Impact of Maternal Health and Disease on Neonatal Outcome

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2.1 Introduction

Low birth weight (LBW) and Preterm births make babies more vulnerable for disease and death in the neonatal period in India and Worldwide. Of 20 million LBW babies born annually, global, 97% are from low-middle income countries (nearly 40% from India), and responsible for 80% of neonatal deaths (neonatal mortality). However, incidence of preterm births is independent of income status, and is the most common cause of disability, and death. in India, premature birth rate is 14 per 1000 live births, with nearly 44% mortality rate. [1] of various factors affecting Neonatal Mortality Rate (NMR), maternal factors (undernutrition, anemia, diseases) and health have a direct and profound impact on intrauterine fetal health, the foundation of neonatal and infant health. Surgical mortality in this age group is very high, depending on a country's development and health infrastructure, nearly 6.7% in South Korea [2], 7.5% in Japan [3], 35% in India [4] and 45% in Nigeria [5]. To optimize neonatal outcome, it is extremely important to maintain good maternal health.

Health is not merely absence of disease and starts with preconceptional nutritional status of the woman, along with the absence of adverse environmental factors (smoking, alcohol, drug abuse, and stress), and encompasses supervised healthy antenatal period.

Undernutrition is an important factor, basis of most diseases in women in the reproductive age group, worldwide. Undernutrition tops the list of medical disorders, obstetric, and miscellaneous maternal factors that impact neonatal health.

Besides maternal health and disease status, other factors contributing to neonatal mortality rate (NMR) are age at delivery, educational status, nutritional status, and

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Table 2.1 Maternal factors that can Impact fetal health

Medical disorders	Obstetric factors	Miscellaneous factors
Undernutrition	Undernutrition	Undernutrition
Pregestational diabetes	Fetal growth restriction (FGR)/IUGR	Maternal age at delivery
Liver and renal disease	Hypertensive disorders of pregnancy—gestational hypertension, preeclampsia, eclampsia	Educational status
Anaemia in pregnancy	Gestational diabetes	Nutritional status
Cardiac and pulmonary ds	Preterm birth	Parity
Chronic hypertension	Multiple pregnancies	Addictions—alcohol, smoking, tobacco/drugs
Thyroid disease		Socioeconomic status
Under nutrition, Obesity		
Infections: TORCH, TB, HIV, COVID-19		Effect of sanitation, hygiene, environment
Neurological disorders		

parity. Risk of neonatal deaths and low birth weight (LBW) babies is 50% more in mothers under 20 years of age.

Maternal factors affecting fetal health and thereby neonatal death are listed in Table 2.1.

2.2   Undernutrition in Pregnancy

Maternal nutrition plays a key role in ensuring appropriate fetal growth and development. Nutritional requirement (macronutrient and micronutrients) is greatly augmented in pregnancy, with additional 350–450 kcal/day in the 2nd and 3rd trimesters. Adequate balanced diet is essential for good feto-maternal outcome and neonatal well-being.

Maternal undernutrition impairs the formation of placenta, uteroplacental circulation, and nutrient delivery to the fetus, resulting in FGR/IUGR, LBW, small for gestational age (SGA), preterm delivery, and birth defects.

Prematurity and congenital anomalies are two important factors of high NMR. 74.8% of all deaths due to prematurity occur in 1st week of life (30% within 1st few hours of birth). 75% of all deaths from congenital defects occur in 1st week of life (almost 50% within 24 h of birth).

Maternal weight gain and gestational weight gain are parameters of maternal nutritional status and fetal growth. Optimal maternal weight should be > 45 kg at any period of gestation, and gestational weight gain should be >300 g/week. **The Barker hypothesis** [6] postulates that undernutrition during pregnancy results in fetal programming, i.e., permanent alteration in fetal morphology and physiology. Epidemiologic studies have shown increased risk of ischemic heart disease and related disorders in later life in babies born during famine situation.

2.2.1 Micronutrients [7–10]

Deficiency of micronutrients (iron, vitamins, calcium, zinc, iodine, folic acid, and magnesium) is also associated more with feto-maternal complications.

1. **Iron** is a cofactor for synthesis of haemoglobin (Hb) and myoglobin, and various cellular functions (O2 transport, respiration, growth, gene regulation, and iron-dependent enzymes). Iron deficiency is the most common cause of anaemia in pregnancy worldwide and is associated with greater risk of preterm birth, LBW, SGA, infections, and abnormal psychomotor and cognitive function development in babies.

2. **Vitamins**
   (a) **Vitamin A** is important for growth, bone metabolism, immune and antioxidant function, gene transcription, vision, and sight. Its deficiency increases the risk of LBW and neonatal mortality. Vitamin A supplement does not reduce the incidence of complications.
   (b) **Vitamin B complex** (B_1 (Thiamine), B_2 (Riboflavin), B_3 (Niacin), B_6 (Pyridoxine), and B_{12} (Cyanocobalamin)) are required metabolism and energy production at cellular level, RBC formation, and conversion of homocysteine to methionine (role in methylation of RNA, DNA, neurotransmitters, and phospholipids). Vitamin B deficiency affects cellular growth and nerve tissue development. **B1 deficiency** impairs fetal brain development, **B2 deficiency** increases risk of CHD and LBW, and **B12 deficiency** causes macrocytic anaemia and increases the risk of abruptio placenta, still birth, LBW, and preterm delivery.
   (c) **Vitamin C and Vitamin E** promote antioxidation and reduce production of free radicals, thereby reducing oxidative stress. Vitamin C also mobilizes iron from body stores, increases GI absorption of iron, and prevents megaloblastic and iron deficiency anaemias, besides its role in collagen synthesis and connective tissue stabilization. Vitamin C by its antioxidant role, and ability to cross-placental barrier, reduces the effects of PET, IUGR, preterm birth, and premature rupture of membranes. Vitamin E cannot cross placental barrier.
   (d) **Vitamin D** has a role in calcium homeostasis and bone integrity. It also has a role in glucose metabolism, inflammatory and immune responses and angiogenesis, and gene transcription. It is important for fetal bone growth, and its deficiency is the cause of neonatal rickets, preterm, and LBW babies.

3. **Calcium** is essential for bone mineralization and maintains cell wall integrity and role in haemostasis and coagulation cascade, muscle contraction, enzyme and hormone homeostasis, neurotransmitter release, and nerve cell function. Its deficiency is a risk factor for preterm labor, LBW, preterm birth, and reduced fetal mineralization. Calcium supplement reduces the risks of these complications.

4. **Zinc** is a catalytic for various enzymes and is a part of nucleotide, proteins, and hormones. It has a role in protein nucleic acid synthesis and metabolism, cell division, gene expression, antioxidation, wound healing and immune responses, vision, and neurological function. Its deficiency is associated with LBW, IUGR, congenital defects, and pre- and post-term births and is a reason for high maternal and infant deaths in developing countries. Zinc supplement is beneficial.

5. **Iodine** is essential for growth and development and synthesis of thyroid hormones. It has a key role in fetal brain and CNS development, and myelination. Its deficiency causes fetal and neonatal hypothyroidism, goitre, and cognitive impairment. Severe deficiency leads to stunted growth (cretinism), irreversible neurological damage, and death.

6. **Folic acid** is a coenzyme for methylation process (DNA, neurotransmitters) protein metabolism, and cell multiplication, and is especially important mineral in the fetal embryonic stage. Its deficiency leads to homocysteine accumulation, fetal anomalies, and neural tube defects. Folic acid supplementation is preventive. Folic acid supplements are beneficial.

7. **Magnesium** is important for enzyme functioning, cell membrane integrity, synthesis of DNA, RNA ATP, and cAMP. Fetal effects of its deficiency are growth retardation, SGA, IUGR, and preterm birth. Magnesium supplementation can reduce these risks.

2.3   Assessment of Fetal Health

Impact on fetal growth and development and thereby neonatal outcome can be assessed by:

1. Estimated fetal weight (EFW)
2. BW

2.3.1   EFW [11–14]

Both small and large for gestational age (SGA, LGA) neonates carry high risk of morbidity and mortality. Timely detection can reduce this risk. Various methods to detect growth in antenatal period include **symphysis fundal height** (SFH in centimetres is equal to the GA in weeks), **ultrasonography** (Hadlock equation is used for GA and Shepard and Hadlock equation for fetal weight), **and biometric parameters (BPD—**biparietal diameter, **HC—**head circumference, and **FL—**femur length**).**

Average fetus weighs 80 g (2.8 oz) by end of 1st trimester and grows reaching weekly weight increase of 220 g (7.8 oz) up to 35 weeks, followed by a decline to weekly gain of 185 G (6.5 oz) until 40 weeks.

2.3.1.1 Fetal Growth Restriction (FGR/IUGR) [15–18]

The fetus fails to attain full growth potential, as estimated by EFW or abdominal circumference less than 10th percentile for the GA (ACOG). Moderate FGR is BW in the 3rd–10th percentile, while severe FGR is BW less than 3rd percentile.

FGR is associated with mild-to-moderate chronic O_2 and substrate deficiency and depending on the time of pathological exposure (Table 2.2), and is classified as:

1. **Symmetric** (20–30% of all FGR): exposure early in the gestation period, characterized by global impairment of cellular hyperplasia and proportional decrease in all fetal organs
2. **Asymmetric** (70–80% of all FGR): exposure late in gestation, characterized by a greater decrease in abdominal size (liver volume and subcutaneous fat tissue) than the HC. The fetus adapts by redistribution of blood flow to vital organs

Table 2.2 Causes of FGR

Fetal factors	Placental factors	Maternal factors
Chromosomal abnormalities: – Trisomy 21, 18, 13 – Turner syndrome – Chromosomal deletions – Uniparental disomy – Placental mosaicism	Abruption	Constitutional factors: Race, Height, weight
Structural malformations: Anencephaly Omphalocele/ gastroschisis CDH Renal agenesis/dysplasia Cardiac & other malformations	Placental infarction	Nutritional factors: – Low pre pregnancy weight – Poor pregnancy weight gain – Inflammatory bowel disease – Chronic pancreatitis – Gastrointestinal surgeries
Multiple pregnancies – Monochorionic gestation – Single anomalous fetus – Twin-to-twin transfusion	Preeclampsia	– Chronic hypertension – Preeclampsia – Collagen vascular disease – Antiphospholipid antibodies – Insulin-dependent diabetes
Fetal infections: – Rubella – Cytomegalovirus – Varicella-zoster	Velamentous cord insertion	Hypoxic conditions: -Congenital heart disease, Severe lung disease, Sickle cell anaemia
	Placenta previa	Environmental: high altitude, smoking, drug abuse
	Circumvallate placenta	Renal diseases: Chronic renal failure, Glomerulonephritis Renal transplantation
	Chorioangioma	Bad obstetric history: still birth, IUGR

(brain, heart, and placenta), compromising flow to nonvital organs (abdominal viscera, lungs, kidneys, and skin)

FGR causes fetal heart rate (FHR) abnormalities and fetal distress (passage of meconium, preterm births, birth asphyxia, still births, and acidosis), 10% are associated with congenital abnormalities (omphalocele, gastroschisis, diaphragmatic hernia, skeletal dysplasia, and congenital heart defects), and 20–60% of malformed neonates are SGA.

Reduced subcutaneous fat and impaired thermoregulation puts them at risk of hypothermia. Chronic intrauterine hypoxia results in polycythemia, hyperviscosity, hypoglycaemia (low hepatic glycogen reserve), and other metabolic abnormalities. They are afflicted with dual morbid states (prematurity and dysmaturity) with adverse consequences (necrotizing enterocolitis (NEC), low Apgar score, IVH—intraventricular haemorrhage, and HIE—hypoxic ischemic encephalopathy) and its sequelae, broncho pulmonary dysplasia (BPD), respiratory distress syndrome (RDS), chronic lung disease, retinopathy of prematurity (ROP), prolonged NICU stay, sepsis, and death. Long-term adverse neurodevelopmental outcomes (cognitive impairment and cerebral palsy) occur in survivors.

FGR neonates require expert care at birth and baby should be evaluated for signs of structural and chromosomal abnormalities and infections. Because of accelerated postnatal growth, they are at risk of obesity, hyperlipidaemia, metabolic dysfunction, insulin resistant type 2 diabetes, cardiovascular, and renal disease in childhood.

2.3.2   Birth Weight [19–22]

Antenatal fetal weight estimate is important because of the potential complications during labor and puerperium arising from fetal prematurity or IUGR. Common classification uses BW alone: **LBW** (1501–2500 g), **very** LBW **(VLBW)** (1001–1500 g), **extremely** LBW **(ELBW)** (500–1000 g), and **micropremies** (<400 g).

BW over 4000 g is considered as overweight (fetal macrosomia) and may be associated with birth injuries (shoulder dystocia, brachial plexus palsy, and fractures), prolonged/obstructed labor/cephalopelvic disproportion (CPD)/instrumental/Caesarean deliveries, birth asphyxia/low Apgar scores, maternal injuries, and post-partum hemorrhage (PPH).

Factors that influence BW include:

– a. **Fetal factors** (GA, gender)
– b. **Maternal factors** [race, height, weight, parity, weight gain, physical activity, Hb concentration, tobacco use, DM, pregnancy-induced hypertension (PIH), and eclampsia]
– c. **Others** (paternal factors and ambient altitude)

2.4   Maternal Diseases Affecting Neonatal Health

2.4.1   Anaemia [23–28]

Anaemia is the most common haematological disorder in women of reproductive age group. As per the World Health Statistics data 2016, almost 30% of reproductive aged and 40% pregnant women are anaemic. There is wide regional and global variation in the prevalence of anaemia in pregnancy, reflecting socioeconomic and nutritional status differences. In the South–East Asian countries, about 50% of all maternal deaths are due to anaemia or its complications. Prevalence of anaemia in pregnancy in India has decreased from 58% in NFHS-3 (National family health survey-3) to 50% in NFHS-4 survey (2015–16).

   Causes of anaemia in pregnancy include:

1. Physiological (dilutional)
2. Iron deficiency
3. Other nutritional deficiencies: folate and vitamin B12
4. Hemoglobinopathies
5. Hypothyroidism
6. Chronic kidney disease (CKD)
7. Chronic infections/helminthic infections
8. Autoimmune haemolysis

   There is a correlation between maternal anaemia and risk of preterm birth, low BW, SGA, low Apgar scores, and increased perinatal and maternal mortality. Iron deficiency is the most common cause of anaemia and a leading cause of anaemia-related maternal deaths [2]. Hb <10.9 g% as a cutoff to define anaemia in pregnancy. Prevalence of anaemia increases from 7% in 1st trimester to 24–39% in 2nd and 3rd trimesters. (Table 2.3)

   The incidence and severity of anaemia is much higher in resource poor as compared to the developed countries, due to low socio-economic status, poor nutrition, lack of access to adequate health care facilities, prevalence of helminthic infections, malaria, inflammatory, and infectious conditions. Severity of anaemia is graded into mild (10–10.9g%), moderate (7–9.9g%), severe (4–6.9g%), and very severe (<4g%), depending on the Hb concentration.

Table 2.3   Definition of Anemia in pregnancy [23, 28]

Trimester of pregnancy	Threshold for defining anaemia
1st	Hb <11 g% (Hct <33%)
2nd	Hb <10.5 g% (Hct <31–32%)
3rd	Hb <11 g% (Hct <33%)
Postpartum	Hb <10 g% (Hct <30%)

Iron requirement in pregnancy is three times that of nonpregnant state, and the demand increases as pregnancy progresses from 4 to 6 mg/day in the 2nd trimester to 10 mg/day in the 3rd trimester. The total iron requirement is 840 mg (accounting for fetus, placenta, expansion of maternal red cell mass, and the blood loss at delivery).

Maternal iron deficiency predisposes fetus to iron deficiency. Iron is important for normal brain development, dendritic growth, synapse formation, and behaviours (grooming, timidity, poor spatial learning, and tasks requiring executive function). Long-term follow-up of infants who had iron deficiency for 3 months or more in their 1st year of life revealed that they were at high risk of cognitive impairment and autistic disorders, but since iron deficiency coexists with other nutritional deficiencies, it is difficult to attribute iron deficiency as a direct cause of cognitive impairment [29].

2.4.2 Haematological Disorders in Pregnancy

2.4.2.1 Thalassemia

Beta thalassemia minor is not associated with any higher risk of adverse outcomes in the neonates, except for higher incidence of neural tube defects due to relative folate deficiency in the mother. **β-Thalassemia major** women tend to be infertile due to chronic iron overload and associated endocrinopathies. However, pregnancies are associated with higher risk of pregnancy loss, prematurity, and FGR due to fetal hypoxia from maternal anaemia. Teratogenic effects of iron chelating agents include vertebral aplasia, abnormalities of ribs and retarded bone ossification, cephalo-pelvic disproportion, and operative deliveries.

2.4.2.2 Pregnancy in Women with Sickle Cell Disease

Pregnancy in women with **sickle cell disease** may cause worsening maternal anaemia and sickling crisis. They may also develop pyelonephritis, haematuria, PET, prematurity, IUGR, and abruption.

2.4.3 Obesity and Pregnancy

Obesity is associated with an array of maternal and perinatal complications, degree of risk amplified with increasing severity of obesity. Class II obesity or greater and high gestational weight gain are at the highest risk of complications. Obesity is defined by a body mass index (BMI) >30 kg/m^2 and can be further stratified into three severity classes, class 1 (30–34.9 kg/m^2), class 2 (35–39.9 kg/m^2), and class 3 (>40 kg/m^2). In Indian population, BMI >25 kg/m^2 is classified as obese, on account of the higher metabolic risks at lower BMI as compared to the west.

Obesity is a metabolic dysregulator. Excessive adipose tissue has a dysregulatory effect on metabolic, vascular, and inflammatory pathways, affecting placental growth and function, with risk of preeclampsia and FGR. Obesity-associated insulin

resistance exposes fetus to high sugar levels, insulin, lipids, and inflammatory mediators, inducing epigenetic changes in the metabolic pathways and increasing the risk of hypertension, coronary artery disease, and diabetes in middle age **(Barker hypothesis)** [6].

Obese pregnant women are at risk of obstructive sleep apnea (OSA), early pregnancy loss, developing gestational hypertension and diabetes, occult type 2 diabetes, and PIH, and eclampsia. Multifetal pregnancy, congenital abnormalities, preterm and post-term birth, operative delivery, fetal death, still birth, birth asphyxia, and congenital defects (neural tube defects, cardiovascular anomalies, cleft palate, Anorectal atresia, and limb reduction anomalies) are also common [30].

2.4.4   Antiphospholipid Syndrome

Antiphospholipid syndrome can present with recurrent miscarriages, uteroplacental insufficiency and FGR, preterm delivery, PET, abruption, and fetal death. These occur due to impaired development of trophoblast and thrombosis of uteroplacental vasculature. Babies born are at a higher risk of vascular thrombosis (arterial, venous or small vessel).

2.4.5   Diabetes Mellitus in Pregnancy [31, 32]

Gestational diabetes mellitus (GDM) accounts for 90% cases of DM in pregnancy and 50% develop DM within 5–10 years. In 2019, there were 223 million diabetic women (20–79 years) and 20 million births. In 16% of live births, there was form of hyperglycaemia during pregnancy, and 1 in 6 births was affected by GDM. A vast majority of GDM cases were from low- and middle-income countries.

In GDM, pancreatic β-cell dysfunction prevents increase in insulin secretion, leading to maternal and fetal hyperglycaemia. In the fetus, insulin secretion increases. Insulin is an important growth factor. Hyperinsulinemia results in fetal macrosomia (BW > 4000 g), increased subcutaneous fat, and muscle mass.

2.4.5.1 Effects Maternal GDM on the Baby
The risks to the newborn are due to macrosomia, hyperglycaemia and hyperinsulinemia and increased incidence of intra uterine death (IUD) and perinatal asphyxia:

1. **Diabetic embryopathy** and congenital anomalies—heart disease, anencephaly, spina bifida, microcephaly, and caudal regression syndrome
2. **LGA**, i.e., BW at or above the 90th percentile for GA, and macrosomia (BW ≥4500 g), fetal hyperglycaemia, hyperviscosity, polyuria, hyperinsulinemia (fetal islet cell hyperplasia), and asymmetric fetal growth (broader shoulders, large thoracic, and abdomen). These increase the risk of operative or instrumental delivery, still birth and birth injuries (shoulder dystocia, brachial plexus injury, and fracture), and neonatal depression

3. Newborn **hypoglycaemia** due to islet cell hyperplasia, hyperbilirubinemia, hypocalcaemia, hypomagnesemia, polycythemia, cardiomyopathy, and birth defects
4. Risk of **RDS** from hyperinsulinemia blocking cortisol-induced lung maturation
5. **Long-term consequences**: risk of childhood obesity, diabetes, insulin resistance, cardiovascular diseases, and poor neurodevelopmental outcomes

2.4.6   Pregnancy and Infectious Diseases [33–35]

Infectious diseases are the major cause of late **neonatal death** (8–28 days). 30–40% of all neonatal deaths occur from infections, 50% occur in 1st week, 30% in 2nd week, and 20% in the 3rd–4th week of age. Common infections are acute respiratory infections (ARI) (30%), bacterial sepsis (40%), meningitis (40%), diarrhea (0.6%), and tetanus.

(a) **ARI:** commonest organism isolated is streptococci pneumonia. Mortality is high in LBW, malnourished, and preterm neonates.
(b) **Maternal tuberculosis** increases the risk of fetal loss, preterm delivery, and LBW.
(c) **Neonatal diarrhea contributes** to 3% of all deaths.
(d) **Neonatal tetanus** is contracted from an unimmunized mother, unhygienic delivery, and poor cord care. Once contracted, it is almost fatal. Newborn loses ability to suck at 3–10 days of age and develops spasms, stiffness, and convulsions, and dies.
(e) **Sexually transmitted diseases (STD)**: **Syphilis** is usually transmitted from the mother via placenta and can result in fetal death or disability in 50–80% affected pregnancies. Congenital syphilis is associated with IUGR, anemia, thrombocytopenia, jaundice, hepato-splenomegaly, and neurological manifestations (mental retardation, hydrocephalus, cranial nerve palsies, and seizures) in the baby. **Gonorrhea** increases the risk of conjunctivitis in the newborn and later blindness. **Chlamydia** also exposes newborn to conjunctivitis and pneumonia. **Genital herpes** can lead to neonatal herpes with high mortality and neurodevelopmental sequelae among survivors.
(f) **UTI** and untreated bacteriuria are associated with increased risk of LBW, preterm birth, and high perinatal mortality [33].
(g) **Malaria** is associated with IUGR and LBW.
(h) **Omphalitis** (umbilical infection) is a unique problem in developing countries, attributed to unhygienic home deliveries, poor cord hygiene (nonsterile cutting and unhygienic tying), and local umbilical infection (leads to necrotizing fasciitis).
(i) **Omphalitis along with neonatal tetanus** increases the risk of neonatal sepsis and death.

2.4.6.1 Rubella (German Measles) [36–39]

Rubella is a self-limited infection, but maternal rubella can spread trans placentally to the fetus. Hematogenous spread in the fetus causes vascular cellular damage and ischemia of the affected organs. Rubella infection in pregnancy gains its significance from its teratogenic effects. Preconception or 1st trimester Rubella is associated with the risk of abortion, still birth, and birth defects. The risk of fetal infection is up to 81% in 1st trimester, 25% in 2nd, and 35% at 27–30 weeks and 100% after 36 weeks of gestation. Rubella is an important cause of severe birth defects in endemic countries. During 1996–2010 of more than one lakh infants with congenital rubella syndrome (CRS), 38% were from India.

During the global rubella pandemic of 1964–65, there were thousands of abortions, neonatal deaths, and CRS in newborns in United States. Rubella vaccine was introduced in 1969 and US has been able to eliminate CRS only in 2004. Rubella outbreaks (>2000 cases) were reported from Romania, Japan, and Poland in 2012.

Indian scenario: during a surveillance (2016–18) of 645 suspected CRS cases, 21.2% (137) were confirmed CRS. Of these 137 CRS patients, 78.8% had cardiac defects, 59.9% had eye signs (cataract, glaucoma, and retinopathy), and 38.6% had hearing impairment. 24.1% died over 2-year period.

CRS and the neonate: the classical triad of CRS includes Congenital cataract and glaucoma, congenital heart disease (CHD) patent ductus arteriosus (PDA), pulmonary stenosis (PS), and sensorineural deafness. Other effects are developmental delays, purpura, retinopathy, hepatosplenomegaly, jaundice, IUGR, myocarditis, microcephaly, and meningoencephalitis. DM, thyroid disorder, and panencephalitis can occur later in life [39].

Active rubella infection in a woman is a contraindication to conception until sero-negativity is achieved.

2.4.7 Liver Disease [40–42]

Babies of mothers with hepatitis are at risk of getting the infection from the mother:

(a) **Intrahepatic cholestasis of pregnancy (IHCP)** is associated with adverse perinatal outcomes (preterm birth, fetal distress, perinatal death, and meconium staining of liquor). Bile acids in circulation cause vasoconstriction of placental chorionic vessels, fetal asphyxia, and uterine hypertony.

(b) **Acute viral hepatitis (Hepatitis B)** may be associated with miscarriage, preterm labor, and LBW. The risk of vertical transmission to the newborn is 20–30%. If the mother is both HBsAg and HBeAg positive, the risk of transmission is 90%.

(c) In **Hepatitis C infection**, risk of vertical transmission is 5–10%.

2.4.8 Renal Disease [43–46]

Women with significant chronic kidney disease (CKD) are less likely to become pregnant. Even mild disease is associated with adverse maternal and fetal outcomes. Acute pyelonephritis can trigger preterm labor from fever-induced uterine hyperactivity but usually with no fetal loss.

CKD (with proteinuria and hypertension) is associated with higher incidence of **SGA, LBW, FGR, and preterm birth. Fetal survival** is poor when preconception blood pressure is uncontrolled (>140/90 mmHg). MAP >105 mmHg at conception carries tenfold higher risk of fetal death, higher risk of maternal events than in normotensive CKD, while during dialysis, intravascular volume and blood pressure fluctuations can be deleterious to the fetus.

Renal transplant recipients have a much lower pregnancy rate either due to infertility or from counselling (use of teratogenic drugs). There is **fetal risk of prematurity, FGR, congenital anomalies, RDS, suppressed haematopoiesis, and liver dysfunction**.

Drugs for CKD: angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are preferred drugs because of their antihypertensive and antiproteinuric effects. However, they can cause fetal abnormalities. Diuretics also should be used sparingly and in minimal doses (to prevent volume contraction and electrolyte abnormalities). Loop diuretics (Lasix) are safe in pregnancy. Women on immunosuppressants (calcineurin inhibitors/glucocorticoids) are at higher risk of GDM, infections, and bacterial UTI and adverse fetal consequences.

2.4.9 Maternal Malignancy and the Fetus [47–49]

With advancement in perinatal care and cancer therapy, one is more likely to face a situation where pregnancy is complicated by malignancy in the mother. Malignancy is a high stress state with pathophysiological, metabolic, and biochemical effects in the body, and adverse maternal and fetal effects.

Four treatment modalities exist: surgery, chemotherapeutic (CT) drugs, radiotherapy (RT), and a combination of these:

1. Surgery can be performed during any trimester.
2. Radiotherapy can be given in the 1st and 2nd trimesters, but is associated with risk of birth defects, IUGR, miscarriage, higher risk of childhood cancer.
3. Chemotherapy is rarely used during pregnancy. The risks depend on the drug used and period of gestation. They should not be used in the 1st trimester when organogenesis is occurring because of the risk of congenital malformations and fetal loss. The effect of CT drugs on the fetus may be in the form of IUGR, LBW, SGA, bone marrow toxicity, cognitive impairment, and cardiac effects. Prematurity is most common accompanied by its own adverse effects on the baby.

4. Tamoxifen and Transtuzumab are contraindicated in pregnancy. Women with history of breast cancer are at higher risk of Preterm labor, LBW, or SGA, especially if they received CT or gave birth within 2 years of diagnosis.

However, a study in 2015 could not demonstrate a significant difference in cognitive ability, school performance or behavioral competence in children exposed to CT in utero compared to nonexposed children > 18 months of age, though prematurity was more prevalent in the CT exposed children.

2.4.10 Epilepsy in Pregnancy [50–55]

Epilepsy is a common neurological disorder with prevalence up to 1% in pregnancy. Pregnancy is usually uneventful, but they are at risk of fetal complications (poor fetal growth FGR/IUGR, congenital malformations, prematurity, preterm labor, and adverse neurodevelopmental outcomes in neonates).

Women with epilepsy suffer from anxiety and distress, for fear of harming or injuring the baby and the effect of anti-epileptic drugs (AED). Maternal AED exposure is associated with increased risk of preterm birth, FGR, and congenital malformations (4–6%). Common malformations include neural tube, congenital heart and urinary tract defects, skeletal abnormalities, and oral clefts (Table 2.4). Babies born to mothers on AED may have excessive sedation, lethargy, feeding difficulty, and withdrawal symptoms with inconsolable crying, particularly in preterms.

AEDs have anti folate reductase activity. Low serum folate level is independently associated with higher risk of congenital malformations. Folic acid supplementation diminishes this risk and improves autistic, cognitive, and behavioural outcomes. Family history of birth defects and low level of maternal education are additional risk factors.

Valproate is the major risk, while topiramate, phenytoin, and phenobarbital are of intermediate risk, and levetiracetam and Lamotrigine are least teratogenic and safer in pregnancy.

Table 2.4 Congenital Malformations associated with AED

AED exposure	Congenital malformations
Valproate	Neural tube defects: Spina bifida, lumbosacral myelocele, orofacial clefts, CVS and urogenital malformations, polydactyly, hypospadias
Phenytoin, Phenobarbitones	Orofacial clefts, cardiac malformations, genitourinary defects
Carbamazepine	Neural tube defects. Genitourinary defects, orofacial clefts, cardiac malformations
Topiramate	Oral clefts, FGR, SGA
Lamotrigine	Oral clefts in 1st trimester at high dose (200 mg/day)
Levetiracetam	Low risk of major malformations. Does not affect early development.
Pregabalin	Increased risk of major birth defects
Gabapentin	No increase in malformations. Risk of preterm, LBW, NICU admissions.

Enzyme-inducing drugs (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, and topiramate) can affect the fetal microsomal enzymes and vitamin K degradation in the fetus, inhibiting clotting factor precursors, increasing the risk of haemorrhagic disease of newborn.

Maternal seizures, especially generalized tonic–clonic seizures (GTCS), are hazardous for the fetus. Hypoxia and lactic acidosis during a seizure episode leads to fetal hypoxia due to decreased placental transfer of O2 or postictal apnea in the mother, with decelerations lasting up to 30 min after the seizure. GTCS of 5 or more can cause developmental delay in the fetus and is a negative predictor of verbal intelligence quotient. Other types of seizures are associated with FGR, preterm delivery, and fetal injury. Epileptic seizures in labour are managed by benzodiazepines. There is a risk of neonatal withdrawal syndrome with use of benzodiazepines and AED.

2.5   Multiple Pregnancy

This is associated with higher miscarriage rate, preterm labour (due to overdistension of uterus, hydramnios, and premature rupture of membranes), discordant twin growth (difference of EFW of >25% between the twins), and single IUD with neurological complications in second twin. Fetal anomalies are more common in monozygotic twins including anencephaly, microcephaly, hydrocephalus, cardiac anomalies, and Down's syndrome.

2.6   COVID in Pregnancy

COVID is a new infection, and much data are not available, suggesting increased risk of miscarriage or congenital malformations, FGR, because of COVID-19. However, possibly 2/3rd pregnancies with SARS suffered FGR. Maternal COVID can lead to placental insufficiency and poor uteroplacental perfusion (chorionic intervillous inflammation, thrombosis, and focal avascularisation of the villi), fetal hypoxia, and risk of prematurity.

As per the UK obstetric surveillance system (UKOSS) cohort in 2020, of 265 newborns born to COVID positive mothers, 75% were preterm, 25% required NICU care, and 5% tested positive for COVID [56].

2.7   Conclusion

Maternal health and disease are the most important factors that can affect development and growth of the fetus. Maternal undernutrition, micronutrient deficiency, diseases commonly being anaemia, and others can have adverse effects on the fetus and the newborn baby. Common is IUGR/FGR, SGA, congenital defects, perinatal

asphyxia, CHD, craniovertebral anomalies and neural tube defects, RDS, BPD, IVH, and prematurity.

Anaesthesiologist will likely face these neonates during the course of treatment in NICU or for surgery, and complete evaluation must be done for any birth defects and anomalies. Maternal details, e.g., age at delivery, educational and economic status, parity, whether ANC care provided and regarding complications during the period of pregnancy, etc., can provide a clue to the status of the neonate, and help assess risk of anesthesia and surgery, and take precautions to reduce them.

Most mishaps happen during transport of these sick premature babies from one area to another, especially if unsupervised. These neonates must be transported in preheated incubators with humidity and temperature control and facility for providing O_2 and under supervision of a medical personnel. This can go a long way in improving perioperative outcome.

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