Chapter

The Pathogenesis of Congenital Anomalies: Roles of Teratogens and Infections

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Abstract

Congenital anomalies present with significant financial, social, and moral issues and questions to the family and society and are difficult to rehabilitate. In utero exposure to teratogenic agents and infection are the two most important causes of nongenetic acquired anomalies presenting at birth. Teratogens such as drugs, adverse maternal conditions, and toxins are environmental factors that cause permanent structural or functional malformations or death of the embryo or fetus. Teratogens may cause significant congenital anomalies if encountered during the organogenesis period of 3–8 weeks of fetal life, which is the stage of tissues and organs formation, whereas minor morphological and functional disorders may occur with exposure during the fetal period of first 2 weeks. TORCH group infections (toxoplasmosis, others, rubella, cytomegalovirus, and herpes) are the most serious infectious diseases during pregnancy due to the severity of possible embryo-fetal lesions. With expanding scientific knowledge and clinical experience about the association of these toxins and infections with significant, at times crippling congenital anomalies, the avoidance of exposure to pregnant mothers has become the most important part of their prevention and management.

Keywords: teratogens, drugs, toxins, alcohol, smoking, congenital infections, cytomegalovirus

1. Introduction

In utero exposure to teratogenic agents and infection are the two most important causes of nongenetic, acquired anomalies presenting at birth. The fetal response and susceptibility to such agents are variable, and the effects depend on the type, timing, and duration of intrauterine exposure [1, 2] (**Figure 1**). The end results of such exposures may be organ system malformations; aberrations in organ growth, function, and development; and even death. The developmental stage of organogenesis, which is characterized by rapid cellular differentiation and migration, is the most vulnerable period, as the actively dividing cells are highly sensitive to the adverse effects of noxious agents [3]. The effects of teratogens during the preimplantation embryonic phase of the first two postconceptional weeks might present as all or none, as the uterine implantation of a defective embryo may fail and the pregnancy end with undetected abortion, thus nullifying the possibility of congenital malformations [4, 5] (**Figure 1**).

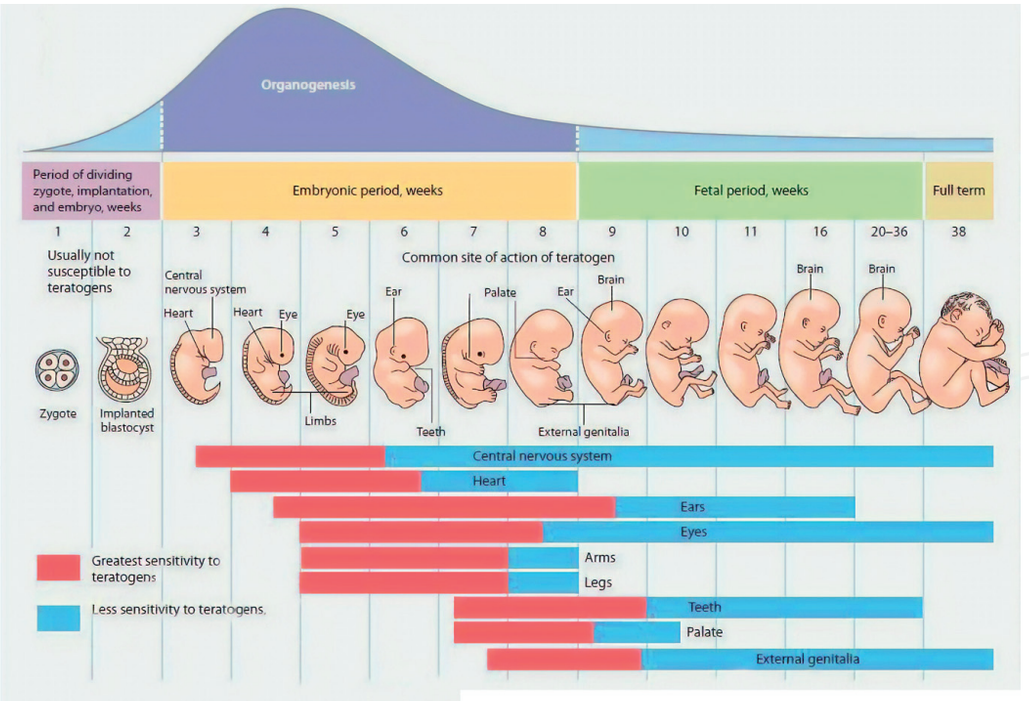

Figure 1.
Sensitivity to teratogens during pregnancy.

Congenital anomalies are health problems that are difficult to rehabilitate. They generate high treatment costs and might bring on huge financial and moral burdens to the family and society. According to the congenital anomalies survey conducted by the World Health Organization (WHO) in 193 countries in 2010, 270,000 of the 3.1 million newborn deaths were caused by congenital anomalies [6]. In the United States, 2–3% cases of the 3–5% of children born with birth defects are attributed to environmental or iatrogenic teratogen exposure during the intrauterine (IU) life [7]. Most of the teratogen-induced anomalies are preventable.

2. Teratogenic agents

Teratogens may cause significant congenital anomalies if encountered during the organogenesis period of 3–8 weeks of fetal life, which is the stage of tissue and organ formations (**Figure 1**). Minor morphological and functional disorders may occur with exposure during the fetal period of the first 2 weeks [8]. Multiple factors come into play for the teratogens to impart their effects. These are the genetic specifications of the conceptus, the dose and duration of exposure, and the mechanism of action of the offending agent. Teratogens effectuate primarily by disrupting cell-specific biochemical metabolism and by compromising blood circulation which lead to cell death. They can destroy and deplete essential nutrients, block enzyme activities, disrupt mitosis, interfere with nucleic acid functions, and derange membrane functions, osmolar balance, and energy production [9, 10]. Genetic differences in response to teratogens have been documented and may be due to the presence of genetic polymorphisms in the activities of enzymes involved in the excretion of toxic substances [11]. Animal studies have shown differences in the susceptibility to teratogen-induced damage within the same as well as between different species. Fetal hydantoin syndrome is detected in 5% of embryos exposed to phenytoin (PTN), and about 30% of them show some congenital anomalies, while more than half display no teratogenic effects [12]. Aspirin, corticosteroids,

and some vitamins are teratogenic in mice and rats, but not in humans. Cleft palate and cleft lip are more common in mice with consanguineous matings [13].

2.1 Drugs

Drugs can directly affect the product of conception and cause malformation and/or embryo-fetal demise. They can impair the fetal development by compromising the transplacental transfer of nutrients and oxygen from the mother. They may diminish fetal blood supply and initiate premature myometrial contractions resulting in premature birth [14]. Drugs can play roles in the intrauterine development of gene-encoding proteins, thereby altering transcription regulation signals which adversely affect embryogenesis [15]. Drugs can exert their effects at different stages of cell development, namely, replication, proliferation, gene expression, signal transduction, programmed cell death, and cell migration (**Table 1**) [16, 17].

2.1.1 Phenytoin

Although the exact pathogenesis of phenytoin (PTN) embryo toxicity is unclear, some possible mechanisms have been proposed [18]. Phenytoin acts as a membrane stabilizer by inhibiting sodium (Na) and calcium (Ca) channels, as a result of which free radicals are released and cause endothelial damage, myocardial depression, bradycardia, and consequently fetal hypoxia. Phenytoin induces cytochrome P450 activation which results in the release of teratogenic free radicals, sourced via the metabolism of epoxides, folate, and vitamin K in the liver [19, 20]. Phenytoin, like other antiepileptic agents, namely, valproic acid (VPA) and vigabatrin, induces

Drug	Most susceptible period	Effects
Phenytoin	Organogenesis (18–60 days)	Fetal hydantoin syndrome, facial cleft, cognitive impairment
Lithium	Organogenesis (18–60 days)	Ebstein's anomaly
Warfarin	Second part of the first trimester (6–9 weeks)	Nasal hypoplasia, limb hypoplasia, optic atrophy, bone abnormalities, neurological impairment
Amphetamines	All trimester	Cleft palate, heart defects, intestinal atresias, and structural brain abnormalities
Sodium valproate	Organogenesis (18–60 days)	Neural tube defect, cleft palate, atrial septal defect, hypospadias, polydactyly, craniosynostosis
Cyclophosphamide	Organogenesis (18–60 days)	Skeletal and ocular defects, cleft palate
Aminopterin	Organogenesis (18–60 days)	CNS, limb, and skeletal defects
ACE inhibitors	Second. or third trimester (13th week term)	Craniofacial abnormalities, neonatal renal failure, pulmonary hypoplasia
Benzodiazepines	Organogenesis (18–60 days)	Cleft lift and palate abnormalities
Lithium	First trimester	Ebstein's anomaly

Table 1.
Some teratogenic drugs and their effects.

carnitine deficiency in the fetus which may lead to cardiomyopathies and ventricular septum defects [21]. Infants born to women with mutations in the methylenetetrahydrofolate reductase (MTHFR) gene are at an increased risk for fetal hydantoin syndrome as its protein products compromise the metabolism of phenytoin and/or its metabolites. Free radicals released as intermediate metabolites of phenytoin bind to deoxyribonucleic acid (DNA), proteins, and lipids and adversely affect the neurodevelopment. The wide variation in the presentation of anomalies related to PTN may be due to the genetic differences in the formation of free radicals, drug clearance, and repair mechanism. Fetal hydantoin syndrome can be seen in approximately 5–10% of infants with in utero exposure to phenytoin, whereas incomplete clinical syndrome can be seen in about one third of them [22]. The characteristic features of fetal hydantoin syndrome include microcephaly, craniofacial anomalies, hypertelorism, flattened nasal root, ptosis, wide mouth, cleft palate-lip, cardiac defects, urogenital malformations, and hypoplastic distal phalanx and nails. There is also an increased risk of neural tube defects (NTD) as this antiepileptic reduces fetal serum folate levels [23].

2.1.2 Valproic acid

Depending upon the dose and duration, the in utero exposure to VPA may increase the incidence of congenital malformations in neonates by 2–16 times [24]. The teratogenic effects of VPA on the fetus are typically caused by maternal ingestion of drug in doses over 1000 mg/day. However, adverse effects can be seen at lower doses of 500 mg/day as well. In one study, the rate of major congenital malformations with fetal exposure to VPA via maternal medication in the doses of <700 mg/day for 1 year was 6%, which increased to 10% when the doses were between 700 and 1500 mg and to 24% when over 1500 mg [25].

Like PTN the exact mechanism of action of VPA is unknown and various theories have been forwarded. Crudup et al. showed that VPA can increase γ-aminobutyric acid (GABA) levels in the brain via the inhibition of its catabolism [26]. VPA can directly inhibit voltage-gated sodium channels or bind to the proteins by acting as a histone deacetylase inhibitor (HDACi). HDACi can disrupt cell cycle, stop growth, and induce apoptosis [27, 28]. Furthermore, VPA induces chromatin changes and reduces the transcription of mRNA by converting chromatin segments to heterochromatin. The high affinity of valproic acid to folate receptors causes their competitive inhibition and increases the frequency of neural tube defects by as much as 20 times [29].

Valproic acid may cause multi-organ system anomalies, including those of craniofacies (epicanthal fold, small wide nose, anteverted nostril, long philtrum, thin upper-thick lower lip, retroverted ears), extremities (polydactyly, arachnodactyly, rudimentary fingers), and spinal column (neural tube defects, spina bifida). Other important defects include those of cardiovascular (ventricular septal defect (VSD), patent ductus arteriosus (PDA), aortic coarctation), respiratory (tracheomalacia), and urogenital systems (inguinal hernia, hypospadias, cryptorchidism, incomplete fusion of the Müllerian duct). The incidence of meningomyelocele, especially lumbar or lumbosacral, is reported to be 1–2% with in utero fetal exposure during the first trimester [30, 31]. Developmental anomalies and autism are other teratogenic effects of VPA described in the literature.

2.1.3 Thalidomide

Thalidomide (TD), which is currently being used for the treatment of multiple myeloma and leprosy, was initially prescribed for pregnancy-associated nausea and

emesis in Europe, Asia, and America, without any preceding drug phase studies in the 1950s. Its teratogenic effects were first noticed in Europe in the early 1960s [32] when several case reports of phocomelia in babies born to mothers treated with TD during pregnancy were published. This revelation became a turning point in the history of pharmacovigilance. In November 1961, Lenz presented the specific features including limb anomalies in 52 in utero exposed infants to TD at a Pediatric Congress. This was followed by a publication documenting an association between the drug and congenital malformations in 1962 [33] (**Figure 2**). Subsequently, 115 case reports of similarly affected infants in Germany, Belgium, Sweden, and the UK were published, and the drug was withdrawn from the market [34]. Thalidomide affected about 10,000–15,000 infants and caused death in more than half of them during this period.

The incidence of congenital malformations is 50% if 50 mg of TD is ingested during the postfertilization days of 20–36 [35]. If given earlier it may cause miscarriages as demonstrated in rats. More than 30 scientific theories for thalidomide embryopathy have been forwarded over the past 50 years [36]. DNA mutagenesis, chondrogenesis, nerve/neural crest toxicity, and inhibition of cell adhesion molecules have been proposed as the potential mechanisms of thalidomide embryopathy. However, the most widely accepted theory is that of the antiangiogenic action of the drug on fetus [37]. D'Amato et al. showed that thalidomide inhibits angiogenic vascularization of the rodent cornea induced by a fibroblast growth factor protein. It is believed that thalidomide exerts its teratogenic effects by adversely affecting the embryonic blood vessels, which results in the disruption of vascularization during organogenesis leading to abnormal fetal growth and congenital malformations [38, 39]. The congenital anomalies caused by thalidomide are phocomelia, dementia, dysosmia, bone hypoplasia, cardiac malformations, ear malformations, splenic agenesis, gallbladder agenesis, and esophageal, duodenal, and anal atresia as well as stenosis [40].

2.2 Toxins

There has been a rapid progress in the awareness of adverse effects of a wide variety of environmental, medical, infectious, and nutritional toxins on the developing fetus since the end of the twentieth century. With the expanding scientific knowledge and clinical experience about the association of these toxins with significant, at times crippling, congenital anomalies, the avoidance of exposure to pregnant mothers has become the most important part of their prevention and management. The congenital malformations associated with exposure to the current known toxins

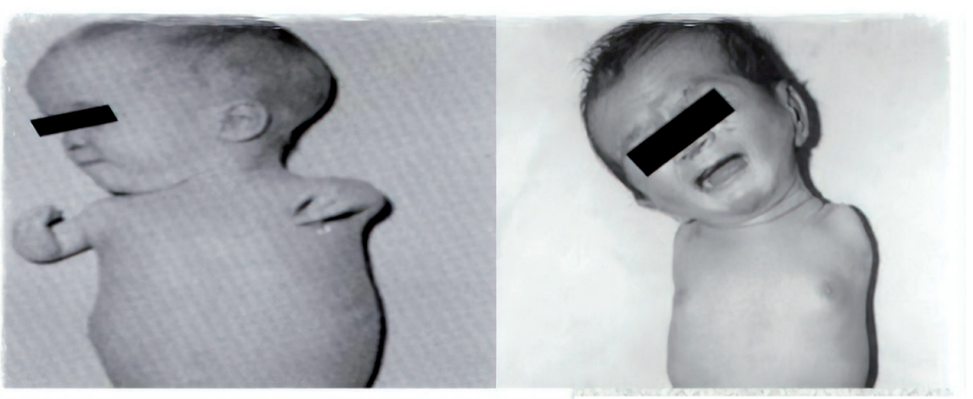

Figure 2.
Phocomelia and amelia.

are deafness, visual impairment, skeletal anomalies, and central nervous system (CNS) malformations, apart from embryonic loss and fetal demise [41].

2.2.1 Radiation

Radiation is a highly teratogenic toxic agent which exerts its adverse effects at cellular, subcellular, and molecular levels. It disrupts the molecular structure by both direct and indirect actions. No cell is known to be completely resistant to the toxicity of radiation. The risks are highest during the organogenesis phase [42], and the most vulnerable part of the cells to radiation injury is the highly active nucleus. The radiation-induced damage to the DNA may result in cell death, genetic mutations, and malformations, the severity and extent depending on the radiation dose and the stage of cell development at the time of exposure. Chromosomal anomalies are observed in cells when they are exposed to radiation during mitosis and DNA molecule formation [43, 44]. Cellular interruption and suppression of cell growth are the most common manifestations of radiation exposure during mitosis. Bergonie and Tribondeau (1906) documented that the most sensitive cells to radiation are the ones that are un- or underdifferentiated with undetermined function and morphology and are undergoing the highest mitotic activity [45]. The effects of radiation exposure during the first 14 days after fertilization are abnormal or failed embryo implantation resulting in miscarriage.

The dose is an important determinant of the radiation toxicity, and, accordingly, all pregnancies may not suffer from adverse effects [46]. As per the International Commission on Radiation Protection (ICRP), the chances of adverse or lethal effects in the preimplantation period of embryonic development are very low if the dose is less than 100 milliSieverts (mSv), and the actual threshold dose for the production of malformations is around 100 mSv [47]. The embryo is most susceptible to radiation-induced congenital malformations during the postconceptional ninth day and sixth weeks, the phase of organogenesis. Cerebral structural and functional anomalies such as microcephaly and mental retardation occur following exposure to doses over 100 mSv during the 8–16 weeks of intrauterine life, whereas ocular and skeletal abnormalities result with doses exceeding 200 mSv. After the sixth week of pregnancy and when the major part of organogenesis is competed, radiation causes neurodevelopmental delays. It is stated that the therapeutic risks of radiation are minimal in doses less than 50 mSv (**Table 2**) [48]. These dose-effect relationships were demonstrated in animal experiments. In humans, microcephaly and mental retardation were the most common anomalies identified in children exposed to radiation during early conception in Hiroshima and Nagasaki survivors

Gestational period (weeks)	Effects	Estimated dose amount
Preimplantation (0–2)	Miscarriage or is not affected	50–100 mSv
Organogenesis (2–8)	Congenital anomaly (skeletal system, genital, or eye)	200 mSv
8–15	Severe mental retardation (high risk)	60–130 mSv
8–15	Intellectual influence	Reduction of 25 intelligence coefficients per Sv
8–15	Microcephaly	200 mSv
16–25	Severe mental retardation (mild)	250–280 mSv

Table 2.
Effects of radiation doses according to the gestational age.

after World War II. Other anomalies noted were low birth weight, cataract, genital and skeletal malformations, and microphthalmos [49]. Streffer et al. suggested that after organogenesis, the effects of exposure may be similar to the postnatal effects with no major congenital anomalies encountered. They reiterated that the mammalian embryo and fetus are highly radiosensitive and the nature and sensitivity of induced biological effects depend upon the dose and developmental stage at irradiation [50].

2.2.2 Alcohol

Alcohol is an important teratogen with multisystemic adverse effects. No amount of consumption is safe during pregnancy. In the USA, one "standard" drink contains approximately 14 g of pure alcohol. This translates to 12 ounces of regular beer (5% alcohol), 5 ounces of wine (12% alcohol), and about 1.5 ounces of distilled spirits (40% alcohol). The 2016 National Institute on Alcohol Abuse and Alcoholism has defined prenatal alcohol exposure as follows: ≥6 drinks per week for ≥2 weeks or ≥3 drinks per occasion on ≥2 occasions, started at 3 months before pregnancy, or at diagnosis, and continued until delivery [51]. The fetus eliminates alcohol poorly at a rate of only 3–4% of the maternal rate. Moreover, part of the alcohol excreted via the fetal urine into the amniotic fluid is swallowed back, thus recirculating it into the system, and a small volume of amniotic fluid alcohol is absorbed into fetal compartments via a transmembranous route. These factors make fetus specifically more vulnerable to the adverse effects of maternal alcohol consumption [52].

As with other teratogenic agents, the effects of alcohol in the fetus vary according to the gestational age and the duration and dose of exposure [53]. Alcohol damages the structure, neuronal migration, and synaptogenesis in the developing CNS of the fetus. The consumption of two glasses of alcohol per day during pregnancy, especially the first 3 months, leads to the typical fetal alcohol spectrum disorder (FASD), which is characterized by structural, behavioral, emotional, and neurological problems in the offsprings [54]. The typical features of this syndrome are the minor facial anomalies, including short palpebral fissure, thinner upper lip, and flat philtrum. Significant pre- and postnatal growth retardation is a common feature, along with variable mental retardation which may manifest as a decrease in intelligence quotient, difficulties in perception, and delays in certain skills-seeking tasks (**Figure 3** and **Table 3**) [55, 56]. FASD may present with congenital cardiac defects as well, the most common being ventricular septal defect, atrial septal defect, conotruncal anomaly, and tetralogy of Fallot. The risk of conotruncal anomaly increases as per the amount of alcohol consumed during the periconceptional period [57].

2.2.3 Smoking and secondhand smoking

Cigarette smoking during pregnancy remains a major worldwide problem despite a significant decrease in incidence as a result of an increasing awareness of its adverse fetal effects. It is estimated that around 10–24% of women smoke while pregnant [58]. Fetal exposure to nicotine negatively affects its growth and increases the risk of neonatal and infant mortality and morbidity [59]. Nicotine and carbon monoxide (CO) decrease the placental blood flow via the vasoconstrictive effects of catecholamines, which are released from adrenals by nicotine activation. Nicotine promptly crosses the placental barrier and reaches its maximum activity in the fetus within 30 min of exposure. The concentration of nicotine in the amniotic fluid is demonstrated to be six times higher at 88% compared to 15%

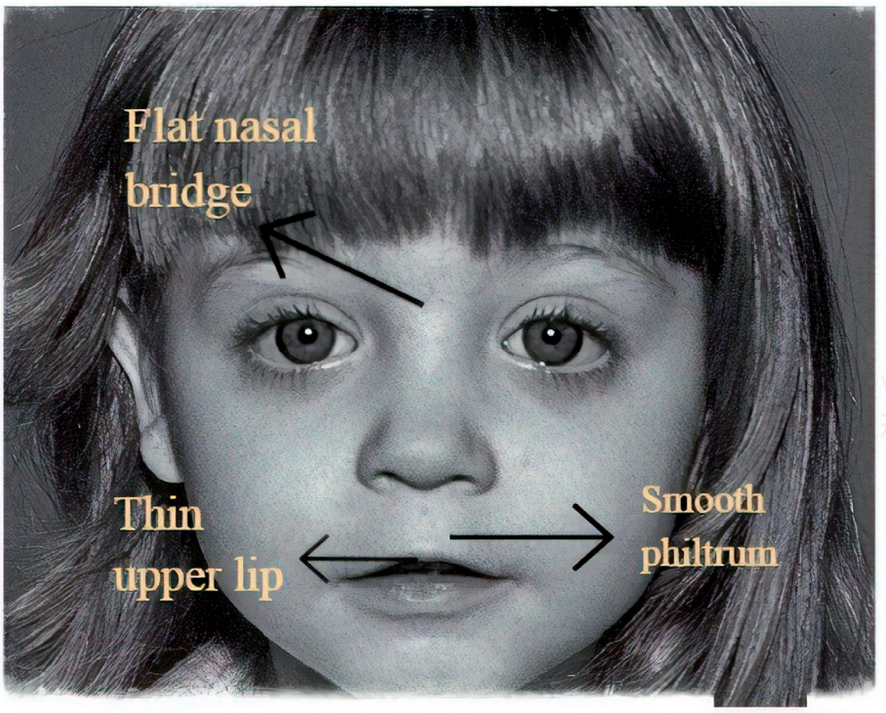

Figure 3.
Fetal alcohol syndrome (© 2009 University of Washington. With permission, Susan Astley, PhD).

1. Fetal alcohol syndrome (FAS) (all conditions will be met)
A. Confirmation of alcohol use during pregnancy
B. The presence of characteristic minor facial anomalies (at least two of the following):
i. Short palpebral fissure (≤10th percentile)
ii. Thin upper lip (score 4 or 5 in the lip/philtrum guide)
iii. Straight philtrum (score 4 or 5 in the lip/philtrum guide)
C. Prenatal and/or postnatal growth retardation:
i. Length or weight ≤ 10th percentile
D. Mental development disorder or abnormal morphogenesis (at least one of the following):
i. Structural abnormalities in the brain
ii. Head circumference ≤ 10th percentile
2. FAS in which alcohol use cannot be confirmed during pregnancy
3. Partial FAS in which alcohol use is confirmed during pregnancy
4. Partial FAS in which alcohol use cannot be confirmed during pregnancy
5. Alcohol-related congenital disorders
6. Alcohol-related neurodevelopmental disorders

Table 3.
Fetal alcohol spectrum disorders.

in the mother's blood. Nicotine acts on the brain by binding to nicotinic acetylcholine receptors (nAChRs) in autonomic ganglia and at neuromuscular junction. The binding results in the release of neurotransmitters and important neuromodulators, such as dopamine, adrenaline, acetylcholine, Seratonin (5- hydroxytryptamine), GABA, glutamate, and substance P [60].

Both nicotine and carbon monoxide induce degenerative changes and premature aging in the placenta. The degenerative changes are marked by an increased amount of collagen in the chorionic villi and the thickening of subtrophoblastic basement membrane [61]. Premature aging is suggested by the increase in the syncope buds and apoptosis in the placentas. Both premature aging and degenerative changes significantly reduce the placental functional capacity and lead to multiple adverse fetal effects. The incidence of premature births is significantly higher in mothers who

smoke [62]. The results of a recent meta-analysis by Hackshaw et al. demonstrated that maternal smoking increases the risks for a variety of system malformations, including those of cardiovascular (cardiac septal defects, malformations of pulmonary and tricuspid valves, and malformations of the great arteries), musculoskeletal (limb reduction, clubfoot), craniofacial (craniosynostosis, cleft lip and palate), and gastrointestinal (gastroschisis) [63].

2.3 Adverse maternal conditions: nutritional deficiencies, diseases, and infections

Nutrients taken during pregnancy can have significant and lasting effects on maternal and newborn health. Inadequate or excessive intake of nutrients if associated with consequent pathophysiological changes during pregnancy can bring about epigenetic changes in the fetus with adverse short- and long-term implications. Optimum intakes of energy and nutrients during pregnancy as well as during breastfeeding are essential for the initiation and maintenance of a healthy life during childhood. It may also protect against several adulthood diseases [9, 64].

2.3.1 Zinc

Zinc is essential for normal fetal growth and development. It is a component of over 200 enzymes which take part in the formation and release of various proteins, hormones, and neuropeptides. The element is involved in the transcription process in which a gene's DNA sequence is copied to make an RNA molecule. Zinc is required for proper cell division, growth, and differentiation. Severe zinc deficiency is embryotoxic and teratogenous and may cause lethal fetal developmental and structural anomalies [65].

It has been shown that maternal zinc deficiency can affect embryonic protein and DNA synthesis and cause chromosomal damage characterized by terminal deletion [66]. Maternal zinc deficiency is associated with increased apoptosis in the embryonic cells. TUNEL analysis has shown that cell death is increased in the peri-implantation embryos if the cultured cells have low zinc levels [67]. The cell cycle may not be adversely affected if the maternal zinc deficiency is short term [68]. In zinc deficiency, the formation of free radicals is increased as they cannot bind to the membranes and intracellular regions of redox-active metals, such as copper and iron [69], which results in increased oxidative stress and teratogenicity. Zinc can prevent oxidation of numerous proteins, including zinc finger transcription factors of redox-sensitive cysteine and sulfhydryl groups. Zinc is a component of copper-zinc superoxide dismutase and is the regulator of metallothionein, a metal-binding protein which has important roles in the execution of various physiological processes and in the prevention of stress [70]. Metallothionein releases zinc, which plays a central role in the antioxidant defense system during oxidative stress. Inadequate zinc uptake of the mother leads to a decrease in the circulating zinc levels which may adversely affect the neural tube development of the fetus as demonstrated in both animals and humans. In humans, the risk of neural tube defects is found to be increased in women with acrodermatitis enteropathica, a rare genetic disorder of zinc metabolism. It is noted that the prevalence of neural tube defects is higher in Africa and the Middle East, where zinc intake is chronically low due to ecological reasons [70, 71]. The relationship between zinc deficiency and cleft palate and lip was demonstrated in a study which showed the zinc levels in the blood of such infants and their mothers to be significantly low [72].

2.3.2 Folic acid (FA)

Folic acid, a group B vitamin, plays an important role in the production of new cells by assisting in the production of DNA and RNA that control cell proliferation [73]. It also works with vitamin B12 to form hemoglobin in erythrocytes. It has a protective effect against heart diseases. It decreases the risk of birth of infants with neural tube defects (spina bifida), obstructive urinary tract anomalies, limb deficiencies, orofacial clefts, and congenital hypertrophic pyloric stenosis [74]. After absorption, folic acid is carried as a monoglutamate in the blood and is converted to various compounds in the cell, the most important being the reductase enzyme, tetrahydrofolate (THF). THF functions as the donor of single carbon units at various steps of DNA synthesis, which is required for the synthesis of purines, thymidylate and hence thymine [75, 76].

Research on the effect of folic acid on NTD began in the 1980s when studies showed that FA is effective in preventing both primary NTD and its recurrence [77]. In a multicenter randomized controlled study which included 1200 women with a history of NTD in their prior pregnancies, FA intake in the dose of 0.4 mg/day started at least 1 month before conception and continued during the first 3 months of pregnancy reduced the risk of NTD by 3.6 times [78]. In a cohort study in China, which included approximately 250,000 women, it was demonstrated that maternal intake of 0.4 mg folic acid reduces the risk of NTD in the fetus by 85% in high-prevalence areas and by 40% in low-prevalence areas [79, 80]. Folic acid has been also reported to reduce the incidence of CHD if used during the preconceptional period [81]. The use of folic acid antagonist drugs, which cause the inhibition of dihydrofolate reductase enzyme, increases the frequency of CHD.

2.3.3 Maternal diabetes mellitus

The discovery of insulin in 1922 and advances in obstetrics and neonatal intensive care reduced perinatal mortality in pregnancies complicated by diabetes mellitus by approximately 30 times. By maintaining maternal euglycemia, such pregnancies were able to continue until term with a resultant decrease in prematurity-related complications including respiratory distress syndrome [82]. Still, perinatal mortality in diabetic women continues to be about twice that of nondiabetic women. Also spontaneous abortion rates are higher in diabetic women, especially if the glycemic control is suboptimal in the periconceptional period [83].

Hyperglycemia has been shown to induce oxidative stress in the developing embryonic and fetal cells and tissues in animal studies, with the release of reactive oxygen species (ROS). Increased concentrations of ROS induce organ malformation and birth defects via membrane changes, mitochondrial dysfunction, and the initiation of abnormally programmed cell death (apoptosis). In mice models injected streptozotocin (STZ) to induce type 1 diabetes hyperglycemia caused changes in the yolk sac, as well as abnormalities in the endoplasmic reticulum and premature aging. It induced oxidative phosphorylation in the mitochondria and increased the concentration of ROS [84]. If appropriate glycemic control is maintained during the third and sixth weeks of pregnancy, the periods when the embryo is most susceptible to teratogens, congenital anomaly rates are found to be the same as in the general population [85]. Vitamins E and C, which are antioxidants, have been shown to reduce hyperglycemia-related anomalies in animal models. Some prostaglandins may have the same effects.

The incidence of congenital anomalies, which is 1–2% in the general population, is 4–8 times higher in infants of mothers with pregestational diabetes. Congenital anomalies are the most important cause of perinatal death in pregnancies

complicated with diabetes mellitus [86]. Although anomalies can be seen in all organ systems in the neonates of diabetic mothers, the most important ones are those in the cardiac and central nervous systems (**Table 4**). Caudal regression syndrome is a rare congenital anomaly caused by maternal diabetes. No increase in the rate of congenital anomalies is seen in normoglycemic mothers or those with gestational diabetes occurring after the first trimester, which reiterates that glycemic control during embryogenesis plays a major role in the pathogenesis of fetal anomalies. Congenital anomalies are found to be more common in pregnant women with high HbA1c levels in the first trimester with a direct relationship with its level and the rate of anomalies [87].

2.3.4 Maternal phenylketonuria (PKU)

Maternal phenylketonuria is one of the most common teratogenic syndromes of pregnancy. Phenylalanine crosses the placenta by active transport and increases the level of phenylalanine in fetal blood by 70–80% of maternal phenylalanine concentration [88]. Increased levels of phenylalanine are toxic and teratogenic to the developing fetus. Spontaneous abortions are observed in 24% of pregnancies with phenylketonuria, and in those who survive, microcephaly is found in 73%, mental retardation in 92%, congenital heart diseases in 12%, and intrauterine growth retardation in 40% of the offsprings [89]. If maternal phenylalanine levels are well controlled before conception and during pregnancy, the incidences of microcephaly and abnormal physical and neurological fetal development are significantly reduced. The prognosis is best in infants of mothers with a blood phenylalanine level of 120–360 μmol/L prior to pregnancy with no increase in the risks, while the prognosis is poor in those infants whose mothers had a phenylalanine level exceeding 360 μmol/L during pregnancy. Severe congenital heart diseases were reported in infants born to untreated pregnant women with high blood phenylalanine levels, especially if the diet restriction was not started until the 7th and 18th weeks of gestation. There is no increase in the risk in pregnant women with phenylalanine level 120–360 μmol/L during the first 8 weeks of pregnancy. Serious fluctuations in maternal phenylalanine levels in pregnancy also have a negative impact on prognosis [90].

In pregnant women with phenylketonuria, sapropterin dihydrochloride, an orally active synthetic form of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin, has been used in the doses of up to 20 mg/kg/day, in combination with a restricted diet for therapy, and the short-term results have been good. Large neutral amino acid

• Cardiac anomalies	• Atrial septal defect
• Central nervous system anomalies	• Ventricular septal defect
• Renal anomalies	• Transposition of large vessels
• Gastrointestinal abnormalities	• Aortic coarctation
• Neural tube defect	• Fallot tetralogy
• Anencephaly	• Trunkus arteriosus
• Uretral duplication	• Dextrocardia/cardiomegaly
• Duodenal-anorectal atresia	• Caudal regression syndrome
	• Sacral agenesis
	• Omphalocele

Table 4.
Congenital anomalies seen in children of diabetic mothers.

(LNAA) treatment, which is one of the other dietary alternatives used in patients with phenylketonuria, is contraindicated in pregnancy because it does not reduce blood phenylalanine levels to safe levels [91].

3. Maternal infections

Congenital anomalies caused by intrauterine exposure to infectious pathogens, especially certain viruses, continue to be a significant clinical problem around the world, despite the availability of vaccines (effective against rubella, varicella-zoster, and hepatitis B viruses), drugs (against herpes, toxoplasma, and HIV), and specific and sensitive immunological diagnostic tests for the majority of them. With the help of highly sensitive diagnostic procedures, the incidence of intrauterine infections during pregnancy is estimated to be about 12–20%. These infections cause a wide range of major anomalies and dysfunctions, including deafness, blindness, neurodevelopmental aberrations, growth failure, and congenital cardiac defects [92]. These diseases have been traditionally dealt with under the title of TORCH complex [93] representing toxoplasmosis; other (syphilis, parvovirus); R, rubella (German measles); C, cytomegalovirus; H, herpes simplex virus (**Table 5**).

The fetus and embryo are highly susceptible to infections, especially during the organogenesis period, while those encountered earlier may end in abortion. The fetus does not synthesize IgG and cannot adequately synthesize IgM and IgA until the second half of pregnancy. It has a very poor cellular immunity and the production of the necessary cytokines is suboptimal [94]. Some pathogens may infect the mother and the placenta without showing any clinical symptoms in mother and lead to miscarriage, congenital anomalies, preterm birth, fetal hydrops, and premature rupture of the membrane.

3.1 Toxoplasmosis

Congenital toxoplasmosis occurs due to the transplacental passage of acute maternal infection with the protozoan organism *Toxoplasma gondii* to the fetus. In neonates, it presents with a wide spectrum of clinicopathological features. It may be clinically asymptomatic and present in a serologically detected form only, at times, to manifest clinically only in later years. On the other end, it may display severe multisystem involvement with debilitating features, such as chorioretinitis, hydrocephalus, and intracranial calcifications [95]. The severity of fetal infection depends on the gestational age during the parasitemia. In early pregnancy, the placenta is an effective barrier to the parasite. The risk of congenital infection increases with increasing gestational age, the incidence being 15–17% in the first, 25% in the second, and 65% in the third trimester [96]. However, the severity and sequelae of the infection are much higher if encountered during early pregnancy. The incidence

• Cytomegalovirus	• Varicella-zoster virus (VZV)
• Human immunodeficiency virus (HIV)	• *Trypanosoma cruzi* (Cong. Chagas disease)
• Herpes simplex virus (HSV)	• Parvovirus
• *Toxoplasma gondii* (Cong. toxoplasmosis)	• Rubella
• Zika virus	• *Treponema pallidum* (Cong. syphilis)

Table 5.
Some strains of infection causing congonse to teratogens are very diverse and depend on the genetic sensitivity and severity of exposure.

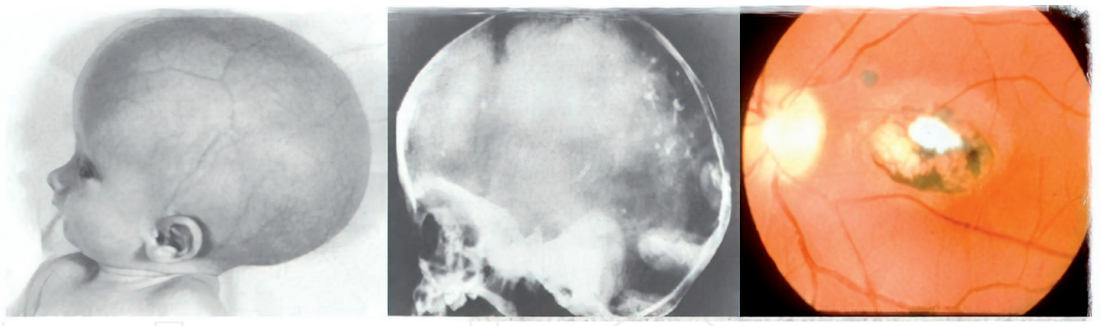

Figure 4.
Hydrocephalus, chorioretinitis, and intracerebral calcification findings in congenital toxoplasmosis.

of organ anomalies is 75% with the fetal infection in the first trimester and 5% if the infection happens during the third trimester. Overall, organ anomalies in congenital toxoplasmosis can be detected in 10–20% of infected fetuses. Preterm birth and intrauterine growth retardation are other complications of intrauterine toxoplasmosis [97]. Fetal infection during the first trimester of pregnancy may result in miscarriage or otherwise present as congenital infection with organ abnormalities specific to toxoplasmosis. Fetal infection occurring in the third trimester of pregnancy is often mild and asymptomatic depending upon the maturation of the fetal immune system and may at times only be serologically detected [98]. In addition, clinical symptoms may appear months or even years after birth. In a prospective study, it was reported that visual disturbances developed and detected during the regular well-child visit examinations of newborns asymptomatic at birth were diagnosed by serological to be due to toxoplasma by age as late as 20 years.

Other features of congenital toxoplasmosis are hydrocephalus, corpus callosum agenesis, cerebral calcification, microcephaly, intrauterine growth retardation, and nonimmune hydrops fetalis (**Figure 4**) [96, 99]. Pathologically, the placenta becomes first infected and appears to be pale, sludge-like, and edematous. Placental vasculitis along with granulomatous inflammatory lesions characterized by polymorphonuclear and lymphocyte infiltration in chorionic villi is specific for the disease. Following fetal transmission, fetal vasculitis develops [100], and the spreading trophozoites tend to settle in the brain and eyes. They form a granulomatous infectious lesion in the brain and its membranes. Eventually tissue necrosis happens around the parasite followed by fibrosis. These pathological processes cause congenital toxoplasmosis-specific microcephaly, cerebral calcifications, hydrocephalus, and chorioretinitis. It is reported that brain damage is more prominent in fetal infection before the 18th week of gestation. Eyes are the most commonly involved organ in congenital toxoplasmosis in which melanin pigment distribution disorder in the uvea and yellow-white edematous retinitis in the retina can be detected [101]. Microphthalmia and optic nerve atrophy may develop in infection encountered during early pregnancy. Deafness may develop in infants due to internal ear involvement. Skeletal muscles and myocardial infections are frequently involved. Moderate pneumonitis emulating viral pneumonia can be detected in the lungs. The liver usually enlarges and may present with pathological changes such as bile stasis, extramedullary hematopoiesis, dystrophic calcification, and portal fibrosis, while the pancreas, genital organs, urinary system, and gastrointestinal organs are generally not affected by the organism. The lymphoid tissue is affected and splenomegaly and adenopathy are commonly seen [102]. Clinically, fever, jaundice, espy direct, respiratory distress due to lung involvement, cardiovascular compromise due to myocarditis, hydrocephalus, and at times convulsions may be seen during neonatal period and in later life. In childhood, retardation is evident in mental and physical development. Vision and hearing disorders may occur in later life [103].

3.2 Rubella

Despite the availability of an effective vaccine, over 100,000 cases of congenital rubella syndrome are reported every year. Congenital rubella infection occurs via transplacental transmission of the RNA virus to the fetus during maternal viremia [104]. The infection may be asymptomatic, present with mild common cold-like symptoms, or devastating. Clinical features such as fetal-neonatal cataract and glaucoma, microphthalmia; patent ductus arteriosus, cardiac septal defects, pulmonary vascular stenosis, sensorineural deafness, fetal growth restriction, thrombocytopenia, anemia, hepatosplenomegaly, hepatitis, direct hyperbilirubinemia, chronic diffuse interstitial pneumonia, osseous changes, and even chromosomal abnormalities are grouped in congenital rubella syndrome. Fetal infection is found to cause necrosis, apoptosis, and division errors of cells involved in organogenesis, resulting in malformations. The mitotic activity is noted to be reduced in rubella-infected cells. Another potential mechanism is that of a direct viral invasion into vasculatures causing tissue necrosis without inflammation (**Figure 5**) [105]. The capsid of the rubella virion (RV) plays an important role in mitochondrial damage and viral replication complexes, as evidenced by immunogold electron microscopy and indirect immunofluorescence studies. Cardiolipin is a phospholipid associated exclusively with mitochondria, and its presence in rubella virions suggests the involvement of the internal mitochondrial membrane of cells in viral proliferation. Both the mitochondrial distribution and morphology are abnormal in RV-infected cells, and the mitochondria tend to cluster in the perinuclear region along with viral replication complexes. In advanced infection electron-dense plaques between opposing mitochondria are formed, and the mitochondrial cristae may be lost in RV-infected cells [106]. The risk of congenital malformation is low after 17 weeks of IU life. It is thought that the immune response mechanisms (immunoglobulins like IgM, IgG, and IgA, T cells, natural killer cells, and interferons) appear during the second half of pregnancy and are not sufficiently mounted against the infection during the first trimester [107].

3.3 Parvovirus

Parvovirus, a non-enveloped single-stranded DNA virus, is the only member of the *Parvoviridae* family known to cause human disease. Failure to produce the virus in cell culture has made it difficult to elucidate the pathophysiology. The symptoms of parvovirus B19-related infection are usually related to the host's immunological and hematological status. Since the immunological functions of the fetus are not optimum, parvovirus B19 infection may cause intrauterine infection, presenting as fetal anemia, hydrops fetalis, congenital malformations, and at times fetal-neonatal death [108].

Figure 5.
Chorioretinitis, cataract, and blueberry muffin skin rash due to congenital rubella.

The vertical transmission of acute infection during pregnancy happens in 17–33% of the cases of maternal infection. Intrauterine infection is often asymptomatic. The fetus is highly susceptible to erythroid hypoplasia due to parvovirus B19 infection, and due to the shorter life span of fetal erythrocytes and the destructive effect of the virus, especially on rapidly proliferating erythrocytes, severe aplastic anemia may develop with the consequent hydrops fetalis. In addition to anemia, thrombocytopenia, leukopenia, elevated transaminase, and increased bilirubin, espy direct may also occur. Intrauterine parvovirus infections may also cause central nervous system anomalies. Fetal loss rate due to parvovirus B19 infection in pregnancy has been reported to be 3–9% and that of hydrops fetalis as 18% [109]. Overall the short-term prognosis of neonates with intrauterine parvovirus B19 infections is reported to be good.

If parvovirus B19 is diagnosed during pregnancy, serial fetal monitoring by Doppler ultrasonography to measure the fetal middle cerebral artery flow velocity in order to evaluate the need of intrauterine fetal blood transfusion is important. The mortality is reduced from 50 to 18% with intrauterine erythrocyte transfusion in conditions of hydrops and/or anemia detected antenatally. One transfusion is often sufficient [110]. The infection usually does not cause intrauterine death if appropriate transfusion and other supportive treatments are provided, and the fetus if born alive has good prognosis [109, 111]. Currently, no specific antiviral agent or vaccine is available for parvovirus B19.

3.4 Cytomegalovirus (CMV)

CMV is the most common organism causing congenital infection around the world. The frequency is reported as 5–12/1000 live births. The risk of transmission increases with increasing gestational age, but the severity of fetal disease decreases. Approximately 10–15% of the fetuses infected in early pregnancy are symptomatic at birth, and in those cases severe systemic invasive disease marked by intrauterine growth restriction, hepatosplenomegaly, cholestasis, transaminitis, abnormal liver function tests, pneumonia, pancytopenia, hemolytic anemia, petechia, purpura, and central nervous system anomalies is noted [112]. Central nervous system findings in congenital CMV infection are quite diverse. Microcephaly, sensorineural hearing loss, chorioretinitis, and convulsion are the most common presentations. Abnormal neuroradiological findings, including ventriculomegaly-hydrocephalus, increased periventricular echogenicity and calcification, white matter involvement, and lenticulostriate vasculopathy, are detected in 70% of the cases. Neuronal migration anomalies, temporal cystic periventricular leukomalacia, occipital intraventricular septa, cerebral atrophy, corpus callosum dysgenesis, and cerebellar hypoplasia are other relatively uncommon findings [113].

The inflammation process in the placenta infected with CMV is characterized by ICAM-1 expression on the membranes of placental trophoblasts, with enhancement in the adhesion of maternal blood cells [114]. During the mother's primary infection, virus-bearing infectious leukocytes transmit CMV infection to the trophoblasts, and through the trophoblasts, the CMV reaches the stromal fibroblasts and fetal endothelial capillary cells [115]. Further in the process the virus is directed toward and proliferates in the major target fetal organs, namely, the brain, liver, inner ear, spinal cord, kidney, and the vascular epithelium. Viral DNA replication takes place in the infected organs with the production of infectious viral progeny. Neurons, oligodendroglia, microglia/macrophages, and neural progenitor/stem cells, especially astrocytes, are particularly predisposed to CMV infections and may act as hosts in the replication and assist in the spread of the virus. The activated apoptosis during organogenesis is the important mechanism that leads

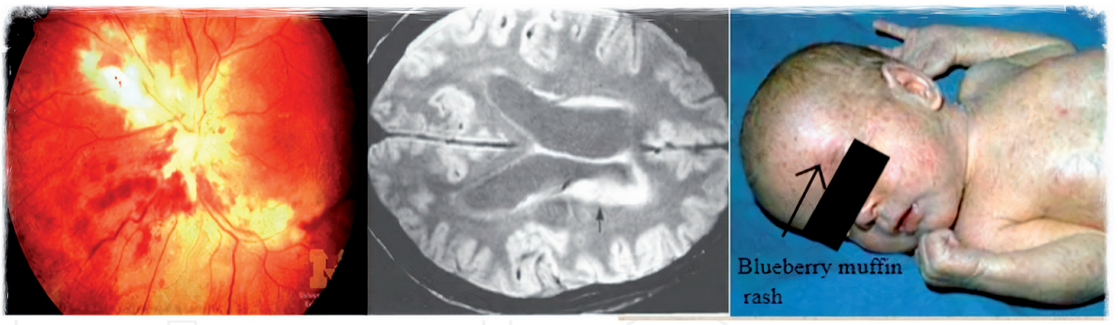

Figure 6.
Congenital CMV-induced chorioretinitis, intracerebral calcifications, and blueberry muffin skin rash.

to malformations [114, 116]. The sensitivity of CMV IgM test, which is frequently used for the diagnosis of congenital CMV infection, is low, and the false positivity rate is high. Urine and saliva cultures for the virus are the recommended investigations for the identification of infection (**Figure 6**) [113, 116].

The Infectious Diseases Committee and the American Academy of Pediatrics recommend that ganciclovir treatment be considered in patients with congenital CMV infection with symptomatic central nervous system involvement (microcephaly, intracranial calcification, hearing impairment, and retinitis). Ganciclovir is a deoxyguanosine analogue and the first antiviral drug shown to be effective in the treatment of CMV infection in humans. It is first phosphorylated to ganciclovir monophosphate by a viral kinase encoded by the CMV gene UL97 during infection. Then cellular kinases catalyze the formation of ganciclovir diphosphate, and ganciclovir triphosphate is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA and preferentially inhibits viral DNA polymerases. Ganciclovir triphosphate inhibits the binding of deoxyguanosine triphosphate to viral DNA, slows viral DNA chain construction, and forms noninfectious viral DNA fragments. The concentration of ganciclovir triphosphate in infected cells is 10 times that of uninfected cells with a half-life in the cell longer than 24 hours [117]. Ganciclovir triphosphate also serves as a poor substrate for chain elongation, thereby disrupting viral DNA synthesis via a second route. However, clinically, ganciclovir treatment remains controversial in congenital CMV infection due to the need of long-term intravenous therapy, frequency of side effects, and limited healing from the infection. The use of valganciclovir, the L-valyl ester of ganciclovir, which is rapidly metabolized to ganciclovir in the body after oral administration, is increasing as with this treatment the need of parenteral therapy, hospitalization, and the risk of catheter-related infection are eliminated. The antiviral therapy may reduce the risk and duration of hospitalization in infants and is also reported to have a positive long-term effect on hearing [117, 118].

3.5 Varicella-zoster

The incidence of varicella infection in pregnancy is approximately 0.4–2.4/1000. The infection can result in severe fetomaternal complications. Spontaneous abortion with varicella infection is observed in the first trimester [119]. Congenital varicella syndrome occurs secondary to infection in the first two trimesters, and the infection is thought to result from the reactivation of varicella and invasion of the placenta, similar to the mechanism of herpes zoster. The syndrome generally presents with an abnormal development of musculoskeletal system, dermatomal pattern of skin lesions, and segmental dysfunction of somatic

and autonomic nervous systems [120]. About 2% of fetuses exposed to the virus during the first 20 weeks of pregnancy (particularly during the 6th–20th week of gestation) may develop congenital varicella syndrome if the mother had no prior exposure to varicella. If varicella-zoster virus (VZV) infection occurs later during pregnancy (i.e., in the middle of the second or in the third trimester), the fetal immune system may be able to mount a response to the invading organism, typically resulting in a benign course. Embryopathy is not reported after 28 weeks. In one study, the incidence of varicella syndrome due to varicella infection during the first 20 weeks of pregnancy was reported as 0.91%, and the syndrome was not observed after 28 weeks [121]. In congenital varicella syndrome, the frequencies of occurrences of various systemic anomalies are as follows: skin lesions approximately 70%; limb hypoplasia 46–72%; nervous system abnormalities, such as cortical atrophy, microcephaly, and mental retardation, 48–62%; eye anomalies such as microphthalmia, cataract, and chorioretinitis 44–52%; and muscle hypoplasia, gastrointestinal, genitourinary, and cardiovascular system abnormalities, and developmental delay 7–24% [122].

3.6 Zika virus

In 2016, the US Centers for Disease Control and Prevention pronounced Zika virus infection as a risk for severe CNS defects in the fetuses of infected mothers. After crossing the placenta, the virus proliferates in the fetal brain tissues and infects the progenitor neural cells, leading to the growth failure and death of neural cells [123]. Although very few cases of Zika embryopathy are reported, the Zika virus-related CNS abnormalities are noted to be as follows: microcephaly, ventriculomegaly, cerebral calcifications, absent corpus callosum, and atrophy of the cerebellum and brainstem.

4. Summary

Congenital anomalies present with significant financial, social, and moral issues and questions to the family and society and are difficult to rehabilitate. In utero exposure to teratogenic agents and infection are the two most important causes of nongenetic, acquired anomalies presenting at birth. Teratogens are environmental and other agents that can cause structural or functional anomalies, or even demise in the embryo or fetus. TORCH (toxoplasmosis, others, rubella, cytomegalovirus, herpes) and other more recently identified infections during pregnancy may present with embryo-fetal systemic lesions of varying severity and result in significant morbidity and mortality. Most of the teratogen-induced and several infection-associated anomalies are preventable. Multiple factors determine the occurrence, presentation, and severity of congenital malformations in neonates who are exposed in utero to teratogens or infections. The individual response to teratogens is very diverse and depends on the genetic sensitivity of the product of conception and the severity of exposure.

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