxic-ischemic **encephalopathy (HIE)**
- and **multiorgan failure**

Multiorgan Dysfunction

- The initial physiologic response to perinatal asphyxia(in fetus and neonate) is **redistribution of blood flow from the nonvital organs (eg, skin and splanchnic area,liver ,kidney,gut) to the vital organs (brain, heart,adrenal)**

- Within these organs now deprived of blood flow

local vasoconstriction

decrease in oxygen delivery.

- If prolonged:

-cause cellular injury and inadequate tissue function

- **multiorgan dysfunction after birth**

- In most cases of infants with moderate to severe HIE, there will be evidence of dysfunction in at least one other organ system.

Clinical manifestations :

- **Before the peripartum period:**

-**IUGR** with increased vascular resistance may be an indication of **chronic fetal hypoxia**

- **During labor: The fetal heart rate slows**

Beat-to-beat variability declines

Continuous heart rate recording may reveal a variable or late deceleration pattern

- **At delivery**:

meconium-stained amniotic fluid indicates that fetal distress may have occurred

- At birth:

  Neurologic impairment ,

  -Fail to breathe spontaneously

  Pallor

  cyanosis

  apnea

  a slow heart rate

  unresponsiveness to stimulation HIE

- **Systemic effects of perinatal asphyxia may be present even in the absence of encephalopathy**.

- Therefore, all major organ functions are evaluated after a well-documented **perinatal event**, including cases in which there is an **absence of findings associated with encephalopathy**

Clinical manifestations:

- The severity of HIE can be defined as:(depending on clinical findings)
  - **mild**
  - **moderate**
  - **Severe**
- **Sarnat classification** is widely used
- Other clinical scoring systems have been developed to assess the severity of HIE**(Thompson score)** and are used to select infants for therapeutic hypothermia

TABLE 54.1 Clinical Staging of Hypoxic–Ischemic Encephalopathy

Variable	Stage I	Stage II	Stage III
Level of consciousness	Alert	Lethargy	Coma
Muscle tone	Normal or hypertonia	Hypotonia	Flaccidity
Tendon reflexes	Increased	Increased	Depressed or absent
Myoclonus	Present	Present	Absent
Seizures	Absent	Frequent	Frequent
Complex Reflexes			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal or exaggerated	Exaggerated	Absent
Doll's eye	Normal	Overactive	Reduced or absent
Autonomic Function			
Pupils	Dilated, reactive	Constrictive, reactive	Variable or fixed
Respirations	Regular	Variations in rate and depth, periodic	Ataxic, apneic
Heart rate	Normal or tachycardia	Bradycardia	Bradycardia
Electroencephalogram	Normal	Low voltage, periodic paroxysmal	Periodic or isoelectric

Modified from Sarnat HB, et al. Hypoxic-ischemic encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol*. 1976;33:695.

TABLE 54.2 Thompson Score

Sign	Score 0	1	2	3	Day 1	Day 2	Day 3
Tone	Normal	Hypertonic	Hypotonic	Flaccid			
Level of consciousness	Normal	Hyper alert stare	Lethargic	Comatose			
Fits	None	Infrequent <3/day	Frequent >2/day				
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate			
Moro	Normal	Partial	Absent				
Grasp	Normal	Poor	Absent				
Suck	Normal	Poor	Absent ± bites				
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)			
Fontanel	Normal	Full, not tense	Tense				
				Total score per day			

IPPV, Intermittent positive-pressure ventilation.

From Thompson CM, et al. The value of a scoring system for hypoxic–ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta Paediatr.* 1997;86:757-761.

Neonatal periods neurologic finding:

- Stupor and coma
- Seizures
- Hypotonia
- Hypertonia-dystonia
- Oculomotor disturbances
- Disturbed sucking, swallowing,
- Tongue movements

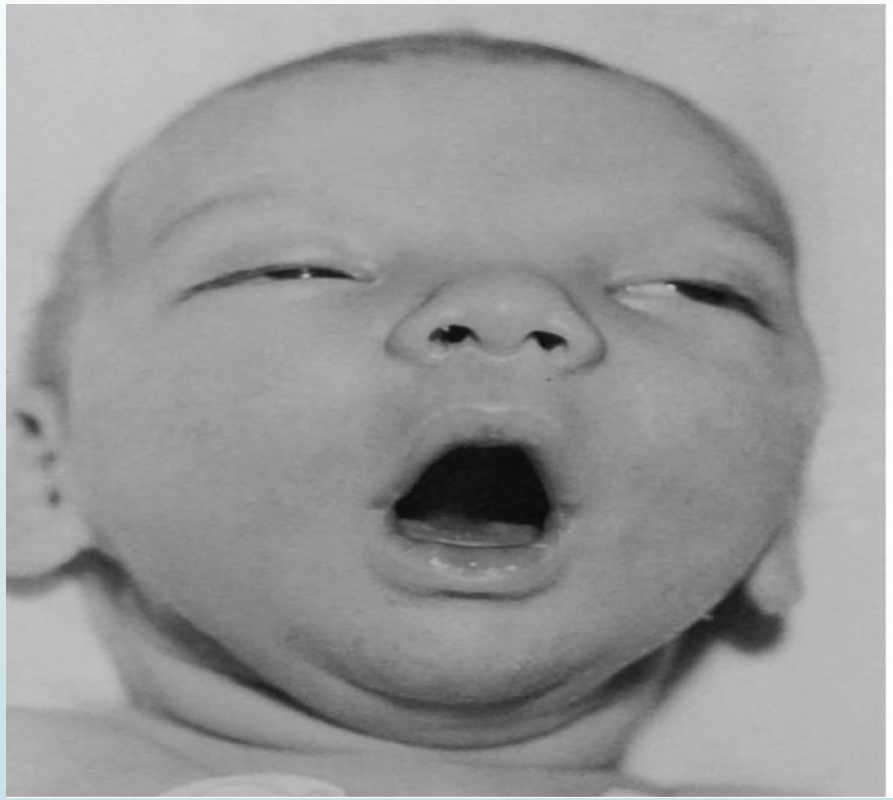
Hallmarks of neonatal encephalopathy:

- depression of the level of consciousness
- often with respiratory depression
- abnormality of muscle tone and power
- disturbances of cranial nerve function
- seizures.

- Evidence of **low Apgar scores** and **metabolic acidosis** (in arterial cord oxygen or newborn blood oxygen levels) **must accompany the neurologic dysfunction.**
- **Metabolic acidosis strongly suggests HI injury**
- Concomitant injury to other organs, such as the liver (the kidneys and/or the heart provides further evidence of HI injury.

Facial appearance at age 1 month in an infant who experienced perinatal asphyxia

Note the disconjugate gaze, ptosis, marked facial weakness, and wide-open mouth. The infant also exhibited fasciculations of the tongue on physical examination.



LONG-TERM SEQUELAE

- Cognitive deficitsc
- Spastic quadriparesis
- Choreoathetosisc
- Dystoniac
- Seizure disorder
- Ataxia
- Bulbar and pseudobulbar palsyd

TABLE 18.4 Sites of Predilection for the Diffuse Form of Hypoxic-Ischemic Selective Neuronal Injury in Premature and Term Newborns[a]

BRAIN REGION	PREMATURE	TERM NEWBORN
Cerebral neocortex		+
Hippocampus		
Sommer's sector		+
Subiculum	+	
Deep nuclear structures		
Caudate-putamen	+	+
Globus pallidus	+	+
Thalamus	+	+
Brain stem		
Cranial nerve nuclei	+	+
Pons (ventral)	+	+
Inferior olivary nuclei	+	+
Cerebellum		
Purkinje cells		+
Granule cells (internal, external)	±	±
Spinal cord		
Anterior horn cells (alone)		±
Anterior horn cells and contiguous cells (? infarction)	±	

+, Common; ±, less common.

[a]See text for references.

Multiorgan Dysfunction

In most cases of HIE, injury to other major organ systems occurs, including:

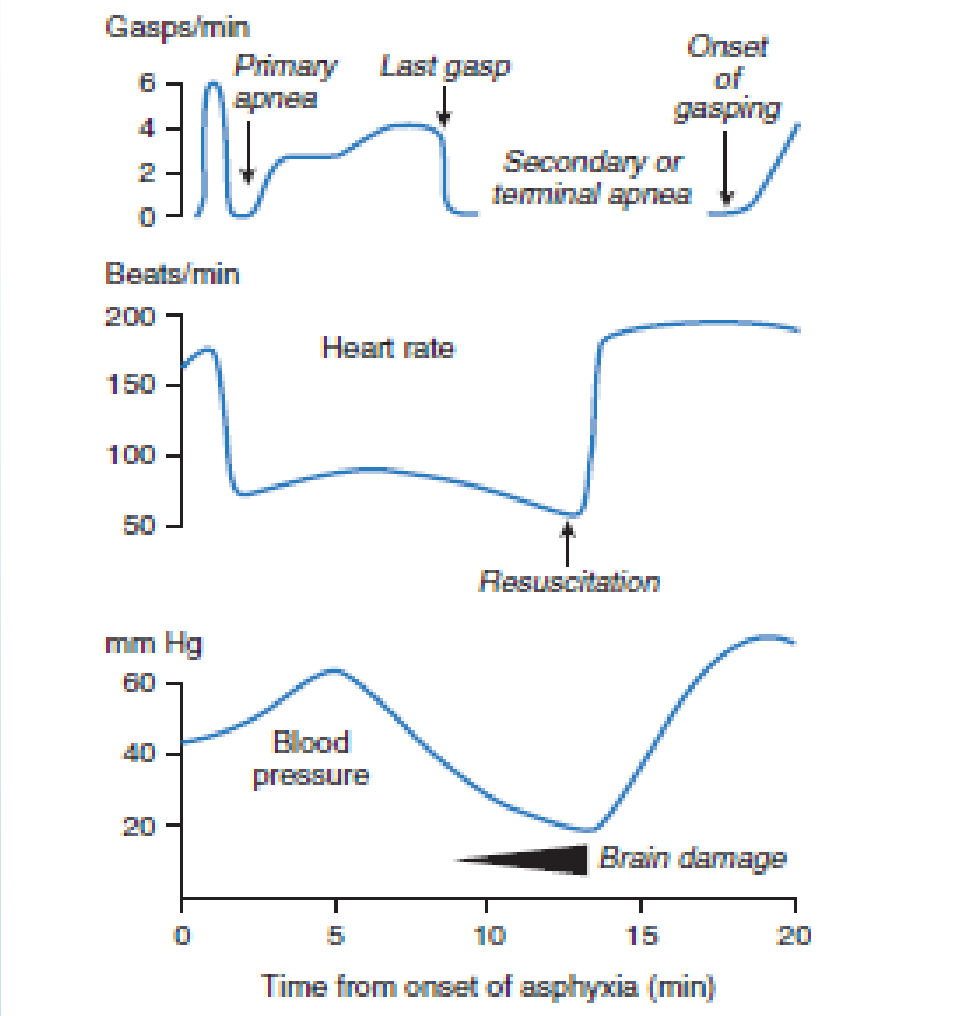
- the heart(Cardiovascular system)(62%)
- kidney(56-70%)
- Lung
- Liver(80-85%)
- GI
- Hematologic system
- Skin

Cardiovascular system involvement:

- The most studied organ affected by hypoxia is **the cardiovascular system,**
- Resulting **hemodynamic instability** that occurs because of hypoxia, either :
  - **-in utero**
  - **- during resuscitation**
  - **-newborn transition**
- causes **downstream effects on other organs**.
- other cardiovascular consequences of asphyxia can also have **long-term consequences** to asphyxic newborns.

Cardiovascular response to asphyxia

- Shortly after the onset of asphyxia, **primary apnea** : **profound bradycardia.**
- **Blood pressure is normal during primary apnea** (peripheral vasoconstriction and the redirection of blood from non vital organs)
- If asphyxia continues, after a period of gasping the fetus enters **secondary apnea or terminal apnea.**
- Secondary apnea is associated with a **large decrease in blood pressu**re, without intervention, the newborn eventually has **cardiac arrest**



Ventricular output , Myocardial dysfunction

- severe asphyxia is associated with significantly reduced :

  -ventricular output

  - stroke volume.

- **Myocardial contractility**, **cardiac output** and **blood pressure** are all negatively impacted
- Asphyxiated newborns are at increased risk of **ischemic cardiac injury** caused by decreased cardiac output and **decreased coronary perfusion**

Echocardiography

The ischemic effects on the cardiovascular system are detected by:

- **Blood pressure measurement** (hypotension)

-**Assessment of myocardial function**

- **Functional cardiac echocardiography** is useful in demonstrating **ventricular dysfunction** due to **myocardial ischemia**
- Echocardiography can also identify infants with **PPHN,** and can also assess volume status to guide volume therapy to restore blood pressure and avoid fluid overload

ECG changes:

ECG demonstrating**(non specific)**

- **myocardial ischemia**
- **ST depression**
- **T-wave inversion**

Cardiac markers:

- Cardiac markers are used to **assess myocardial damage**, but they are not specific to injury caused by perinatal asphyxia.
- **Cardiac troponins (**protein located on the actin filament of myocardium , an **indicator of myocardial cell death and myocardial damage**), as a marker of myocardial injury appear in the **blood 2-4 hours after perinatal asphyxia**
- Both **troponin-T and troponin-I** have been demonstrated to be sensitive markers of cardiac dysfunction
- They remain detectable for up to **21 days**
- **The association between elevated troponins and long-lasting cardiac depression is uncertain**.

- **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 .**
- **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.

Progressive asphyxia in newborns without intervention leading to:

- **Myocardial dysfunction**
- **Circulatory shock**
- **Right and left ventricular failure**
- **Tricuspid regurgitation**
- **Hypotension**(up to 62% of patients and may cause secondary multiorgan ischaemic injury)
- **Cardiac arrest.**

Clinical management of cardiac dysfunction relies on

- Maintaining **adequate perfusion to organs**
- Maintaining **blood pressure**
- Assisting in **cardiac contractility**

LUNG

- **Most infants** with significant birth asphyxia have **injury to the lungs** and many require mechanical ventilation.
- 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)**

- As with any critically ill infants, infants after birth asphyxia should have **oxygenation maximized to decrease shunting away from vital organs**
- **If allowed to recover using minimal mechanical ventilation, the lungs often respond well and many infants with severe brain injury remain on room air**

Pulmonary hypertension

- **Pulmonary hypertension is also common in birth asphyxia**
- PH may be caused by:

  -**the underlying cause of the birth asphyxia (in utero hypoxia with vascular hypertrophy)**

  -**a response to the concurrent hypoxia.**
- It can be treated with nitric oxide, muscle relaxation, and medications for pain and anxiety.
- Occasionally infants with birth asphyxia require extracorporeal membrane oxygenation **(ECMO)** for pulmonary reasons, but many centers use severe birth asphyxia as a contraindication for ECMO.

Pulmonary hemorrhage

- **Pulmonary hemorrhage** has been reported in severe asphyxia and with significant coagulopathy.
- Overall, the lung can repair itself quickly
- **Prolonged ventilation is often necessary for neurologic reasons instead of intrinsic issues with the lungs**

Renal manifestations(Acute kidney injury(AKI)

- There are poor definitions for acute kidney injury (AKI) in neonates because of the **variation in serum creatinine levels at birth**, which often reflect:
- the **maternal levels for the first 48 hours**
- the **large changes in glomerular filtration rates (GFRs)** that occur at birth and cause variations in urine production

Renal manifestations(Acute kidney injury(AKI)

- In **56-70**% of asphyxiated infants
- A **combination of oliguric and nonoliguric** renal failure
- AKI persisted in 17% of infants at 96 hours after birth asphyxia
- It is due to either:
  - **Reduced cardiac output**
  - **Tubular necrosis**
- Impaired renal function is detected by **an elevation in serum creatinine**

AKI:

Renal impairment defined as:

- urine output **<1 mL/kg /h[oliguria]** for 24 hours and an **creatinine level > 1.13** mg/dL
  - **-or** oliguria for >36 hours **or creatinine 1.41** mg/dL
  - **-or** any creatinine level that increased postnatally

Renal manifestations

- **The degree of kidney injury is correlated with the clinical severity of the birth asphyxia**
- **Infants with AKI were more likely to have abnormal findings on the brain MRI**
- Asphyxiated infants with AKI are also **ventilated on average for 4 days longer than infants without kidney disease**

Electrolyte abnormalities

- **Electrolyte abnormalities were seen in more than 50% of infants**, with(the most prominent):

  - hyponatremia

  - hypokalemia

  -hypocalcemia

Renal manifestations

- Serum creatinine level does not begin to increase until **25%to 50%of renal function is lost**, thus **significant injury can occur without changes in creatinine level.**

- **Renal dysfunction can occur with normal urine output**

(it is important to monitor drug levels and avoid nephrotoxic medications)

Renal manifestations

- **Serial measurements of creatinine and electrolytes** and ongoing accurate **monitoring of urine output** and **body weight** (assess and follow the effect of asphyxia on renal function)
- **The change in serum creatinine levels over the first few days is predictive of renal injury(>50% decline or <**0.6 mg/dl in 70% of infants after HIE)

Renal manifestations

- Depending on the degree of renal impairment further management, including:
  - **adjusting fluid and electrolyte management**
  - **drug dosing for medications that are renally excreted**
  -In very severe cases **renal replacement therapy**, may be warranted

Renal manifestations

- **The use of diuretics in AKI was not shown to be beneficial and could be harmful.**
- Rapid fluid and electrolyte shifts can occur after birth asphyxia, so care needs to be given to correction of the hyponatremia, hypokalemia, and hypocalcemia that are often seen in HIE

LIVER INJURY

- Liver injury is likely caused by **hypoperfusion** rather than hypoxia

- Transaminase levels (aspartate transaminase and alanine transaminase) often **increase from initial measurements**, in **80%-85%** of asphyxiated neonates, but typically **significantly improve by the end of 72 hours of therapeutic hypothermia**

LIVER INJURY

- Some correlation between the severity of the perinatal asphyxia and the increase of liver transaminase levels has been seen
- Significant liver dysfunction can occur in the setting of normal transaminase levels

LIVER INJURY

- 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.
- **Long-term effects of neonatal liver hypoxia-ischemia are unknown**.
- **Irreversible liver damage appears to occur very rarely after asphyxia at birth**.

Gastrointestinal tract effects

- A **reduced tolerance of enteral feedings** in infants with perinatal asphyxia is common 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**
- **Total parenteral nutrition :**has allowed clinicians to rest the gut mucosa for **multiple days** and allow for **reconstituting the gut barrier lost in hypoxic events**

Necrotizing enterocolitis and asphyxia:

- **Increased risk of necrotizing enterocolitis in the term and near-term infants and NEC** is a well recognized complication in infants with asphyxia but this etiology is relatively rare.

Gastrointestinal tract effects

- Current guidelines for **therapeutic hypothermia** have infants receiving nothing by mouth until completion of the hypothermia and this delay in feeding may allow the gut mucosa to repair.
- **Hypothermia might improve gut morbidities after HIE and has been considered as therapy in older infants with necrotizing enterocolitis**.

Hematologic System

- **Disseminated intravascular coagulation (DIC)** occurring after birth asphyxia is also well recognized, with
- low levels of **factor XIII**
- elevated:
  - **thrombin–antithrombin complexes**
  - **D-dimer**
  - **Fibrin**
  - **fibrinogen degradation products**
  - **soluble fibrin monomer complexes**

Hematologic System:

- Levels of coagulation factors **II, VII, IX, and X**; **protein C**; **protein S**; and **antithrombin** are also reduced in preterm compared with term plasma.
- **Prothrombin time** and **activated partial thromboplastin** time are higher in preterm infants
- there is **no correlation with increased risk of intraventricular hemorrhage (IVH) with higher coagulation times**

Hematologic System

- **Coagulation impairment should be anticipated and screening for hematologic abnormalities undertaken in all severely asphyxiated newborn infants**
- **Supportive treatment** with platelets, vitamin K, or clotting factors may be indicated by specific abnormalities on the coagulation screen
- The management of DIC is controversial, but **there is no indication for systemic heparinization .**
- Hypothermia has no effect on coagulation, but thrombocyte counts are lower during hypothermia.

Thrombocytopenia (PLT**<100,000** 106/L)

- Hypoxia is thought to have a :

  -direct effect on platelet formation

  -decrease in the size and production of the megakaryocytes in the bone marrow

- the cells in the bone marrow surrounding them are affected and **decrease the release of platelet promoting factors.**

- **Increased destruction of platelets**

  (as is evident by **the rapid decrease in platelet numbers after platelet transfusions in infants with** birth asphyxia)

THROMBOCYTOPENIA

- Thrombocytopenia was **more common in infants with more chronic hypoxia (>24 hours),** as classified by increased nucleated red blood cell count.
- **Infants with thrombocytopenia after asphyxia were more likely to die** in one study, but the cause of death was not active bleeding or hemorrhagic consequence

THROMBOCYTOPENIA

- **No consensus** could be given because no clear randomized trial on platelet use has been performed.
- British guidelines suggest:

  -keeping platelet counts >**20,000 to 30,000** 106/L in **stable newborns**

  -transfusing platelets if **less than 50,000** 106/L **in sick infants** with active bleeding or coagulation defects
- Until further studies are performed, individual clinicians must decide whether treating thrombocytopenia in stable, nonbleeding asphyxiated infants is necessary.

Coagulation dysfunction

- Coagulation dysfunction in hypoxic infants was reported as early as 1971 in a subset of infants with birth asphyxia, with the cause associated with a **consumptive coagulopathy (increased fibrin degradation products) followed by disseminated intravascular coagulation**
- Coagulation impairment is **relatively common** after a severe asphyxial insul
- The effect on coagulation was of **short duration and may only play a minor role in the overall morbidity of birth asphyxia**

Glucose metabolism

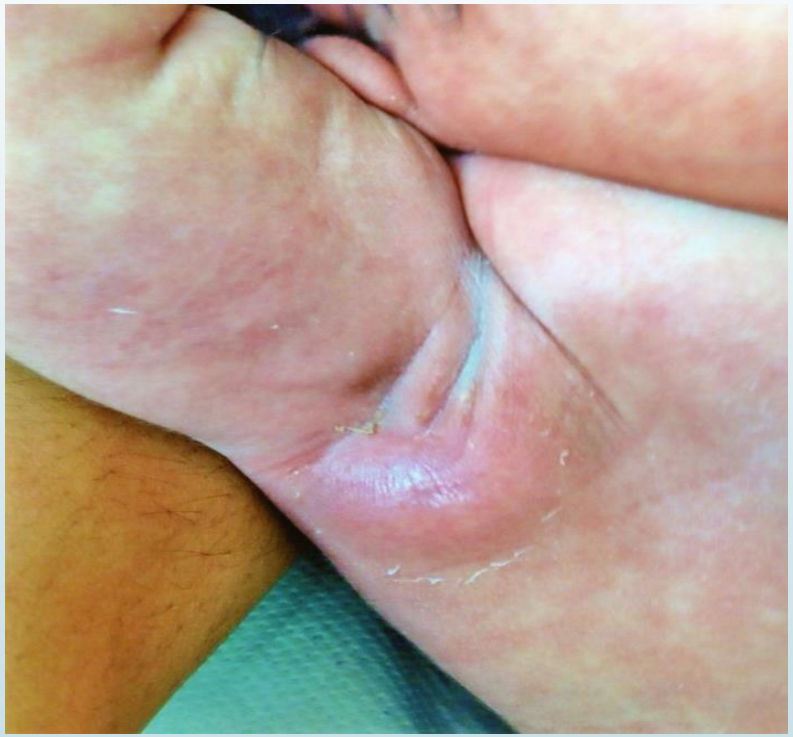
In neonates with perinatal asphyxia,

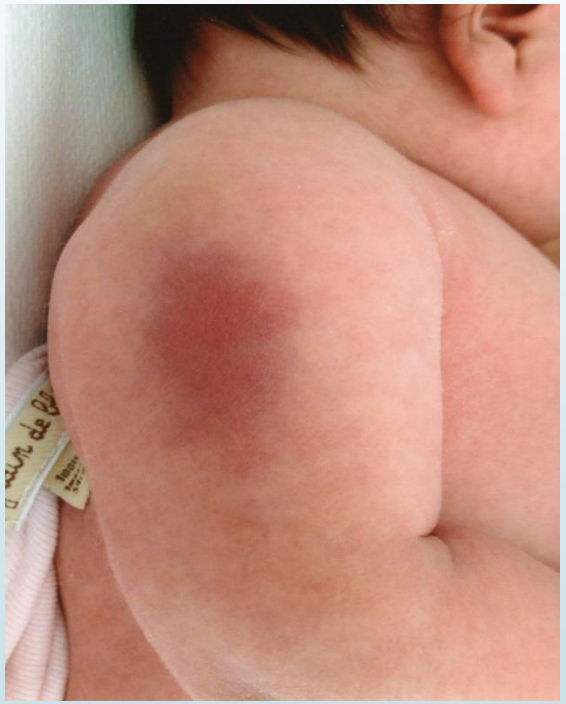
- **initial stress-induced hyperglycemia**
- followed by a **sharp drop in blood glucose levels due to increased glucose consumption**.
- Hypoglycemia is also more common in infants with **severe liver damage** due to inadequate glycolysis.

SKIN

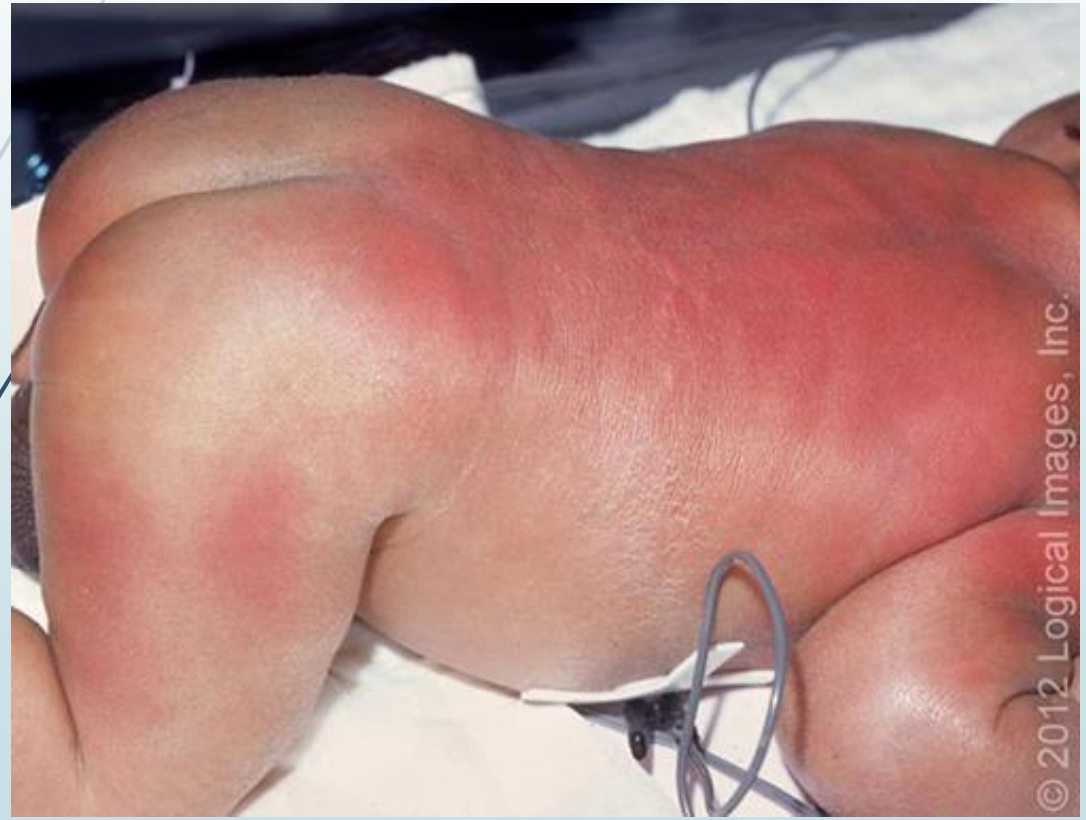
- **Subcutaneous fat necrosis**, a **benign** condition characterized by **inflammation and necrosis of subcutaneous fat**
- In the TOBY RCT **1%** of infants had subcutaneous fat necrosis (204) which can be complicated by **hypercalcemia and require hyperhydration and diuretic treatment**
- **Cold panniculitis** which is an acute nodular, erythematous eruption.
- **Sclerema neonatorum** is a diffuse hardening of the subcutaneous tissue during TH that usually self resolves

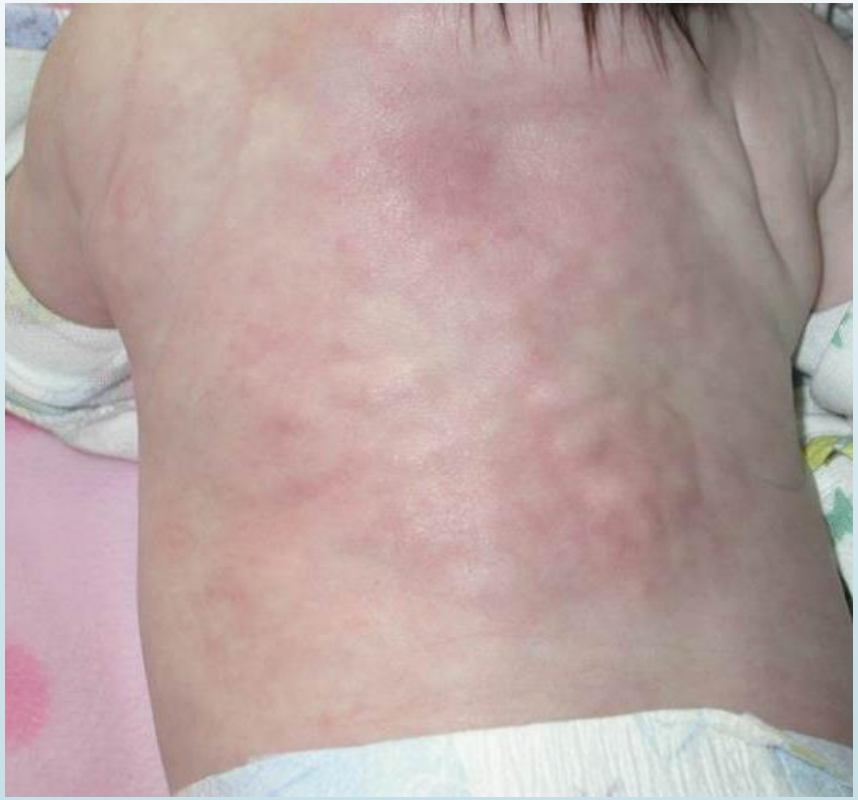
subcutaneous fat necrosis



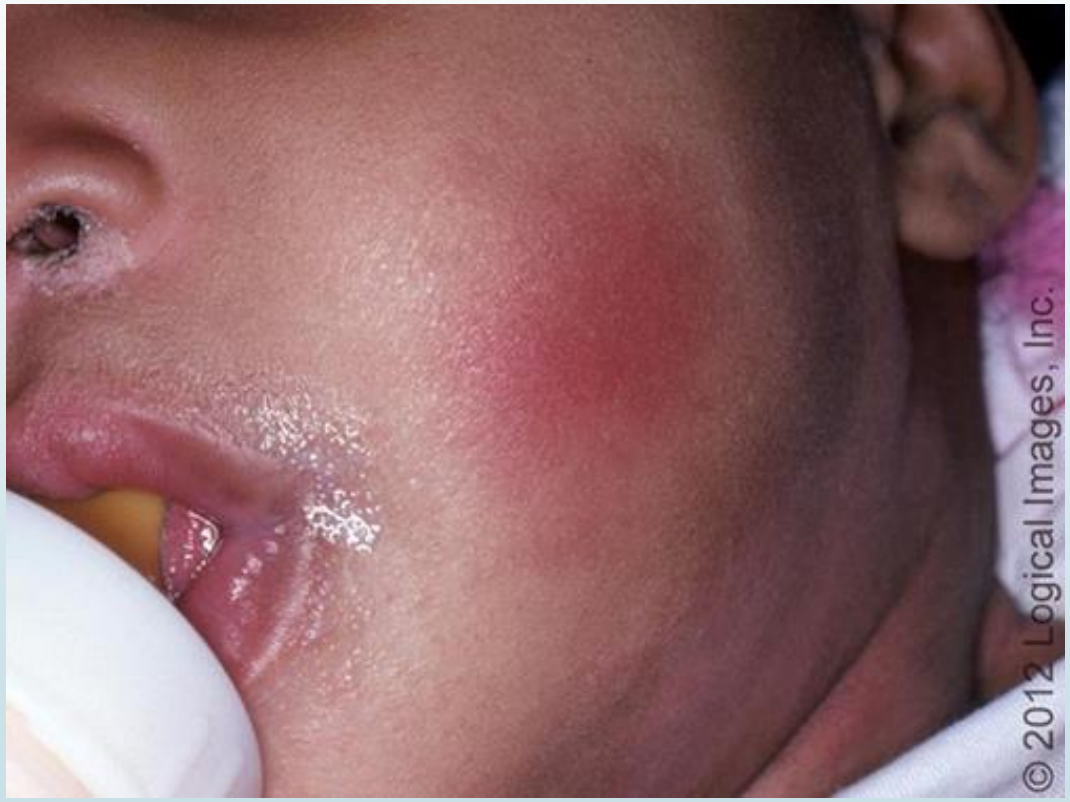


subcutaneous fat necrosis





Cold panniculitis



Basic laboratory tests

- Blood gas analysis
- Complete blood count (CBC)
- Glucose
- Renal function studies (Cr and BUN]) and electrolytes
- Liver function studies
- PT (prothrombin time) and a PTT ,coagulation tests
- Cardiac evaluation
- Infectious disease evaluation(B/C,CRP,CSF analysis
- Cranial ultrasound
- chest radiography
- Brain MRI
- EEG,aEEG

- Thank u….