Hypoxic-Ischemic Encephalopathy

التبييض بالمربع الأبيض
- رهف عبابنه

Dr.A.Tarawneh
M.D , Neonatologist

DEFINITIONS

HIE is an medicolegal aspect
HIE is clinical diagnosis(AAP)criteria
- You have to know in which stage , to determine the prognosis

- ***Hypoxic-Ischemic Encephalopathy*** :
  - abnormal neurologic behavior in the neonatal period arising as a result of a *hypoxic-ischemic event*.
  - The severity of hypoxic-ischemic encephalopathy (HIE) can be defined depending on *symptoms and signs*
    - Mild — Good prognosis (benign)
    - moderate — Take two direction (1- back to mild , normal or 2- progress to 3rd stage)
    - severe — Bad prognosis 55% die due to multi organ failure

DEFINITIONS

- ***Hypoxia or Anoxia*** : ⇩ Po2
  - Partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood.
- ***Asphyxia*** : ⇩ Po2 ⇧ pco2
  - This is the state in which placental or pulmonary gas exchange is compromised or ceases

⇒ typically producing a combination of *progressive hypoxemia and hypercapnia.*

- ***Ischemia*** : This is reduction (partial) or cessation (total) of blood flow to an organ (such as the brain), which compromises both ***oxygen and substrate*** delivery to the tissue.

To make diagnosis (after delivery for high risk baby do umbilical cord arterial and venous blood gas)
Profound metabolic acidosis –acidemia

Incidence

- **Incidence**
  - 2-4 cases per 1000 births
- **Mortality rate**
  - Severe HIE the mortality rate has been reported to be 50-75%
  - Most deaths (55%) occur in the first week of life due to multiple organ failure

SELECTIVE VULNERABILITY

- A number of factors influence the distribution of brain injury, summarized as follows:
  - Cellular susceptibility
  - Maturity
  - Vascular territories
  - Regional susceptibility
  - Type of hypoxic-ischemic insult

SELECTIVE VULNERABILITY

- ***Cellular Susceptibility*** :
  - The neuron is the most sensitive cellular element to hypoxic-ischemic insult, followed by cells cerebral vasculature.
- ***Maturity***
  - Gestational age plays an important role in the changing susceptibility of cerebral structures to hypoxic-ischemic insult.
    - Hypoxic-ischemic insult before 20 weeks' gestational age, polymicrogyria
    - during midgestation (26 to 36 weeks) predominantly damage white matter, leading to **periventricular leukomalacia**
    - Insults at term (35 weeks and beyond) predominantly damage **deep gray matter** (posterior putamen and ventrolateral nucleus of the thalamus).

SELECTIVE VULNERABILITY

- ***Vascular Territories***
  - *Watershed injury* : refers to tissue damage that occurs in regions that are most vulnerable to reduction in cerebral perfusion
    - These tissues are at the furthest points of arterial anastomoses and are exposed to damage when perfusion pressure falls, usually as the result of impaired cardiac output.
    - **In the term brain**,
      - the parasagittal region
      - The paracentral gyrus
      - The motor cortex

       are particularly liable to watershed injury

      - *this accounts for the observation that spastic cerebral palsy is the most common major sequela to hypoxic-ischemic insult at term.*

      - the hippocampus, temporal lobe, and occipital lobes are most resistant to this type of insult.

Types of Hypoxic-Ischemic Insult

Mc cause in 3rd stage
Ex= cord prolapse

- **Acute total asphyxia**
  - *This produced injury to the*
    - *Thalamus*
    - *brainstem*
    - *spinal cord structures*
- **partial asphyxial** insult lasting 1 to 5 hours
  - *This produced damage predominantly in the*
    - *cerebral hemispheres*
    - *basal ganglia*
    - *cerebellum.*

PATHOPHYSIOLOGY

- Early or primary neuronal damage occurs as a result of *cytotoxic changes* due to

mc theory

  - failure of the microcirculation
  - inhibition of energy-producing molecular processes
  - increasing extracellular acidosis
  - and failure of Na+/K+-adenosine triphosphatase (ATPase) membrane pumps
    - which results in ***excessive leakage of Na+ and Cl-*** into the cell with consequent accumulation of intracellular water ***(cytotoxic edema)***

- ***Free radical*** production is also initiated, which further compromises neuronal integrity

- If not reversed, these processes lead to neuronal death within a short time of the acute insult

PATHOPHYSIOLOGY

The primary physiological processes that lead to HIE

- Systemic hypoxemia
- Reduced cerebral blood flow (CBF)

Is a result from Autoregulatory mechanism

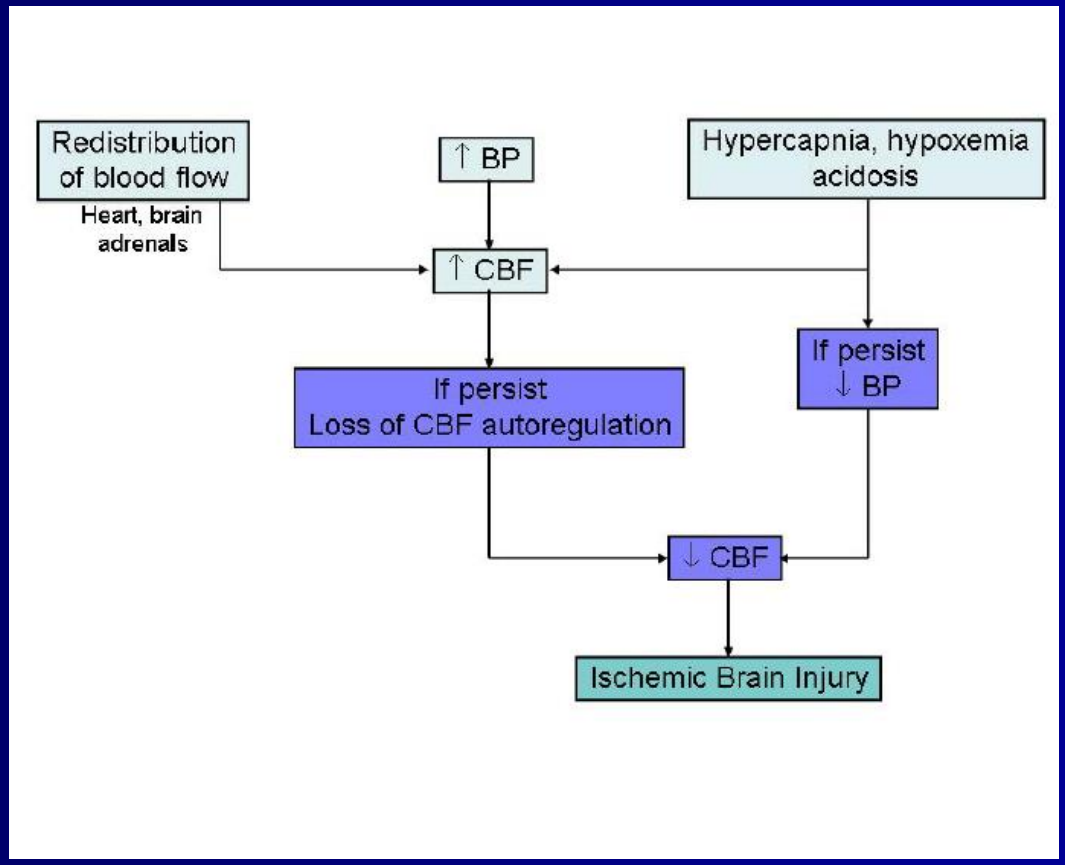
PATHOPHYSIOLOGY

- **Early compensatory adjustments**
  - Hypoxia and hypercapnia
    - Increase in the CBF
      - Increase cardiac output
      - BP increase
- **Early compensatory adjustments fail**
  - BP falls
    - CBF falls below critical levels
      - Brain suffers from diminished blood supply
      - Lack of sufficient oxygen to meet its needs.

Bad compensatory mechanism

(reperfusion from nonvital to vital organ +shifting of oxygen radical from (extremities and skin) to brain

PATHOPHYSIOLOGY



PATHOPHYSIOLOGY

- During the early phases of brain injury, ***brain temperature drops***
  - Local release of neurotransmitters, such as (GABA) increase
  - Reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia

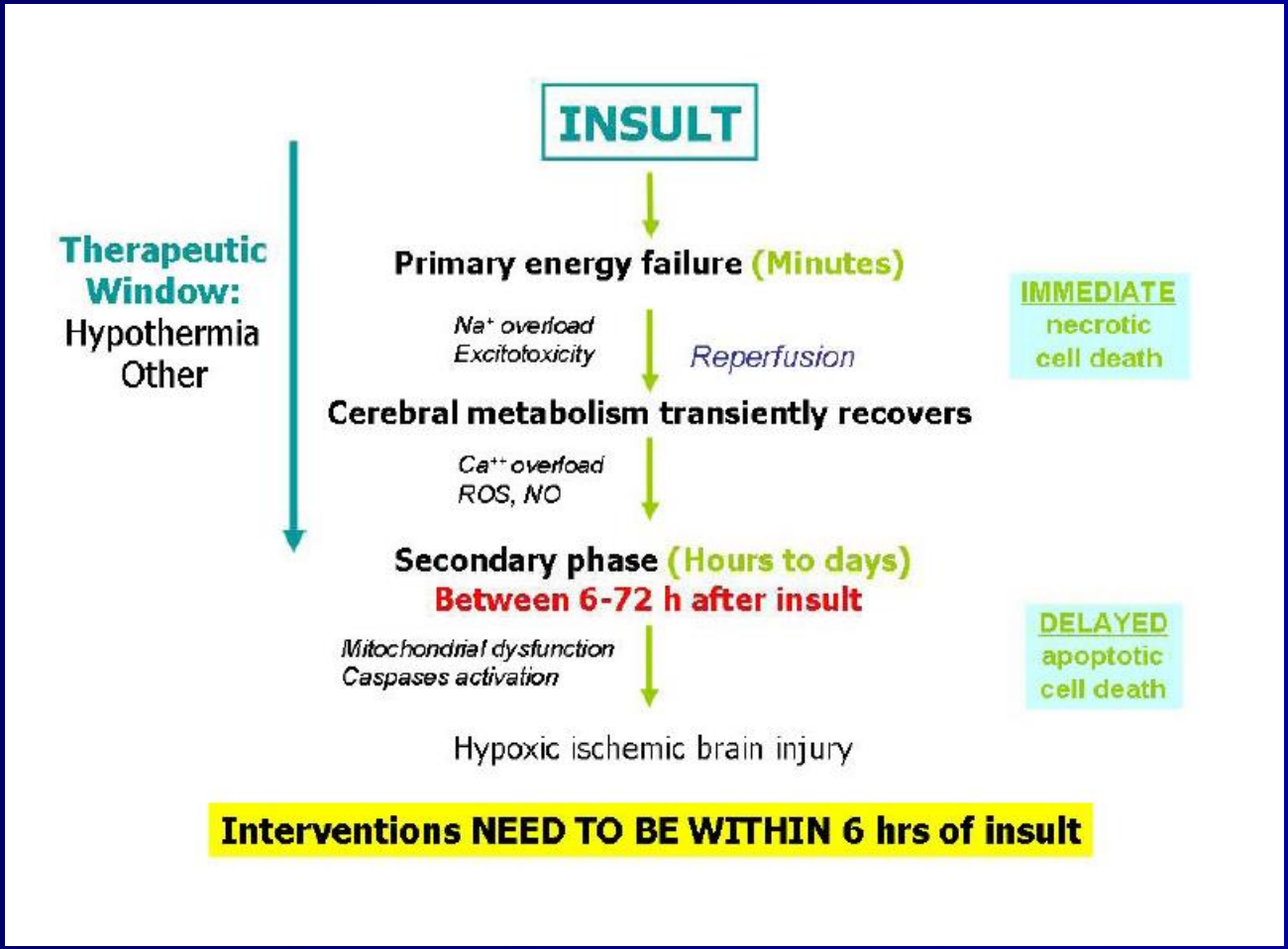
Auto cooling compensatory mechanism

PATHOPHYSIOLOGY

- The magnitude of the final neuronal damage depends
  - Initial insult
  - Damage due to energy failure
  - Reperfusion injury
  - Apoptosis

apoptosis Start after 6h
(the ideal timing for cooling in first 6 h , has no effect after 6h)

PATHOPHYSIOLOGY



HIE History

clinical diagnosis

- **AAP Criteria**
  - Profound metabolic acidosis
  - Mixed acidemia (pH <7) in an umbilical artery blood sample
  - Persistence of an Apgar score of 0-3 for longer than 5 minutes
  - Neonatal neurological sequelae (e.g., seizures, coma, hypotonia)

Seizures in 1st 24 h = stage 2-moderate HIE
Coma = stage 3 sever HIE

History

- **AAP Criteria**
  - Multiple organ involvement (e.g., kidney,lungs, liver, heart, intestines)
- On rare occasions,
  - Difficulties with delivery
  - Particularly problems with delivering the head

95% OF HIE =intrauterine hypoxia
- to differentiate if the cause of HIE is intrauterine or during delivery
Do CBC (nucleated RBCs > 12,000 is chronic hypoxia=intrauterine)

HIE
Physical Examination

- **Mild HIE** no risk for CP
  - Muscle tone may be slightly increased
  - Deep tendon reflexes may be brisk during the first few days
  - Poor feeding, irritability, or excessive crying or sleepiness ,may be observed.
  - By 3-4 days of life, the CNS examination findings become normal

HIE
Physical Examination

- **Moderate HIE**
  - Lethargy
  - Significant hypotonia
  - Diminished deep tendon reflexes.
  - Grasping, Moro, and sucking reflexes may be sluggish or absent.
  - The infant may experience periods of apnea.

I have to protect the airway
apnea in Stage 2 + all pt on stage 3 indication for intubation

HIE
Physical Examination

- **Moderate HIE continue**
  - Seizures may occur within the first 24 hours of life.
  - Full recovery within 1-2 weeks----better long-term outcome.

HIE
Physical Examination

- **Severe HIE**
  - Stupor or coma is typical
  - Breathing may be irregular
  - Generalized hypotonia and depressed deep tendon reflexes are common.
  - Neonatal reflexes are absent.
  - Disturbances of ocular motion
  - Nystagmus
  - Pupils may be dilated, fixed, or poorly reactive to light

HIE

- **Classification of HIE by Sarnat 1976**
  - **Stage I**
    - Consciousness: Hyperalert
    - Reflexes: Overactive
    - Tone: Normal
    - Suck: Weak
    - Pupil: Mydriasis
    - Heart: Tachycardia
    - EEG: Normal
    - Duration: 1-3 days

HIE

- **Stage II**
  - Consciousness: Lethargic
  - Reflexes: Overactive
  - Tone: Mild hypotonia
  - Suck: Weak
  - Pupil: Miosis
  - Heart: Bradycardia
  - EEG: Low voltage
  - Duration: 2-14 days

HIE

- **Stage III**
  - Consciousness: Stuporous
  - Reflexes: Absent
  - Tone: Flaccid
  - Suck: Absent
  - Pupil: Unequal, poor light reflex
  - Heart: Bradycardia
  - EEG: Low voltage
  - Duration: 2-14 days

Classification of HIE by Sarnat 1976

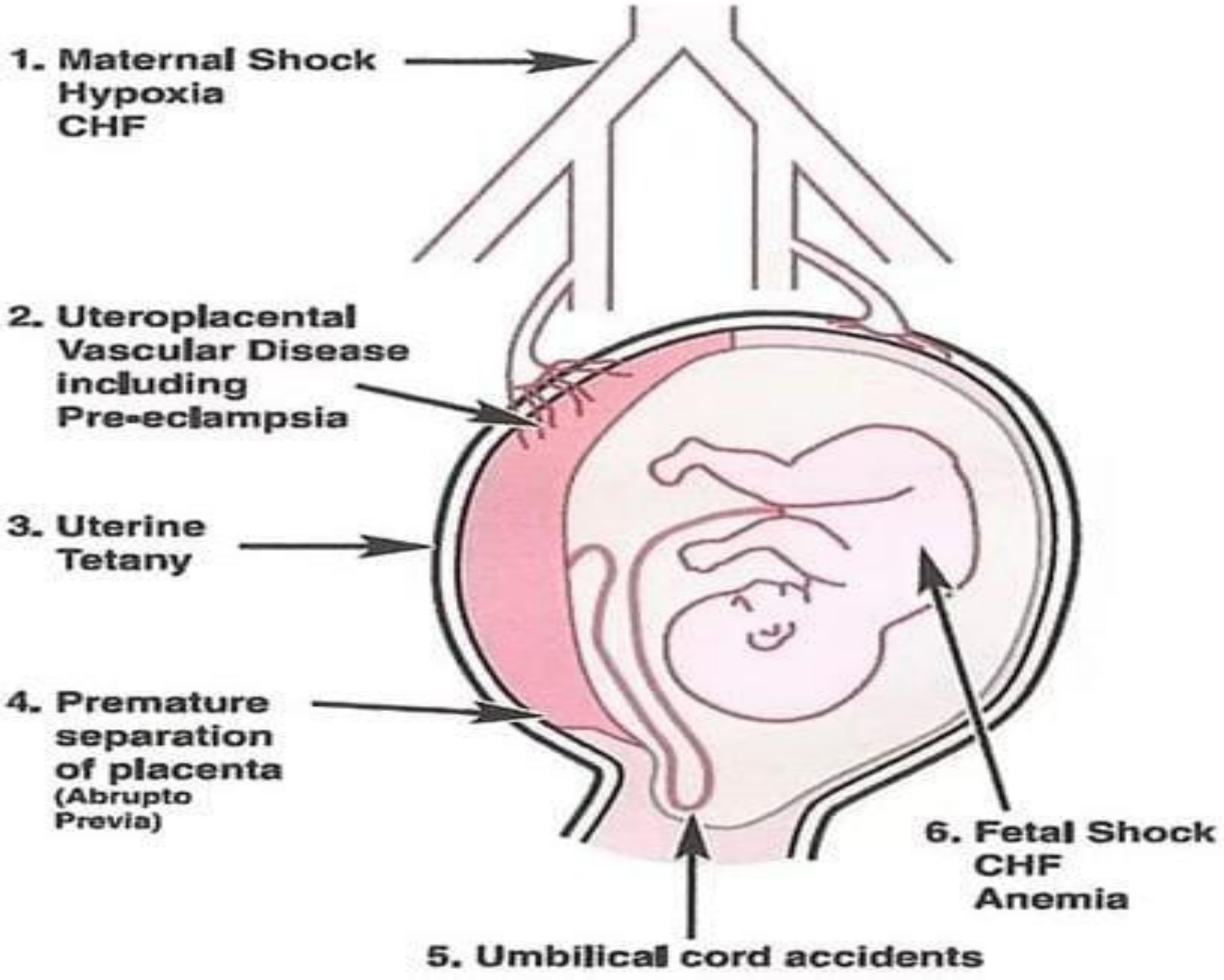
Stage	Stage I	Stage II	Stage III
Consciousness	Hyperalert	Lethargic	Stuporous
Reflexes	Overactive	Overactive	Absent
Tone	Normal	Mild hypotonia	Flaccid
Suck	Weak	Weak	Absent
Pupil	Mydriasis	Miosis	Unequal, poor light reflex
Heart	Tachycardia	Bradycardia	Bradycardia
EEG	Normal	Low voltage	Low voltage
Duration	1-3 days	2-14 days	2-14 days

ETIOLOGY

- **Fetal hypoxia** may be caused by *various disorders in the mother, including*
  - ***(1) inadequate oxygenation of maternal blood***
    - (1) hypoventilation during anesthesia
    - (2) cyanotic heart disease
    - (3) respiratory failure
    - (4) or carbon monoxide poisoning
  - (2) ***low maternal blood pressure***
    - (1) acute blood loss
    - (2) spinal anesthesia
    - (3) compression of the vena cava and aorta by the gravid uterus
  - ***(3) inadequate relaxation of the uterus to permit placental filling*** as a result of uterine tetany caused by the administration of excessive oxytocin
  - ***(4) premature separation of the placenta***
  - (5) impedance to the circulation of blood through the umbilical cord as a result of *compression or knotting of the cord*
  - ***(6) placental insufficiency*** from toxemia or postmaturity

ETIOLOGY

- **After birth**, hypoxia may be caused by
  - (1) ***failure of oxygenation as a result of severe forms***
    - cyanotic congenital heart disease
    - severe pulmonary disease
  - (2) anemia severe enough to lower the oxygen content of the blood
    - severe hemorrhage
    - hemolytic disease
  - (3) shock severe enough to interfere with the transport of oxygen to vital organs from
    - overwhelming sepsis
    - massive blood loss
    - intracranial or adrenal hemorrhage


1. Maternal Shock
Hypoxia
CHF
2. Uteroplacental
Vascular Disease
including
Pre-eclampsia
3. Uterine
Tetany
4. Premature
separation
of placenta
(Abrupto
Previa)
5. Umbilical cord accidents
6. Fetal Shock
CHF
Anemia

Risk Factors

Preconceptual	Antepartum	Intrapartum
IDDM	Severe preeclampsia	Breech/Malpresentation
Thyroid disease	Placental abruption	Cord prolapse
Fertility treatments	Multiples	Instrumentation
Nulliparity	Antepartum hemorrhage	Stat C-section
Advanced maternal age	IUGR	Induction
		Maternal pyrexia

IDDM, insulin-dependent diabetes mellitus; IUGR, intrauterine growth restriction

Multiorgan Systemic Effects of Asphyxia

مهم

- Central nervous system
  - Hypoxic-ischemic encephalopathy
  - infarction
  - intracranial hemorrhage
  - seizures,
  - cerebral edema
  - Hypotonia
  - hypertonia
- Cardiovascular
  - Myocardial ischemia
  - poor contractility,
  - tricuspid insufficiency
  - hypotension

Tt of convulsion in neonate =phenobarbital 40 mg and then 5 mg as a maintenance dose (⇩ metabolism of brain +stope apoptosis ⟹ ↓brain insult)

Sever hypoxia → sever metabolic acidosis → cardiogenic shock
Sever ischemia →rupture of VSD
Necrosis of papillary muscle →mitral regurgitation

Management of hypotension =
avoid iv fluid (just give 2/3 of the maintenance dose of fluid)
The main problem in these pt is the brain insult (syndrome of inappropriate antidiuretic hormone → accumulation of fluid)
1- **dobutamine** the Drug of choice (increase the inotropic effect +slight vasodilation)
2- if fail …. Add **dopamine**
3- if fail ….. Add **epinephrin**
4- if not respond and still hypotension give **corticosteroid** due to adrenal hemorrhage → hypotension (as a result decrease of epinephrin = nor epinephrin)

Multiorgan Systemic Effects of Asphyxia

- **Pulmonary**
  Pulmonary hypertension
  pulmonary hemorrhage
  respiratory distress syndrome

The leading cause of death = PPHN

The goal in neonate for premature infant pco2 = 35-55
but In HIE the goal pco2 = 35
Po2= < 80 ,,,, but in HIE the goal po2= 80 – 100
hyperinflated (pulmonary vasodilatation + systemic vasoconstriction) esp in stage 2
- In stage 3 it not benefit (need high frequency of nitric oxide)

Multiorgan Systemic Effects of Asphyxia

- Renal
  - Acute tubular or cortical necrosis
- Adrenal
  - Adrenal hemorrhage
- Gastrointestinal
  - Perforation
  - ulceration
  - hemorrhage
  - necrosis
- Metabolic
  - Inappropriate secretion of antidiuretic hormone
  - hyponatremia
  - hypoglycemia
  - Hypocalcemia
  - myoglobinuria
- Subcutaneous fat necrosis
- Hematology
  - Disseminated intravascular coagulation

Pt with HIE = keep NPO at least 3 day to prevent NIC (due to ischemia)

Differential Diagnosis

- Inborn errors of metabolism
- Neuromuscular disorders
- Neonatal myopathies
- Brain tumors
- Developmental defects
- Infections

Organ	Manifestations
CNS	HIE, hypotonia, hyporeflexia, cranial nerve palsies, seizures, coma, cerebral edema/hemorrhage etc
Respiratory	hypoxia, respiratory acidosis, PPHN, surfactant dysfunction, RDS, meconium aspiration, pulmonary hemorrhage/edema
Cardiac	myocardial ischemia, tricuspid insufficiency, ventricular dysfunction, CHF
Hematologic	anemia, neutropenia, thrombocytopenia, DIC
GI	NEC, hepatic dysfunction, liver failure
Renal	oliguria, acute tubular necrosis, SIADH, renal failure
Metabolic	acidosis, hypoglycemia, hyponatremia, hypocalcemia

Work-up

- Serum electrolytes
- In severe cases
  - Daily assessment of serum electrolytes are valuable
  - SIADH
- Renal function studies
- Cardiac and liver enzymes
- Coagulation system evaluation
- ABG

1-sodium= syndrome of inappropriate antidiuretic hormone
2- calcium = brain calcification (late calcification)
3- potassium= tubular necrosis + renal insufficiency

Regular , daily follow up for liver enzyme (multi organ failure + side effect of cooling → liver failure

Core body temp
(esophageal)
Avoid axillary

HIE Imaging Study

- **MRI**
  - Loss of cerebral gray and white matter differentiation
  - Basal ganglia or thalamus injury
  - Parasagittal cerebral injury
  - Decreased signal in the posterior limb of the internal capsule

After 1 week no significant findings

HIE

- **Imaging**
  - **Head CT scanning**
    - Cerebral edema
    - Ventricular hemorrhage
  - **Echocardiogram**
    - Myocardial contractility
    - Structural heart defects

HIE

CFM monitor = continuous EEG
-Help in prognosis

- **EEG**
  - Continuous low voltage pattern
  - Seizures

< 5 is indicate cerebral palsy

Spik

Most of causes of infantile spasm due to HIE +tuberous sclerosis (↑ incidence of HIE)

HIE

- **Treatment**
  - Maintain adequate ventilation.
  - Maintain adequate perfusion.
    - Maintain the mean blood pressure (BP) above 35-40
  - Maintain adequate metabolic status
  - Seizures should be treated with :
    - phenobarbital or lorazepam
    - phenytoin can be added if persistent

1st choice = phenobarbital 40 mg

HIE

- **Hypothermia Treatment**
  - Mild hypothermia 3-4°C below the baseline temperature
  - **Mechanism of action**
    - Reduced metabolic rate
    - Energy depletion
    - Decreased excitatory transmitter release
    - Reduced ion flux
    - Reduced apoptosis
    - Reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

HIE

- **Hypothermia Treatment**
  - Timing of initiation of hypothermia therapy:
    - Cooling must begin early, within 1 hour of injury
    - Favorable outcome may be possible if the cooling begins within 6 hours after injury
  - The greater the severity of the initial injury, the longer the duration of hypothermia needed for optimal neuroprotection

HIE

- **Hypothermia Treatment**
  - **Selective head cooling**
    - Acap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34-35°C for 72 hours
  - **Whole body cooling**
    - Infant is placed on a commercially available cooling blanket, through which circulating cold water flows, so that the desired level of hypothermia is reached quickly and maintained for 72 hours

HIE

- **Surgical Care**
  - Posterior cranial fossa hematoma, surgical drainage may be life saving if no additional pathologies are present
- **Consultations**
  - Pediatric neurologist should help assist in the management of seizures, interpretation of EEG
- **Diet**
  - Nothing by mouth (NPO) during 1st 3 DOL or until the general level of alertness and consciousness improves
  - Begin trophic feeding
  - Monitor for NEC
    - Abdominal girth
    - Gastric residuals
    - Stools
- **PT**

PREVENTION

- PRIMARY PREVENTION
  - **RESUSCITATION**
    - following steps should be taken in sequence until the infant responds adequately:
      - Provide tactile stimulation.
      - Open airway. Extend the infant's neck and give chin support.
      - Inflate lungs Use a self-inflating bag and mask if spontaneous respirations have not been established by 30 to 60 seconds
      - Consider giving the infant five lung inflations (pressure of 30 cm of water in a term infant) for 2 to 3 seconds each.
      - Ventilate lungs. If spontaneous respiration has not been established after five inflations, start intermittent positive pressure ventilation at 30 breaths/min.

PREVENTION

- **RESUSCITATION *cont***
  - Intubate. If the infant has not improved after 2 minutes of intermittent positive pressure ventilation
  - Use chest compression. If the heart rate is <60 bpm despite adequate ventilation. Coordinate compressions and ventilation in a 3:1 to achieve 90 compressions and 30 breaths per minute.
  - Administer drugs. Epinephrine (10 µg/kg or 0.1 mL/ kg of 1:10,000) should be given down the endotracheal tube if the heart rate remains below 60 beats/min, and can be repeated up to three times.
  - Epinephrine and other drugs can also be given through an umbilical catheter.
  - volume expansion with normal saline
  - Intramuscular naloxone (200 µg) is indicated if the infant fails to breathe spontaneously and if the mother has received opiates for pain relief within 4 hours before delivery.

PREVENTION

- Conditions in Which the Need for Resuscitation at Birth May Be Anticipated
  - ***Maternal***
    - Toxemia (eclampsia)
    - Diabetes mellitus
    - Drug addiction
    - Cardiovascular disease
    - Infectious disease
    - Collagen vascular disease
  - ***Uteroplacental***
    - Placental abruption
    - Umbilical cord prolapse
    - Placenta previa
    - Polyhydramnios
    - Premature rupture of the membranes
  - **Intrapartum Factors**
    - Isoimmunization
    - Multiple birth
    - Abnormal presentation
    - Precipitous delivery
    - Fetal distress
    - Thick meconium staining
    - Prolonged labor
    - Difficult forceps delivery
    - Intrauterine growth restriction
    - Prematurity

PREVENTION

- **Prevention**
  - Allopurinol: is an inhibitor of xanthine oxidase and has free radical scavenging action
  - High-dose phenobarbital : (40 mg/kg) was associated with a significant reduction in severe neurodevelopmental disability
  - Excitatory amino acid (EAA) antagonists : Magnesium sulfate (MgSO4) is an *N*-methyl-d-aspartate receptor antagonist and has been proposed to be an effective agent for brain protection

Prognosis

- **Good Prognostics**
  - Normal EEG at 7 DOL
- **Poor prognostics**
  - No spontaneous respiratory effort within 20-30 minutes
  - Seizures is an ominous sign
  - Abnormal clinical neurological findings >7-10 DOL
  - Persistent feeding difficulties
  - Poor head growth during the postnatal period

Thank you