Review Article

Understanding the Complex Etiology and Complications of Preterm Birth – A Narrative Review

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ABSTRACT

Preterm birth, which is defined as the delivery of a newborn before 37 weeks of gestation—remains a great problem for the medical community. Preterm birth has a complicated etiology that involves interactions between environmental, genetic, and maternal health factors. The relevant factors include genetic predisposition, inflammation, infection, and maternal stress. Inadequate prenatal care, and other lifestyle choices can also increase the chance of premature birth. These risk variables' complex underlying mechanisms are still being understood. Preterm birth has a wide range of effects on many organ systems and developmental stages. Due to their underdeveloped lungs, preterm newborns frequently have respiratory distress syndrome, which makes them more susceptible to infections. Long-term effects frequently include neurodevelopmental difficulties, such as cerebral palsy and learning difficulties. Care is made more difficult by gastrointestinal problems including necrotizing enterocolitis. Furthermore, families may experience significant emotional and financial hardships as a result of preterm birth.

The complex web of circumstances that contribute to premature delivery and the wide range of difficulties that preterm newborns experiences were elaborated in this article.

Keywords: Preterm birth, Preterm labour, premature causes Complications, Cervical insufficiency.

INTRODUCTION

The World Health Organization (WHO) defines preterm birth as babies born before 37 completed weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period (LMP).[1] Preterm babies are born either by spontaneous preterm delivery or by induction of labor or cesarean due to any medical condition.[1]

Globally, prematurity is the leading cause of mortality in children under 5 years. In low-income countries, half of the babies born before 32 weeks die due to lack of cost-effective care while in high-income countries, almost all of the babies survive with optimal care. In middle-income countries, there is an increased burden of disabilities among babies who survive the neonatal period.[1]

According to WHO, Preterm is subdivided based on gestational age (GA):

- Extremely preterm (<28 weeks)
- Very preterm (28–32 weeks)
- Moderate or late preterm (32–37 completed weeks of gestation).[1]

EPIDEMIOLOGY:

In 2020, 13.4 million babies were born preterm which is approximately 1 in 10 babies.[1] About 30–35% of preterm births are indicated, in which 40–45% are spontaneous preterm labor, and 25–30% follow PPROM. Preterm births are classified according to gestational age: about 5% of preterm births occur at less than 28 weeks (extreme prematurity), about 15% at 28–31 weeks (severe prematurity), about 20% at 32–33 weeks' (moderate prematurity), and 60–70% at 34–36 weeks' (near term). Though most preterm births occur in Southern Asia and sub-Saharan Africa, it is still a global burden.

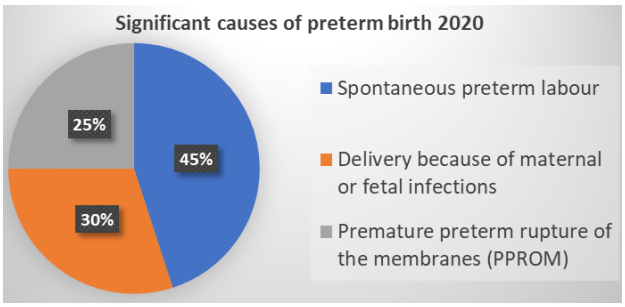


Figure 1: Significant causes of preterm birth 2020

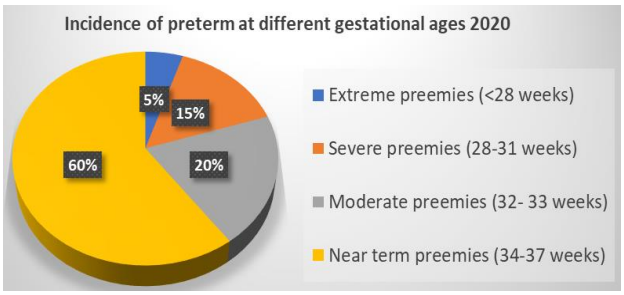


Figure 2: Incidence of preterm at different gestational ages 2020

SYMPTOMS:

Symptoms observed in pregnant women that indicate preterm delivery include regular contractions, which may

occur every 10 minutes or more often and develop into stronger and more painful contractions which are associated with cervical change. Symptoms also include pelvic pressure, menstrual-like cramps, watery discharge from the vagina, and lower back pain (Although lower back pain is seen in normal pregnancy, back pain occurring before term maybe be associated with preterm).[3]

Other symptoms include mild abdominal cramps and vaginal bleeding (which includes light bleeding). Some women get harmless false labor called Braxton hicks contractions, it usually stops after moving around or resting.[4]

RISK FACTORS:

High-risk factors

The following risk factors increase a woman's likelihood of giving birth to a preterm child: Previous history of preterm delivery, multiple gestations (twins or triplets, etc.), use of assisted reproductive technology like In vitro fertilization (IVF), Gamete intrafallopian transfer (GIFT), certain maternal anomalies of the reproductive organs like the short cervix.

Certain clinical conditions of the mother like, urinary tract infections, sexually transmitted infections, increased blood pressure, being obese or underweight, placenta previa, gestational diabetes, problems with blood clotting, and vaginal infections such as bacterial vaginosis and trichomoniasis can also increase the risk of preterm delivery.[5]

Other factors

African American and Indian/Alaskan moms are more likely to deliver preterm babies than white mothers are. Other risk factors include the mother's age (mothers under the age of 18 and beyond the age of 35 are more at risk), and a pre-pregnancy body mass index of 19 kg per m^2. Lack of prenatal care, alcohol and drug use, illegal drug use, domestic abuse (physical, sexual, or emotional), a lack of social support, stress, long work hours with prolonged standing, and exposure to certain environmental pollutants are some examples of lifestyle and environmental risk factors.[5]

ETIOLOGY:

There are various causes for preterm birth (PTB) which can be broadly classified into two categories,

- ❖ Maternal cause
- ❖ Placental cause

MATERNAL CAUSES:

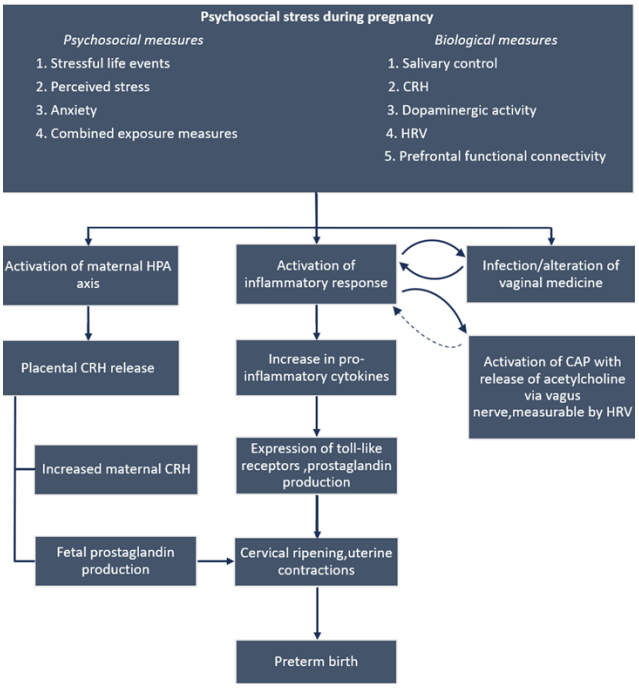
Psychological and social stress

Pregnant women experiencing high levels of psychosocial stress leads to an increased risk of preterm birth (PTB). Stressful conditions are housing instability, material hardship, smoking, drug, and alcohol use, poor nutritional intake & pregnancy-related anxiety. The mechanism involved in psychosocial stress is corticotropin-releasing hormone and increased serum concentration of inflammatory markers. i.e., C-reactive protein.[2]

Table 1: Causes of Preterm birth

CAUSES OF PRETERM BIRTH	
MATERNAL CAUSES	**PLACENTAL CAUSES**
• Psychological and social stress • Systemic inflammation • Maternal complications • Maternal deficiency • Pregnancy interval • Vaginal bleeding • Cervical insufficiency • Abdominal surgery • Multiple gestations • History of preterm labor • Pre-pregnancy weight • Teratogenic effect	• Placental abruption • Placental previa • Chorioamnionitis and Funisitis • Umbilical cord complications • Prolonged membrane rupture • Maternal and fetal vascular malperfusion

Table 2: Pathophysiology of Psychosocial stress during pregnancy



Systemic inflammation

Preterm labor (PTL) is a common and significant disease-causing mechanism, often resulting from intrauterine infection or systemic administration of microbial products to pregnant animals. Premature parturition is linked to extrauterine maternal illnesses, such as pyelonephritis, subclinical infections, and inflammation in the middle of pregnancy. Prematurity can be avoided by treating asymptomatic bacteriuria. Intrauterine infections activate the innate immune system, leading to preterm delivery. Microorganisms are recognized by pattern-recognition receptors, eliciting the release of inflammatory chemokines and cytokines. Prostaglandins, other inflammatory mediators, and matrix-degrading enzymes

are produced by the stimulation of microbial endotoxins and proinflammatory cytokines, leading to uterine contractility and preterm labor.[2,6]

Maternal complications of pregnancy

Maternal complications like thyroid disease, eclampsia, pre-eclampsia, asthma, diabetes, and hypertension increase the risk of preterm delivery.[2]

Maternal deficiency

Pregnant women who have low serum concentrations of iron, folate, or zinc, are at high risk of preterm labor which is associated with reduced uterine blood volume and decreased blood volume.[2]

Inter-pregnancy gap

When the interval between two consecutive pregnancies is less than 6 months, it is considered a risk factor for preterm birth. This is because the uterus of the mother takes some time to recover completely after the previous parturition and also there occurs depletion of vitamins, minerals, and amino acids which takes time to get replenished in the maternal body. Younger maternal age (<19 years) also largely affects the growing fetus leading to preterm birth.[2,6,7]

Vaginal bleeding

Vaginal bleeding is brought on by placental abruption or placental previa, which carries a significant risk of preterm delivery. Particularly bleeding during the first and second trimesters is linked to subsequent preterm. Preterm delivery and PPROM are also caused by excessive amniotic fluid volume.[2]

Cervical insufficiency

Cervical insufficiency, caused by a structural or functional problem, is the inability of the cervix to retain the fetus in the uterine. The human cervix is a sophisticated organ that goes through a great deal of change during pregnancy and delivery. During pregnancy, the cervix undergoes a complicated remodelling process that includes timed biochemical cascades, interactions between the extracellular and cellular compartments, and inflammatory cell infiltration of the cervical stroma. Pathways of the competent cervix are,

Cervical remodeling /ripening → decidual activation → uterine contractions.

Any distraction in this timed interaction could result in early cervical ripening, cervical insufficiency, and preterm birth or miscarriage. According to recent research, cervical incompetence functions are influenced by both endogenous and exogenous factors, such as uterine contraction and decidual/membrane activation.[2,8]

Abdominal surgery

The surgeries include those are adnexal masses, acute appendicitis, gallstone disease, and others. In surgeries, no maternal or fetal death occurred, and no observable newborn birth abnormality existed. In patients in their second and third trimesters, preterm labor occurred. Patients with appendicitis and those who underwent adnexal surgery were most likely to experience preterm labor. Only 5% of the patients' preterm deliveries seemed to be directly related to abdominal surgery.[2,9]

Multiple gestation

More than 50 percent of multiple births result in preterm delivery occurring before 37 weeks of gestation. The causes of twin pregnancies being born preterm are still not fully understood. Due to the increased fetal and placental bulk, physiological variables that trigger the commencement of parturition, which includes increased stretching of the womb, placental corticotrophin-releasing hormone, and lung maturation factors, may be stronger in multiple pregnancies. A role is also played by pathological processes like infection and cervical insufficiency. Progesterone therapy and cervical cerclage, which are used to prevent premature birth in singleton pregnancies, don't seem to work as well in multiple pregnancy cases.[2,10,11]

History of preterm labor

A woman who had a previous preterm delivery has an increased risk by 2.5 times. Additional premature births are at risk the gestational age of the preceding preterm delivery is inversely associated. Women who have early spontaneous preterm births are far more likely to have subsequent spontaneous preterm deliveries; women who have indicated preterm births tend to repeat such births. The cause for the recurrence is not always evident.[2]

Pre-pregnancy weight

Maternal body mass index (BMI) is one of the PTB risk factors that may be modified. PTB is linked to both low (18.5) and high (>29) BMI levels.[12]

Teratogenic effect

Pregnant women with a history of drug abuse which includes opioid, cocaine, cannabis, amphetamine, and poly-substances cause preterm birth.[2,6]

PLACENTAL CAUSE

Placental previa

Placenta previa is defined as the complete or partial covering of the internal os from the cervix with the placenta. This condition causes painless vaginal bleeding in the second or third trimester of pregnancy. The placental previa and low-lying placenta are risk factors for preterm birth. Placental previa is a higher risk factor than a low-lying placenta. Placenta previa causes postpartum hemorrhage and leads to morbidity and mortality in mothers and neonates, so it requires delivery of the neonate by Caesarean before the gestational period, i.e., between 28 and 37 weeks.[13,14]

Placental abruption

Placental abruption is the early separation of the placenta from the lining of the uterus before the completion of the second stage of gestation, which is when maternal vessels tear away from the placenta and bleeding occurs between the uterine lining and the maternal side of the placenta, leading to an accumulation of blood that pushes the uterine wall and placenta. It causes the fetus to die, so the fetus is delivered before the gestational period.[14,15]

Chorioamnionitis and funisitis

Chorioamnionitis and funisitis are caused by bacteria commonly found in the vagina. It is a common cause of preterm birth and is associated with fetal inflammatory responses. The placenta is composed of three major structures: the placental disc, the chorioamniotic membrane, and the umbilical cord. Acute inflammatory mediators of the placenta infiltrate the neutrophils in each structure when the inflammatory process affects the chorion and amnion it is chorioamnionitis; when it affects the villous tree, it is acute villitis; and when it affects the umbilical cord, it is funisitis. These infections increase TLR4, TNF-alfa, IL-1, IL-1, and IL-6 in amniotic fluid, which leads to an increase in systemic cytokine concentration, followed by leucocytosis, which results in apoptosis, premature preterm membrane rupture, cervical ripening, and the onset of premature labor.[16,17]

Umbilical cord complication

Umbilical cord complications include the cord being too long or too short, not connecting well to the placenta, or getting knotted or nuchal. These are major complications of the umbilical cord that may cause the fetus to die or stillbirth. Usually, the umbilical cord helps the fetus by providing blood, oxygen, nutrients, and waste disposal. When the baby moves around, the tension on the cord promotes growth, lengthening the cord. If the cord is too short, the baby might not move around enough. The biggest complication of a short cord is placental abruption, resulting in severe bleeding and poor oxygen supply to the fetus. It requires a rapid C-section to prevent further complications.[17]

Premature rupture of membrane (PROM)

Premature rupture of membranes, or PROM, is characterized as membranes rupturing before the start of labor. Preterm PROM (PPROM) is when the membrane ruptures before labor and/or before 37 weeks of gestation. Increased levels of local cytokines, an imbalance in the way matrix metalloproteinases interact with one another, protease activity, and other variables that raise intrauterine pressure are the causes of PPROM. Short cervical length, second- and third-trimester vaginal hemorrhage, dietary inadequacies, low body mass index, smoking, and illegal drug use are additional significant risk factors.[18]

Maternal and foetal vascular malperfusion

Maternal and fetal vascular malperfusion (MVM), which is frequently linked to hypertensive disorders of pregnancy, fetal growth restriction (FGR), and placental abruption—collectively known as clinical ischemic placental diseases (IPD)—is visible in a major fraction of spontaneous preterm birth (SPTB) cases, according to placental histology.[19]

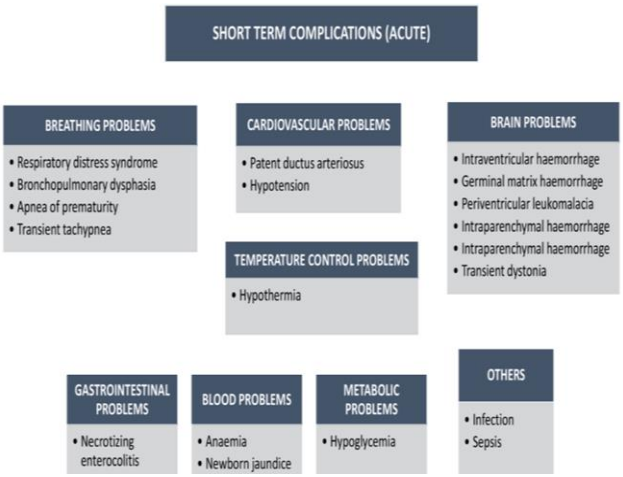
COMPLICATIONS IN PRETERM BABIES

Complications that happen in babies of preterm birth can occur as short-term or long-term complications.

SHORT-TERM COMPLICATIONS (ACUTE)

Preterm delivery occurs for a variety of reasons. Babies born before 37 weeks are more prone to develop postpartum as well as chronic complications. Short-term complications are observed within a month, in the neonatal stage of the preemies.[20]

Table 3: Short term complications of preterm birth



Breathing problems:

Breathing problems in premature babies are caused by an immature respiratory system.[20]

1). Respiratory distress syndrome (RDS)

Neonatal respiratory distress syndrome, or RDS is a frequent cause of respiratory distress in a newborn which happens immediately or within hours after birth. RDS is more prevalently seen in preterm neonates than term infants. The incidence of RDS is inversely proportional to the gestational age of the infant, the smaller and more premature the baby is the more will be the severity of RDS.[21]

Neonatal respiratory distress syndrome (RDS) is due to the surfactant deficiency that prevents the air sacs from collapsing due to insufficient production of surfactants or surfactant inactivation in the case of immature lungs. The diagnosis of neonatal respiratory distress syndrome is imprecise and requires an overall assessment of prenatal and delivery history to identify perinatal risk factors, clinical presentation like non-specific respiratory

symptoms, including tachypnea, nasal flaring, grunting, retractions, and cyanosis, with decreased air entry on auscultation, radiographic findings, and evidence of hypoxemia on blood gas analysis.[21]

The goal of the management of neonatal respiratory distress syndrome is to decrease incidence and severity using antenatal corticosteroids, followed by optimal management using respiratory support, surfactant therapy, and overall care of the premature infant.

Therapy:

- Antenatal corticosteroids
- Monitoring oxygenation and ventilation
- Assisted ventilation of the neonate
- Exogenous surfactant therapy
- Supportive care, including nutritional support, fluid with electrolytes management, antibiotic therapy, etc.[21]

2). Bronchopulmonary dysplasia (BPD)

Bronchopulmonary dysplasia (BPD) is a pulmonary disorder affecting preterm infants. BPD is usually associated with prematurity and it lacks effective prevention and treatment. The etiology and pathogenesis of BPD are yet to be explained clearly. It is believed that the occurrence and development of BPD may have some links with premature birth where the newborns inhale high concentrations of oxygen, on long duration of mechanical ventilation, and are affected by infections. However, some studies showed that there is no significant relationship between the severity of BPD and gestational age/birth weight.[22]

The symptoms of BPD depend on its severity. The most common symptoms of bronchopulmonary dysplasia are rapid breathing, wheezing, difficulty feeding, labored breath, repeated lung infections, and the need for continued oxygen therapy. There is no specific treatment for BPD, and the whole goal of management is to reduce the damage to the lungs and provide support to the infant's lungs. Drug therapies considered are, diuretics, bronchodilators, corticosteroids, viral immunization (especially respiratory syncytial virus – RSV), cardiac therapy, and patients in severe cases, may require oxygen for several months.[23]

3). Apnea of prematurity (AOP)

Apnea of prematurity is defined as a pause in breathing that lasts more than 10-20s accompanied by bradycardia and/ or oxygen desaturation in newborns. AOP has become a common diagnosis in the Neonatal Intensive Care Unit (NICU), affecting almost half of the preterm babies and nearly all whose birthweight is below 1000g. Apnea of prematurity is associated with short-term consequences like hypoxia and long-term consequences like poor neurodevelopmental outcomes. Apneas are divided into central, obstructive, and mixed. AOP is the consequence of immaturity, with insufficient central respiratory drive and subsequent reductions in airway tone.[24]

Clinical presentations of AOP include short respiratory pauses, bradycardia, dyspnea, low oxygen levels, and cyanosis. In severe cases, respiratory pauses occur longer than 20 seconds with bradycardia and cyanosis.[25]

AOP treatment options are limited and include,

- Prone positioning
- Methylxanthine therapy (e.g., caffeine, theophylline, and aminophylline)
- Nasal intermittent positive pressure ventilation (NIPPV)
- Continuous positive airway pressure (CPAP)

Other reported treatments that are not widely used include sensory stimulation, CO_2 inhalation, and red blood cell transfusions. Systematic review studies showed that caffeine and theophylline are effective in reducing apnea within 2 to 7 days of starting treatment but caffeine is safer and has a wider therapeutic range to be used in newborns.[25]

4). Transient tachypnea

Transient tachypnea of the newborn (TTN) is a self-limiting condition that can present in infants of any gestational age, especially before the completion of 39 weeks gestation. It is caused due to delay in the clearance of fluid in the fetal lungs after birth which leads to respiratory distress, affected gas exchange, and tachypnea.[26]

The condition presents within minutes to hours after birth and clinical presentations include, tachypnea, nasal flaring, grunting, crackles, diminished or normal breath sounds on auscultation and intercostal/ subcostal/ suprasternal retractions. Occasionally patients also present with, tachycardia, cyanosis, and barrel-shaped chest because of hyperinflation. Usually, TTN is self-limited, and supportive care is the only need for management with oxygen support and nutritional support.[26]

Cardiovascular problems

1). Patent ductus arteriosus (PDA)

The ductus arteriosus is a fetal vessel that connects the placenta to bypass the lungs to supply oxygenated blood. At birth, the lungs are filled with air, pulmonary vascular resistance is reduced and thus blood flows from the right ventricles to the lungs. The increased arterial oxygen tension and reduced flow of blood through the ductus arteriosus allow it to constrict. The ductus arteriosus loses its function within 12 to 24 hours after birth and anatomically closes within 2 or 3 weeks. But in premature babies, sometimes the ductus arteriosus may not close rapidly and may require medical intervention. If the ductus arteriosus remains patent without closing, it may lead to

pulmonary edema, congestive heart failure, BPD, and renal failure.[27]

Symptoms include a classic PDA murmur – continuous "machinery" murmur, tachycardia, precordial impulses, bounding peripheral pulses, hypotension, and hepatomegaly in case of congestive heart failure. Pharmacologic treatment options include Indomethacin, ibuprofen, and paracetamol, which is considered in preterm babies with a symptomatic PDA. Other conservative management include,

- Increasing peak end-expiratory pressure (PEEP)
- Careful fluid restriction

If PDA is hemodynamically significant and requires increased respiratory support and causes renal impairment, surgical ligation can be considered.[27]

2). Hypotension

Hypotension in preterm is multifactorial and is due to various etiologies. However, it is controversial to define hypotension in preterm babies.[28] One study defined normal blood pressure as less than the 10th percentile for birth weight and postnatal age in infants without IVH.[29]

The treatment of neonatal hypotension should promote the overall status of the cardiovascular health of the infant not just blood pressure. The treatments include,

- Volume expansion
- Inotropes and vasopressors – Dopamine, Dobutamine, and other catecholamines
- Corticosteroids (Mineralocorticoid effect of adrenal glands)

Other agents include methylene blue – a guanylate cyclase inhibitor, dopexamine - a new synthetic catecholamine, and milrinone – a phosphodiesterase inhibitor.[29] Though Antihypotensives are used to treat hypotension in preterm infants, clinicians still face challenges in finding the etiology of hypotension.[28]

Brain problems:

1). Germinal matrix hemorrhage (GMH)

Germinal matrix hemorrhage is one of the major complications of prematurity. The Germinal matrix is a structure located in the periventricular subependymal region which is highly vascularized and acts as a source of glial and neuronal cells during fetal brain development in the immature brain. These glial precursors soon developed into oligodendrocytes, white matter astrocytes, and GABAergic neurons in the thalamus and cerebral cortex.[30]

The GM starts to involute after 32 gestational weeks and the risk of hemorrhage in GM is higher before 32 weeks of gestation. In very low birth weight babies, especially at the time of birth, glial precursors are still migrating into the cerebral cortex and alterations in this process result in a deficit of oligodendroglia and astrocytic precursors which can affect myelination of neurons and cortical development.[30] So, etiology in simple words is due to the rupture of the germinal matrix.[31]

Staging and grading of GMH:

Papile-Burstein classification (based on head ultrasound)

- Grade 1: GMH (typically caudothalamic notch)
- Grade 2: GMH + IVH
- Grade 3: GMH + IVH + ventriculomegaly
- Grade 4: GMH + IVH + ventriculomegaly + parenchymal extension[31]

Volpe (based on head ultrasound)

- Grade 1: GMH + IVH < 10% ventricular area on parasagittal view
- Grade 2: GMH + IVH 10-50% ventricular area on parasagittal view
- Grade 3: GMH + IVH > 50% ventricular area on parasagittal view
- Periventricular echo density (probable PHI – Periventricular hemorrhagic infarction)[31]

Infants are mostly asymptomatic in grades 1 and 2 but they may present, hypotonia seizures, hyperreflexia, falling hematocrit, paresis, acidosis, and feeding difficulties. For now, there is no specific treatment for GMH and the management is usually by keeping the infant stable.[32]

2). Intraventricular hemorrhage (IVH)

Intraventricular hemorrhage (IVH) is also one of the major complications of prematurity. IVH usually starts in the periventricular germinal matrix. The etiology of IVH is multifactorial and is primarily caused by the fragility of the germinal matrix vasculature and problems in cerebral blood flow. The periventricular germinal matrix is highly vascularized and vulnerable to hemorrhage in preterm infants predominantly in the first 48 hours of life. When the hemorrhage in the germinal matrix involves major blood loss, the ependyma breaks, and the cerebral ventricle fills up with blood. Thus, IVH is typically a progression of germinal matrix hemorrhage.[33]

Genetics might play a major role in IVH. In recent studies, thrombophilia was associated with the Factor V Leiden and prothrombin G20210A mutations and these might be candidate genes for IVH.[34]

The majority of the infants with IVH remain asymptomatic and the diagnosis is through cranial ultrasound.[33] There are no specific treatment options for IVH and GMH and there is no way to stop the bleeding associated with IVH. The treatment is mostly based on keeping the infant stable and if the fluid accumulation is high enough to be concerned about cranial pressure, a spinal tap is done to reduce the cranial pressure. If there is still no improvement, surgery may be required to place a shunt or tube to drain fluid.[35]

There are two sequelae of IVH,

- Post haemorrhagic hydrocephalus (PHH)
- Periventricular leukomalacia (PVL)

For the PHH and PVL, intraventricular streptokinase, repeated lumbar or ventricular punctures, and DRIFT (drainage, irrigation, and fibrinolytic therapy) were proved ineffective. In most cases, the patient required permanent stunt placement.[34]

3). Periventricular leukomalacia (PVL)

Periventricular leukomalacia is a type of brain injury more commonly seen in preterm infants that occurs due to changes in the blood flow to the areas around the ventricles of the brain. "Periventricular" refers to the area around ventricles while "leuko" refers to the brain's white matter.[36]

Periventricular leukomalacia is a condition resulting from GM-IVH, where the immature cerebral cortex, containing immature vessels, is damaged by ischemic insults. This damage, near the lateral ventricles, can cause visual impairment and cerebral palsy. Symptoms include unexplained visual loss and systemic abnormalities. Neonatal seizures, fever, infections, pathological jaundice, hypoglycemia during the neonatal period, and feeding difficulties are also noted.[37]

Periventricular leukomalacia is usually diagnosed with ultrasound and MRI of the head. There is no specific treatment for PVL and the management is by keeping the infant stable in the NICU to prevent further complications.[36]

4). Intraparenchymal hemorrhage (IPH)

Intracranial haemorrhage especially in preterm neonates consists of germinal matrix haemorrhage, intraventricular haemorrhage, and Intraparenchymal hemorrhage (IPH). According to the grading system, IPH is also known as Grade 4 hemorrhage.[38]

Grade 4 hemorrhage, primarily seen in preterm infants, is a severe hemorrhage caused by cerebral circulation, neurovascular integrity, coagulation problems, perinatal asphyxia, and birth trauma. It can lead to coagulation disorders, increased intracranial pressure, and developmental issues. The treatment in preterm infants is to assist ventilation, treating seizures with anticonvulsants, and blood transfusions if hemoglobin levels are low.[38]

5). Transient dystonia of the infant

Transient dystonia of the infant is characterized by a unilateral dystonic posture of one upper limb or rarely both limbs that may be associated with dystonia of the trunk or lower limbs. The characteristic posture is an abducting arm, with forearm pronation and wrist flexion, and a varus equine foot posture. These episodes can last from a few seconds to hours and in some infants can even last longer. This episode is usually attenuated during sleep. A good indication is that the dystonia appears on voluntary movements. The diagnostic tool is the Brain MRI.[39]

Temperature control problems

Hypothermia

The World Health Organisation (WHO) defines neonatal hypothermia as a temperature below 36.5 °C (97.7 °F) in neonates. It is classified as below,

- Mild hypothermia/ cold stress – 36.0 to 36.4°C
- Moderate hypothermia – 32.0 to 35.9°C
- Severe hypothermia - <32°C

Hypothermia occurs when there are any alterations in non-shivering thermogenesis (NST), decreased metabolic activity, or reduced peripheral vasoconstriction in newborns. Symptoms usually seen are acrocyanosis, cool/ pale extremities, lethargy, hypotonia, bradycardia, apnea, and poor feeding. In mild to moderate hypothermia, Kangaroo care is preferred to rewarm a hypothermic baby. In severe hypothermia, an incubator or a radiant warmer is used.[40]

Gastrointestinal problems

Necrotising enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is a major gastrointestinal disease affecting 5-12% of neonates at low birth weight, with a 20-30% mortality rate in those requiring surgery. Risk factors include low gestational age, low birth weight, chorioamnionitis, mechanical ventilation, genetic predisposition, intestinal immaturity, microvascular tone changes, and abnormal microbial colonization.NEC is a genetic condition with no clear genetic phenotype, but studies suggest it may be linked to genetic variants of Toll-like receptor-4(TLR-4). Preterm neonates are more susceptible to intestinal injury due to their underdeveloped intestine and lack of GI defense mechanisms. Birth exposure to environmental bacteria and delayed colonization increase inflammatory responses.[41]

NEC is staged using the Bell's Modified Staging Criteria,

- Bell's Stage I – Mild
- Bell's Stage II – Moderate
- Bell's Stage III – Severe

Stage I shows mild systemic signs like temperature instability and bradycardia and mild non-specific intestinal signs like mild abdominal distension and occult blood in the stool. Stage II includes radiological findings of pneumatosis intestinalis and/or portal venous gas with signs like abdominal tenderness, thrombocytopenia, and metabolic acidosis.[41]

Treatment strategies differ based on the severity of the disease and include,

- Broad-spectrum antibiotics

- Bowel rest
- Ionotropic and fluid support
- Conjoint treatment for hypotension, metabolic acidosis, and thrombocytopenia[41]

In severe cases, surgical intervention to remove portions of the ischemic bowel is required. Since there are very limited and non-specific treatment options, studies are more focused on the prevention of NEC. Strategies for the prevention of NEC, early exposure to colostrum, careful nutritional considerations, probiotics, environmental protection, and skin-to-skin care (SSC).[41]

Blood problems

1). Anemia of prematurity

In general, all term and preterm infants undergo physiological loss of hemoglobin when there is a transition between intrauterine to extrauterine environment. In preterm infants, physiological anemia is aggravated by iatrogenic blood loss, especially by phlebotomy and the RBCs of preterm infants have a shorter lifespan of 40-40 days with fewer precursors in the bone marrow. Consequently, the hemoglobin loss is more significant in preterms.[42]

Preventive strategies include,

- Non-pharmacological interventions
  - Delayed umbilical cord clamping
  - Umbilical cord milking
  - Autologous and allogeneic cord blood transfusion
  - Minimising iatrogenic blood loss
- Pharmacological interventions
  - Erythropoiesis stimulating agents (ESAS)
  - Iron supplementation

RBC transfusions are rarely reported in preterms because of complications like Transfusion-related acute lung injury (TRALI) and Transfusion-associated circulatory overload (TACO).[42]

2). Newborn jaundice

Neonatal jaundice is a common condition in preterm infants, causing yellow skin and sclera due to hyperbilirubinemia. It occurs in 80% of preterm infants and requires medical attention and is also the most common condition for re-admission. Symptoms are visible in the face, trunk, and extremities, and visual estimation of bilirubin can lead to errors. Transcutaneous bilirubin is used for screening purposes since visual estimation can lead to errors.[43]

Treatment options include,

- Phototherapy

The unconjugated bilirubin present under the skin is converted to bilirubin photoproducts which are easily excreted in the stools and urine.[44]

- Exchange transfusion

Exchange transfusion is the removal of an infant's blood with high levels of bilirubin and exchange with a fresh donor's blood.[44]

Metabolic problems

1). Hypoglycemia

Neonatal hypoglycemia is a condition where preterm infants and low birth weight infants are at a higher risk due to decreased glucose stores, less adipose tissues, and increased glucose requirements. In diabetic mothers, the fetus produces insulin to reduce blood glucose levels, leading to fetal hyperinsulinemia. Symptoms include sweating, feeding difficulties, weak crying, hypothermia, lethargy, irritability, hypotonia, seizures, apnea, and cyanosis.[45]

Treatment options include,

- Increasing breastfeeding frequency
- Feeding infant formula
- Dextrose gel 200mg massaging in the buccal cavity of the infant

Asymptomatic at-risk infants whose glucose level is <25mg/dL in the first 4 hrs of life,

- Intravenous glucose – bolus of 200mg/kg (dextrose 10%) followed by continuous infusion of 5-8 mg/kg per minute

Second-line therapies include corticosteroids and glucagon.[45]

2). Infection and sepsis

Preterm infants are at more risk for infection and sepsis compared to term infants. Neonatal sepsis is a term used to define infection involving the bloodstream that occurs in infants less than 28 days. It remains the leading cause of morbidity and mortality in preterm infants.

Neonatal sepsis is divided into two,

- Early-onset sepsis
- Late-onset sepsis

Early onset sepsis occurs when pathogens infect an infant during parturition, while late-onset sepsis occurs when pathogens infect the environment. The immature immune system increases susceptibility to infection, and early symptoms include lethargy, poor feeding, and irritability. Empirical therapy and a microbe culture test are necessary, and antibiotic or antimicrobial therapy should be continued depending on the microorganism responsible.[46]

LONG TERM COMPLICATIONS

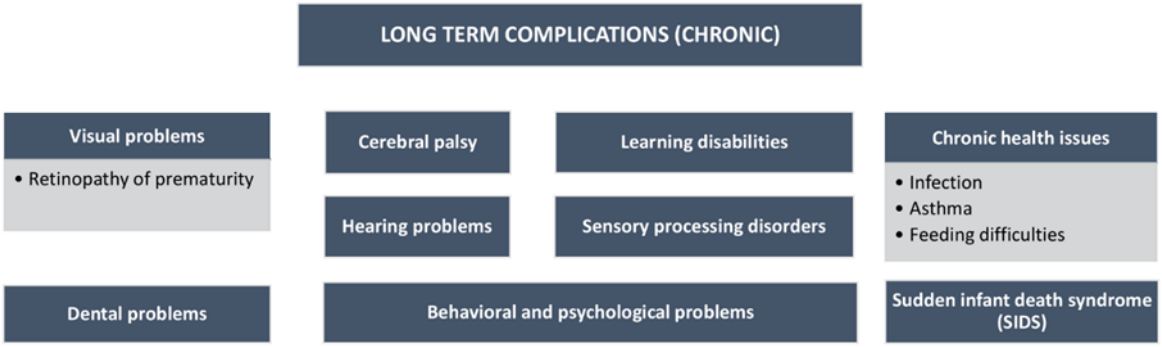


Table 4: Long term complications of preterm birth

Cerebral palsy

Cerebral palsy is a blanket term that is characterized by loss or impairment of motor function. It is caused by changes in the brain which could be a brain injury or abnormal development of the brain during gestation. It majorly affects muscle control, body movement, muscle coordination, muscle tone, reflexes, balance, and posture.[47]

Symptoms are not necessarily visible but signs show clinically identifiable defects of brain injury. The most visible early sign is developmental delay. Symptoms of cerebral palsy include impairment of muscle tone, impaired balance, control, coordination, reflexes, and posture, etc.[47,48]

Diagnosing cerebral palsy is a time-consuming method. There is no specific test that can confirm cerebral palsy and specific treatment to treat. The main goals of management are, to optimize mobility, control pain, prevent and manage complications, maximize independence, enhance social interactions, and optimize the ability for communication and learning.[47]

Learning disabilities

A study showed that children born with extremely low birth weight and preterm infants are vulnerable to learning disabilities at school age which was associated with attention and emotional difficulties. These children showed poor motor experimentation, personal-social immaturity, and language delay. They struggle to manage practical situations at preschool age and academic attainment is affected. All these early indicated risk factors must be brought to attention and child care must be directed according to the child.[49]

- **Visual problems**

1). Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a disease in which retinal vascular and capillary proliferation results in the formation of abnormal blood vessels that supply to the retina.

Preterm babies often experience retina scarring due to oxygen therapy, which can lead to retina detachment and macular folds. This occurs due to incomplete vascularisation of the retina, which is now in a state of hyperoxia due to oxygen therapy. Elevated levels of vascular endothelial growth factor also facilitate retinal angiogenesis.[50]

The treatment of ROP is mostly by surgery.

- Cryotherapy – The sclera, choroid, and full thickness of the avascular retina are frozen from the surface of the eye.
- Argon and diode laser photocoagulation treatment to the avascular retina
- Anti-VEGF agents like Bevacizumab

Retinal detachment is associated with a higher risk of poor visual outcomes. Thus, advanced stages of ROP are indicated to be treated with surgery.[50]

2). Sensory processing disorder

Sensory processing disorder affects interpreting and using environmental sensory information for behavioral regulation and motor performance. It affects half to more than half of preterm children, impacting enjoyment, participation, and skill learning. The exact cause is unclear, but some symptoms can be managed with behavioral therapy.[51]

3). Hearing problems

Hearing impairment is a severe consequence of preterm birth. Its prevalence depends on the maturity of the baby at birth, the more preterm the baby the higher the risk.[52] Ear problems include hearing loss and physical abnormalities of the ear affecting hearing.[53]

Hearing loss in preterm babies is a complex condition exacerbated by ototoxic drugs, noise exposure, hyperbilirubinemia, and hypoxia. Treatment should be initiated within 3 months, and hearing screening programs are being implemented to identify this condition. These programs use non-invasive techniques like Automated Auditory Brainstem Response (ABR) and Otoacoustic emissions (OAE), recording in less than 1 minute.[52]

Symptoms that might be observable, not responding to loud noise, not turning upon calling their name, not letting any first words after 1 year of age, and seeming to hear

some sounds but not all sounds. The treatment is usually dependent on the etiology. In the case of hearing loss, there are several treatment options, cochlear implants, ear tubes, hearing aids, surgery, adjuvant therapy to improve, learning special language, and speech therapy.[54]

4). Dental problems

At the time of premature birth, the primary teeth are still under mineralization and thus affect the teeth development. Previously it was thought that it affects only the primary teeth since the secondary teeth are not yet developed. However recent studies have found that secondary dentition is also affected by preterm birth.[55]

Effects of preterm birth on oral structures,

- Structural changes in the dental crowns
- Palatal distortion
- Retardation of dental growth and development

Enamel defects can be generalized or localized, with generalized defects being symmetrical and primarily caused by birth prematurity illnesses. Localized defects are more likely due to laryngoscopy and intubation. Children under 9 are not eligible for full-banding orthodontic treatment.[55]

Behavioural and psychological problems

Behavioral problems are a sequela of preterm birth. These may contribute to poor academic achievement and educational outcomes. Behavioral and psychological problems include internalizing symptoms – anxiety, depression, externalizing symptoms – oppositional behavior and conduct problems, hyperactivity, and inattention.[56]

Preterm children also have a higher risk for Attention-deficit/hyperactivity (ADHD), autism spectrum disorder (ASD), and anxiety disorder.[57] Sociodemographic factors, such as socioeconomic status (SES), also contribute to behavioral problems. Low SES is associated with less parental education and minimal fiscal resources. In many studies, IQ differentiates preterm from term children, and behavioral symptoms are associated with lower IQ or similar cognitive measures.[56]

Chronic health issues

Some conditions may or may not arise during the childhood of preterm infants till the age of 12. Some conditions are,

- Asthma
- Infection
- Feeding difficulties

1). Asthma

Asthma, a common childhood disease, is characterized by chronic airway inflammation and recurrent breathlessness and wheezing. Preterm infants are at a higher risk of developing asthma due to underdeveloped lung structures, according to a meta-analysis study.[58]

2). Infection

Preterm infants have a higher risk of systemic infections, including early-onset and late-onset infections. Their weaker immune systems make them susceptible to infections during childhood, including urinary tract, pneumonia, and fungal infections. Treatment focuses on eliminating invading microbes and preventing anti-microbial resistance.[59]

3). Feeding difficulties

The phrase "feeding difficulty" could be used to describe a group of causes that result in inadequate intake of nutrition. It could be because of,

- Oral phase disruptions
- Pharyngeal phase disruptions
- Esophageal phase disruptions[60]

Feeding difficulties are also associated with underlying conditions like congenital heart diseases and genetic syndromes associated with hypotonia in infancy.[60]

Sudden infant death syndrome (SIDS)

Sudden infant death syndrome (SIDS) is an abrupt and sudden unexplained death of an infant less than 1 year of age. It usually has no evidence that supports a specific single cause of death. It often occurs during sleep. SIDS comes under the diagnostic term SUID which means Sudden unexpected infant death. SUID includes SIDS, accidental suffocation/asphyxia, and deaths due to uncertain circumstances.[61]

The exact cause of SIDS is not clear but some studies suggest that SIDS is associated with physiologic responses to hypoxemia and hypercarbia and other intrinsic and extrinsic factors.

Unfortunately, SIDS has no symptoms or warning signs. The finding of SIDS involves a review of clinical history, a death scene investigation, and a complete autopsy. The most deaths due to SIDS occur between 12 pm to 6 am.[61]

CONCLUSION

In conclusion, preterm birth continues to be a complex phenomena with numerous underlying causes and related problems. To lessen the burden of preterm delivery on both children and families, a comprehensive strategy combining medical research, public health measures, and improved clinical care is needed to understand the complex etiology and address the myriad problems.

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