Chapter 1

An Overview of Teratology

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Abstract

In this chapter, we provide an overview of the basic principles of teratology, beginning with its definition, the critical point for teratogenesis to occur and the most evident etiological agents to improve the understanding of this science.

Teratology is a recent science that began in the early twentieth century, and has greatly improved over the recent years with the advancements in molecular biology, toxicology, animal laboratory science, and genetics, as well as the improvement on the knowledge of the environmental influences.

Nevertheless, more work is required to reduce the influence of hazardous products that could be deleterious during pregnancy, thus reducing teratogenic defects in the newborn. While some teratogenic defects are attributed to their agents with certainty, the same for a lot of other such defects is lacking, necessitating consistent studies to decipher the influence of various teratogenic agents on their corresponding teratogenic defects. It is here that the laboratory animal science is of great importance both in the present and in the future.

Key words Teratology, Basic principles, Etiological agents, Environmental agents, Genetic factors, Maternal conditions

1 Teratology Definition

Teratology (from Greek, *teratos*, monster) is the science that studies birth defects, congenital malformations or developmental disorders (CDDs). These defects could be obvious or latent at birth, owing to the conjugation effects of internal and external factors during the prenatal developmental processes [1]. Congenital disorders or malformations have been described from the times of Assyrian and Babylonian astrologists as well as physicians and philosophers of the Hippocratic era. In the medieval age, they were considered as supernatural phenomena, terata, from which the term teratology derived.

Teratology was born as a science in the 1930s with the publication of the first studies reported in pigs born with eye defects, correlated with a deficient diet in vitamin A, administered to their mother during pregnancy [2]. The etiological factors of these

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anomalies could be divided into internal factors (genetics, around 30% in man), external or environmental factors (15%), and the conjugation of environmental conditions with the genetic susceptibility that accounts for most part of etiology of these defects (55%) [1].

The concept of teratology was postulated in six main principles by Wilson in 1973 (revised by [2]): (1) Susceptibility of the genotype of the conceptus to teratogenesis and the manner in which this interacts with adverse environmental factors; (2) Susceptibility to teratogenesis varies with the developmental stage of the embryo at the time of exposure to an adverse influence; (3) Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate sequences of abnormal developmental events (pathogenesis); (4) The access of adverse influences to developing tissues depends on the nature of the influence (agent); (5) The four manifestations of deviant development are death, malformation, growth retardation, and impaired function [2].

These anomalies result in a developmental disturbance of organ or tissues depending on the gestation period that these factors act on (Fig. 1). The crucial developmental period to have malformations is the first weeks of the gestation (in human, the first 8 weeks), before the first consultation or even the identification of the pregnancy [1]. This is the embryonic period during which the three germ layers (endoderm, mesoderm, and ectoderm) develop into tissues and organs (blastogenesis and organogenesis). The neuronal tissues and sense organs continue to develop during the next period (the fetal period) and continue until birth [4].

Defects of blastogenesis tend to be severe, frequently lethal, and involve several parts of the developing organism. On the other hand, defects of organogenesis tend to involve single structures.

Despite modern approaches of molecular biology and genetics, along with the best diagnostic techniques, we are still not able to identify the actual cause in more than 50% of all congenital defects. About 2–3% of newborns have a single major malformation, and 0.7% have multiple major defects. Minor defects can occur in approximately 15% of all newborns, with most of them not detrimental to the health of the individual, but some of them associated with major anomalies [1].

The frequency is much higher prenatally, and is the cause of the majority of spontaneous abortions at the beginning of pregnancy. More than 80% of malformed conceptuses are lost during the embryonic period, and more than 90% before birth. Over the last few decades, there has been a rapid expansion of methods for detecting many different types of disorders prenatally. Over the recent years, health professionals have gained extensive knowledge about potential teratogenic agents (genetic, physical, chemical, and biological) and maternal conditions (diseases or occupancy conditions), thereby disseminating this scientific information to

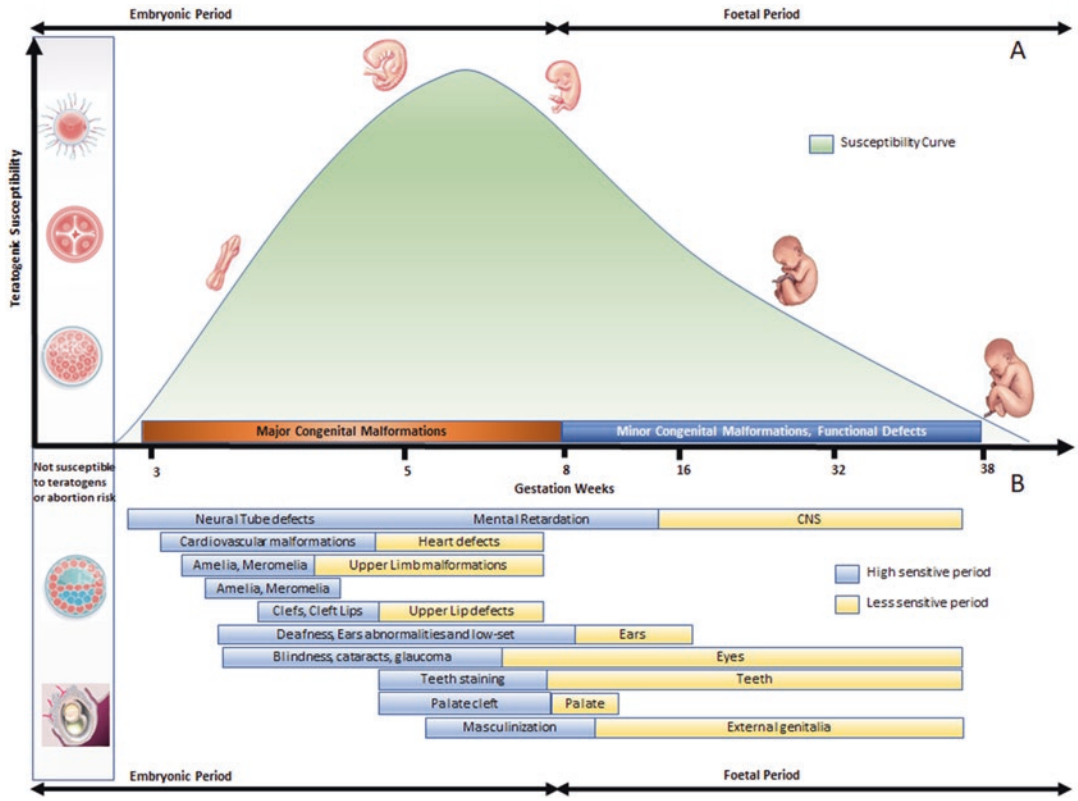

Fig. 1 Critical periods in human development. (**a**) Curve of teratogenic susceptibility during the gestation period; (**b**) Schematic representation of teratogenicity critical phases in the different organs and tissues during embryonic and fetal periods. The blue color represents higher sensitive time, and yellow the lower sensitive period. (Adapted from refs. [1, 3])

the general population, who have become aware of possible exposures and behaviors involving teratogenic risks just before, during the first period of, or even throughout pregnancy.

2 Etiological Agents

The risk factors for developing malformations could be classified as genetic, environmental, modifiable (e.g., prepregnancy obesity and smoking) and nonmodifiable (genetic polymorphisms) [5].

In all etiological conditions, the development stage of the conceptus and its genetic status is fundamental (Table 1). In some cases, the etiological agent could be extremely deleterious and seriously transform the fetus, or as in most cases, it does not have any effect on the fetus.

2.1 Genetic Factors

The genetics of the germinal cells is the first condition to the success of the conceptus. The mother's genetics, diseases, and

Table 1
Teratogenic agents and their effects on fetuses and embryos

Teratogens	Congenital malformations associated with teratogens
Phenylketonuria	Several SNC defects, developmental delay, microcephaly, heart defects, low birth weight
Diabetes mellitus	Fetal death, several SNC defects, anencephaly, spina bifida, hydrocephaly, heart and kidney defects, skeletal malformations, situs inversus, VACERL association
Ionizing radiation	Anencephaly, microcephaly, iniencephaly, encephaloceles, spina bifida rachischisis, microphthalmia, alterations of body axes, conjoined twins, limb defects, duplications, teratomas, diaphragmatic hernia, ectopia vesicae, genital malformations limb defects
Hyperthermia	Microcephaly, heart defects, craniofacial defects, microphthalmia, cataract skeleton and teeth malformations
Mechanical forces	Amniotic band syndrome and sequence, curvature abnormalities vertebral fusions and altered vertebral shape
Anticonvulsants	Club foot, cleft lip/palate, hypospadias; ventricular septal defect, teratology of Fallot, patent ductus arteriosus (PDA), and transposition of the great vessels (TGA), microcephaly, genitourinary anomalies
Fungicides/ antifungals	Brachycephaly, abnormal face, cleft palate, skeleton defects, arthrogryposis, heart defects
Antimicrobials	SNC malformations, ear defects, skeleton and teeth malformations, heart defects, urinary tract defects
Steroids/ nonsteroids	SNC malformations, cleft lip/palate, skeleton defects, masculinization, vagina defects hypospadias
Sedatives/ narcotics	Cleft lip/palate, heart defects
Retinoids	Facial dysmorphia, syndactyly, hip/ankle/rearm malformations, low-set ears, high palate, skull/cervical vertebrae/skeleton defects, heart and cardiovascular malformation
Methylmercury	SNC malformations, eye defects
Lead	SNC malformations
Lithium	Cardiovascular defects, Ebstein's anomaly
Acetazolamide	Ectrodactyly, syndactyly, oligodontia, cleft lip/palate, retarded incisor teeth
Misoprostol	Moebius syndrome, arthrogryposis, talipes equinovarus, gastroschisis
Quinine	SNC malformations, cleft lip/palate, heart defects, musculoskeletal malformations
Thalidomide	Limb defects, heart defects
Warfarin	SNC and skeletal defects
Methylene blue	Intestinal atresia
Alcohol	SNC and skeletal defects

(continued)

Table 1
(continued)

Teratogens	Congenital malformations associated with teratogens
Solvent inhalation	SNC malformations, abnormal auricles, short palpebral fissures, deep-set eyes, micrognathia, small fingernails
Toxoplasmosis	Hydrocephalus, microcephalus, intracranial calcifications, chorioretinitis, skin rash, extramedullary hematopoiesis, purpura, jaundice, hepatosplenomegaly
Rubella virus	Heart disease, encephalitis, mental retardation, thrombocytopenia, deafness, cataracts, glaucoma, aorta thickening, thymus defects, heart defects, hepatocyte swelling and liver histopathology
Cytomegalovirus	Fetal growth restriction, mental retardation, amniotic fluid abnormalities (oligohydramnios or polyhydramnios), SNC disorders (calcifications and enlarged ventricles, polymicrogyria), micromelia, chorioretinitis, blindness, hepatosplenomegaly, unilateral or bilateral hearing loss
Varicella-zoster virus	SNC malformations, microcephaly, mental and psychomotor retardation, musculoskeletal defects, cataract, microphthalmia, chorioretinitis, dysfunction of the bowel or bladder sphincter
Parvovirus B19	SNC malformations
Influenza virus	Spontaneous abortion, SNC malformations
Zika virus	SNC malformations (microcephaly, ventriculomegaly, calcifications, lissencephaly), low birth weight
Schmallemberg virus	SNC malformations (hydranencephaly and cerebrum/cerebellum hypoplasia), torticollis, scoliosis, kyphosis, arthogryposis, brachygnathia, muscle atrophy, lung hypoplasia, micromyelia, diplomyelia
Syphilis	Abortion, prematurity, low birth weight, neonatal and infant death, skeletal malformations, congenital syphilis
Chlamydiosis	Gastroschisis

occupation (described below in Subheading 2.2) are considered as a determinant state in the teratology process.

The influence of the father for the success of the conceptus or in the teratology process is forgotten most of the time. Few reports are recorded about the importance of the father's occupation or his habits that could be determinants in some teratology situations. All these factors are sparsely reported in the literature.

Constitutional chromosomal anomalies that arise during gametogenesis in the mother or in the father, or abnormalities arising in early embryogenesis, affect the majority of the organism's cells, and results in teratology events in the newborn [6].

Constitutional chromosomal abnormities occur in 20–50% of human conceptuses and is considerably higher in other species [6]. Most abortions in the first period of gestation in humans have abnormal chromosome constitution [7]. Even most duplications

(such as trisomies) for all chromosomes have been reported, with most of them lethal during gestation. Nevertheless, some of these alterations are viable and fetuses with trisomies for chromosomes 9, 13, 18, or 21 are viable and born [6].

Other chromosomal conditions are found in individuals with anomalies, such as deletions, duplications, rearrangements such as translocations and inversions, or even aneuploidies. Most of them are correlated with spontaneous early abortions or death of the conceptus at different periods of pregnancy. The frequency of cytogenetic errors in embryos (in humans before 8 weeks of age-related) ranged from 54.3% to 81.3%, with higher anomalies reported in growth-disorganized embryos. In fetuses (developing age after 8 weeks), only 1.7–30.4% presented chromosomal anomalies, particularly higher in fetus with abnormal morphology [6].

The correlation of these chromosomal alterations with environmental or maternal/paternal conditions is the continual aim of the studies in this field, and some are demonstrated to be correlated with for example ionizing radiation and chemicals, viruses, medications, or some maternal diseases.

2.2 Maternal Conditions

Genetic inheritance and a variety of maternal disorders or diseases, as well as deficiency states, may affect the developing embryo. When women with an inherited disorder of metabolism reach childbearing age, they must be counseled with regard to the potential impact of pregnancy on their condition, as well as the impact of their condition on pregnancy and the outcome for their children. The potential teratogenicity of abnormal or elevated metabolites in women with metabolic diseases is poorly defined or unknown. For most conditions and most metabolites, there is simply not enough experience available to allow us to draw any firm conclusions about their teratogenicity [3, 8, 9].

2.2.1 Phenylketonuria

Phenylketonuria (PKU) is one of the most common metabolic diseases in women, caused by an autosomal recessive condition. In PKU, there is a deficiency of the enzyme phenylalanine hydroxylase, which converts the dietary amino acid phenylalanine to tyrosine. High maternal phenylalanine levels are teratogenic to the developing fetus. The maternal PKU syndrome includes developmental delay (92%), microcephaly (73%), cardiac defects (12%), low birth weight (40%), dysmorphic features, and cognitive and behavioral problems [8, 10, 11]. Unlike some harmful substances that affect only a single trimester, excess phenylalanine is associated with a significant increased risk of congenital heart disease in weeks 0–8; brain, fetal, and postnatal growth retardation; wide nasal bridge; anteverted nares in weeks 8–12; and neurologic deficits throughout all 40 weeks of pregnancy in a dose-dependent manner [8].

Girls and women with PKU should therefore be educated and advised to plan their pregnancies in order to achieve good metabolic control of their phenylalanine levels prior to conception. Fortunately, with appropriate specialist management, the teratogenic risk can be eliminated if the mother maintains a very restricted protein diet during the first trimester, and then, as the fetus grows and when protein tolerance increases, protein intake will need to be increased according to her needs [8, 9, 12].

2.2.2 Diabetes Mellitus

Maternal insulin-dependent diabetes has long been associated with fetal death (up to 17%) and multiple congenital malformations involving multiple organ systems. Congenital anomalies, including defects of the heart, central nervous system, kidneys, skeleton, anencephaly, spina bifida, hydrocephaly, situs inversus, caudal dysplasia, and anomalies included in the VACTERL association. VACTERL is an acronym which refers to the relatively common, nonrandom occurrence of costovertebral segmentation defects, anal atresia/stenosis, cardiac malformation, tracheoesophageal fistula and/or esophageal atresia, and renal and limb anomalies [13, 14]. Individuals diagnosed with VACTERL association typically have at least three of these characteristic features [15]. Minor physical abnormalities associated with maternal diabetes include flattened nasal bridge, excess skin folds on the neck, and tapered fingers with hyperconvex nails [3, 15].

The teratogenic mechanism in diabetes remains unknown, and insulin appears to have no teratogenic effect. Diabetes leads to conditions such as hypoglycemia and hyperglycemia, loss of normal homeostasis, and disorders of fat and protein metabolism. The gastrulation and neurulation stages of development are particularly sensitive to hypoglycemia and result in growth retardation as well as cranial and caudal neural tube defects. Hyperglycemia leads to inhibition of the myoinositol uptake that is essential for embryonic development during the gastrulation and neurulation stages of embryogenesis [15, 16].

The mechanisms underlying the association between maternal diabetes and congenital heart defects may also differ between women with pregestational diabetes and women with gestational diabetes. The critical period of heart development is between the third and seventh weeks of gestation. Women with pregestational diabetes would have a diabetic intrauterine environment during this critical period of heart development, and present a high incidence of congenital heart anomalies. On the other hand, gestational diabetes does not develop until the 24th to 28th weeks of gestation, after the critical period of heart development. However, those women with gestational diabetes still show a significant prevalence of every congenital heart diseases, hypoplastic left heart syndrome, Ebstein malformation, and single ventricle [17, 18].

2.2.3 Hypothyroidism

The fetus is dependent on the small supply of thyroxine from the mother until 10–12 weeks of gestation for women (in other species the critical period is the first third of gestation), when the fetal thyroid gland starts secreting thyroid hormones. By 20 weeks of gestation, the human fetal thyroid gland becomes responsive to TSH from its own pituitary gland, but the function of the thyroid gland remains relatively lazy. Hypothyroidism during pregnancy is usually asymptomatic, but needs to be detected and treated to prevent adverse outcomes. Thyroxine is critical for many aspects of fetal brain development including neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and neurotransmitter regulation [19–21].

2.2.4 Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes and thyroid diseases. Hyperparathyroidism usually occurs as the result of sporadic parathyroid adenomas, carcinomas, and can also be associated with multiple endocrine neoplasia, genetic syndromes, or metabolic diseases. Fetuses in mothers with untreated PHPT may suffer from complications secondary to the harmful effects of hypercalcemia [22–24]. Fetal complications include intrauterine growth restriction, fetal death, preterm delivery, and low birth weight. In the postpartum period, neonatal tetany has been reported in 50% of neonates born from untreated women. The newborn hypocalcemia is due to the placental transfer of the elevated calcium levels causing suppression of the fetal parathyroid glands. At delivery, the calcium transfer stops, but the involute parathyroid glands cannot maintain adequate calcium levels. The hypocalcemia is transient, lasting up to 3–5 months (in male babies), but can be managed with calcium and vitamin D supplements [25, 26]. Complications associated with primary hyperparathyroidism during pregnancy have been reported to occur in up to 67% of mothers and 80% of fetuses. Fetal complications include intrauterine growth retardation, low birth weight, preterm delivery, intrauterine fetal demise, postpartum neonatal tetany, and permanent hypoparathyroidism. A fourfold decrease in perinatal complications may be achieved with appropriate therapy [22, 26–28].

Uncontrolled hyperparathyroidism is associated with serious neonatal morbidity and mortality, as well as maternal complications including miscarriage, hypertension, preterm delivery, placental abruption, heart failure, and thyroid storm [29–32].

Mothers with untreated hypoparathyroidism may have transient hyperparathyroidism during the fetal and neonatal periods. The fetal parathyroid hyperplasia that occurs in response to low maternal and fetal serum calcium concentration is mediated by the maternal parathyroid dysfunction. Bone demineralization and subperiosteal reabsorption in the long bones, pulmonary artery stenosis, ventricular septal defects, and muscle hypotonia occur [33, 34].

2.3 Physical Agents

2.3.1 Ionizing Radiation

Ionizing radiation can injure the developing embryo through cell death or chromosome injury. The severity of damage to the embryo depends on the dose absorbed and the stage of development at which the exposure occurs. A study of human survivors of the Japanese atomic bombing demonstrated that exposure at 10–18 weeks of pregnancy is a period of greatest sensitivity for the developing brain. There is also an impact of ionizing radiation on the human sex ratio after nuclear accidents, after nuclear weapon testing, as well as within tens of kilometers from seemingly normal running nuclear facilities of all kinds, including nuclear power plants and nuclear waste disposal sites [35–37]. Populations exposed to chronic low-dose ionizing radiation show disruptions of blastogenesis, neural tube defects (NTDs) including anencephaly, microcephaly, iniencephaly, encephaloceles, spina bifida, rachischisis, microphthalmia, alterations of body axes, conjoined twins, duplications, sacrococcygeal teratomas, diaphragmatic hernia, ectopia vesicae, severe genital malformations, and also multiple congenital malformations and limb defects [3, 36–38].

2.3.2 Hyperthermia

Exposure to hyperthermic conditions during pregnancy appears to induce teratogenesis in all species tested, including humans, although malformations differ between species. The consequences of hyperthermia depend on the extent of temperature elevation, its duration, and the stage of development of the fetus when it occurs. All these effects seem to be mediated via altered expression of heat-shock proteins [39, 40].

High temperatures and/or longer durations are most likely to cause abortions, while lower elevations cause embryonic death and resorption, or abnormalities of embryogenesis, if exposure occurs at this critical stage of development. Mild exposure during the preimplantation period and more severe exposures during the embryonic and fetal development often result in prenatal death and abortion [41].

The central nervous system defects appear to be the most common consequence of hyperthermia in all species, and cell death or delay in proliferation of neuroblasts is one major explanation for these effects. Although cardiovascular anomalies are most common in rats and skeletal malformations in mice, the development of the nervous system is especially vulnerable to defects; a 2.5 °C elevation for 1 h during early neural tube closure in rats resulted in an increased incidence of craniofacial defects, whereas 2–2.5 °C elevation for 1 h during early neurogenesis in guinea pigs caused an increase in the incidence of microcephaly [39].

In experimental laboratory animals, the most common defects are neural tube disorders, microphthalmia, cataract, microcephaly, craniofacial, skeleton and teeth defects, and also heart malformations. Almost all these defects were found in humans, and correlated with maternal fever or other form of hyperthermia during

pregnancy. A recent meta-analysis indicates that maternal hyperthermia during gestation is associated with an enhanced incidence of neural tube defects, showing that the neural tube is heat-sensitive in human embryos too [42, 43]. In humans, there is evidence that an elevation of maternal body temperature by 2 °C for at least 24 h during fever can cause a range of developmental defects, although there is little information on the threshold for shorter exposures [40, 43].

2.3.3 Mechanical Forces

Malformations of the uterus may restrict fetal movements, and the impact of this mechanical force on the fetus is associated with congenital skeletal abnormalities. These abnormalities are classified as deformations or abnormal forms, shapes, or positions of body parts caused by physical constraints. Prolonged rigid paralysis induced severe defects in the spine, including curvature abnormalities, posterior and anterior vertebral fusions, and altered vertebral shape [44]. Amniotic band syndrome is a relatively rare condition, in which congenital anomalies occur as a result of the adherence and entrapment of fetal parts within coarse fibrous bands of amniotic membrane. A large percentage of reported cases have an atypical gestational history. The frequency of this obstetric complication is not associated with fetal gender, genetic abnormality, or prenatal infection [45, 46]. The clinical manifestations are primarily distal deformities, such as constriction of limbs and fingers, syndactyly, acrosyndactyly, phalangeal hypoplasia, pseudoainhum, and amputation of limbs and fingers. There is a predilection for the hand, in particular the central digits, whereas the frequency and severity of thumb involvement are minimal [47]. The thumb is less vulnerable since it lies protected within the palm of the hand in utero, compared to the longer digits, which are more exposed leading to amputations distal to the level of the proximal phalanx. Multiple malformations such as clubfoot (30% of patients), leg length discrepancies (24%), other bone anomalies (12%), special craniofacial defects such as cleft lip and palate (8%), visceral and body wall defects, and anencephaly (5%) have been detected in 70% of infants with the disorder [48, 49].

2.4 Drugs and Chemical Agents

This issue is even more complex since the physiology of the conceptus during pregnancy varies greatly from the first to the third trimester. The lack of information about the appropriate dose for a particular drug, in a particular species, as well as the timing and duration of exposure of this to a sufficient number of pregnant women could be the reason for some teratogenic defects with chemical agents. There is insufficient scientific data to formulate conclusive opinions about the safety and efficacy of several drugs or medications [50]. Concerns with potential fetal or neonatal teratogenicity and toxicity are often incomplete owing to the limited amount of data obtained in a comprehensive sample of pregnant

and lactating women or even primate or other animal species in their natural environment. Hence, conflicts may arise between the theoretical fear of fetal or neonatal adverse consequences and the general bias among most healthcare providers that the successful treatment of medical conditions in the mother is in the offspring's best interest [51–54].

2.4.1 Anticonvulsants

Most anticonvulsant drugs introduce the risk of abnormal or delayed physical development for infants who are exposed in utero. The monotherapies associated with statistically significant risk of malformations and prenatal harms are listed below [51–54].

1. Primidone is teratogenic in the rat, although not dose-dependent, and causes behavioral changes and increased fetal death.
2. Carbamazepine causes major and minor congenital malformations.
3. Clobazam induces prenatal growth retardation and preterm birth.
4. Ethosuximide leads to major congenital malformations, cleft lip/palate, and club foot.
5. Gabapentin can cause cardiac malformations and hypospadias.
6. Phenobarbital induces major congenital malformations, prenatal growth retardation and cleft lip/palate.
7. Phenytoin leads to major congenital malformations, cleft lip/palate, and club foot.
8. Topiramate induces overall major congenital malformations, combined fetal losses, prenatal growth retardation, and cleft lip/palate.
9. Valproate causes overall major and minor congenital malformations, combined fetal loss, hypospadias, cleft lip/palate, and club foot. When children were preexposed to valproate, neurodevelopmental changes are dose-associated and dose-dependent. The higher doses of valproate are associated to poorer overall cognitive abilities known for "fetal valproate syndrome" in humans. Valproate is also teratogenic in the rhesus monkey, rat, hamster, and mouse.
10. Trimethadione is associated with "fetal trimethadione syndrome" in the form of multiple structural abnormalities in humans. This syndrome associated with trimethadione includes a great diversity of anomalies such as growth retardation, microcephaly, cleft lip and/or palate, unusual facies with V-shaped eyebrows, broad nasal bridge, epicanthal folds, anteverted nostrils, cardiovascular malformations (particularly ventricular septal defect, teratology of Fallot, patent ductus

arteriosus, and transposition of the great vessels), and genitourinary and gastrointestinal anomalies. In mice, trimethadione is teratogenic at a dose 8–22 times the human dose. Rats and rhesus monkeys also display signs of teratogenesis at doses up to ten times the human dose.

11. The newer generation anticonvulsant drugs, such as lamotrigine, levetiracetam, oxcarbazepine, and vigabatrin were not associated with statistically significant risks to physical development. However, this does not mean that these agents are not harmful to the offspring of mothers administered with these agents. Additionally, there is insufficient evidence to make any conclusions regarding polytherapy with newer generation anticonvulsant drugs due to a lack of studies reporting these combinations [54].

2.4.2 Fungicides or Antifungals

Topical preparations of antifungal agents are generally poorly absorbed systemically so the teratogenic risk associated with such use is unlikely. Antifungal agents administered parenterally, and therefore at higher doses, have the potential to contribute to an increased teratogenic risk. Conceptus exposed to antifungals such as fluconazole during the first trimester of pregnancy at high doses has been described with a very unusual pattern of congenital anomalies, which includes brachycephaly, abnormal face, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease [55, 56]. Fluconazole is teratogenic in rats but only at doses 5–20 times the typical human dose, and it causes a greater rate of fetal death in rabbits but also at high doses [51, 57, 58].

2.4.3 Antimicrobial Agents

1. Streptomycin is considered nonteratogenic in humans, mice, rabbits, and guinea pigs. In rats, it causes malformations in the inner ear. Rats treated with ten times the human dose had no damaged hearing, whereas injections of streptomycin sulfate are now believed to cause ototoxic harm to the human fetus [3].
2. Tetracyclines cross the placenta and can firmly bind by chelation to calcium in developing bone and tooth structures. This produces brown discoloration of the deciduous teeth, hypoplasia of the enamel, and inhibition of bone growth. The staining of the teeth takes place in the second or third trimesters of pregnancy, whereas bone incorporation can occur earlier. Depression of skeletal growth was particularly common among premature infants treated with tetracycline. Alternate antibiotics currently are recommended during pregnancy in women. Tetracyclines are teratogenic in rats, guinea pigs, and dogs, but has no teratogenic effect in mice and rabbits [59–61].
3. Trimethoprim is an antimicrobial agent often used in conjunction with sulfonamides, which may increase the risk of neural-

tube defects, cardiovascular defects, oral clefts, and urinary tract defects. It is teratogenic in rats only at doses 16–117 times the usual human dose. Teratogenesis and increased fetal loss is evident in mice and rabbits when trimethoprim was administered in combination with sulfamethoxazole [59, 60].

2.4.4 Steroidal and Nonsteroidal Agents

1. All steroids cross the placenta to some degree, but prednisone and prednisolone are inactivated by the placenta. When prednisone or prednisolone is maternally administered, the concentration of active compound in the fetus is less than 10% of that in the mother. Therefore, these agents are used to treat diseases such as asthma. Inhaled corticosteroids also are effective therapy, and little other drugs is absorbed. However, a fivefold increased risk for cleft lip with or without cleft palate in the infant has been reported after exposure to steroids during the first trimester of pregnancy. Inhaled corticosteroid increases slightly the risk of miscarriage, whereas the use of oral corticosteroids does not [62, 63].
2. Cortisone is a naturally occurring glucocorticoid excreted by the adrenal cortex, and is used to treat allergic and inflammatory diseases. It is teratogenic in all animals tested, including beagle dogs, mice, hamsters, rabbits, and rats, promoting cleft palate [64]. However, in human studies, there is no evidence of teratogenicity [65].
3. Dexamethasone exposure during pregnancy can affect skeletal progenitor cells during embryonic skeletogenesis and also affects cognitive functions in girls [66].
4. Danazol is an anabolic steroid used to treat gynecologic and menstrual disorders. There is a strong association between fetal exposure to danazol and human genital malformations, especially masculinization of female external genitalia [66].
5. Diethylstilbestrol is a nonsteroidal synthetic estrogen used to treat ovarian insufficiency, to prevent miscarriages. It is a human teratogen agent that predominantly causes genital and pregnancy problems in the female offspring of exposed mothers. Maternal treatment with diethylstilbestrol during pregnancy can produce vaginal and cervix adenocarcinoma and other abnormalities of the vagina in her daughters when they reach adolescence or adulthood. In most reported cases, maternal diethylstilbestrol treatment was administered prior to the 18th week of pregnancy. Recent experiments have also detected malformations in the offspring of rats, rabbits, hamsters, monkeys, pigs, guinea pigs, and ferrets [67, 68].
6. Estradiol-17β is naturally produced by the ovary, and is the most active estrogen in nonpregnant women. Although there is no evidence of teratogenic effect in humans, it can cause fetal

abnormalities in mice and rats. In oviparous fish species, malformations can be induced by exposure to endocrine-disrupting substances such as estradiol-17β. Female eelpouts exposed to environmental estradiol concentrations during early development increased the abundance of larvae malformations and reduced gonadal volume [51, 69, 70].

7. Progesterone is a natural hormone secreted by the ovary and placenta and it is used to treat amenorrhea, functional uterine bleeding, and corpus luteum insufficiency. Therapeutic doses of progesterone during pregnancy are unlikely to increase the risk of either genital or nongenital congenital anomalies in the offspring. Some synthetic progestins, such as ethisterone and norethindrone, have substantial androgenic activity. Maternal treatment with high doses of such agents can cause virilization of the external genitalia of female fetuses. Hypospadias has been observed in male infants whose mothers took high progestin doses during pregnancy [51, 68].
8. Clomiphene is a nonsteroidal triphenylethylene derivative with both estrogenic and antiestrogenic activity. It is administered orally to induce ovulation and is, therefore, intended to be used prior to conception although an association with maternal ovulation induction was observed among infants with neural tube defects [71].
9. Ethinylestradiol is a synthetic estrogen used in the treatment of menopausal symptoms and menstrual disorders, and is also an ingredient in some oral contraceptives. Results of teratology studies are mostly negative; there is no evidence of fetal malformations in rats, rabbits, and nonhuman primates, although it is classed as a mouse teratogen when used at a dose 20–2000 times the human contraceptive dose [51, 68, 70].

2.4.5 Sedatives/Narcotics

1. Diazepam is a benzodiazepine sedative often prescribed for short-term anxiety problems. This sedative appears to be associated with fetal malformations, such as oral clefts and palatal anomaly after exposure during the first trimester of gestation. Studies suggest that rats and hamsters produce progeny with malformations following exposure to diazepam at doses tens to hundreds of times the human dose [72–74].
2. Meprobamate is a tranquilizer also used to treat anxiety, and like diazepam, there are inconsistent results about its teratogenic effect. There are studies that demonstrate a strong association with the appearance of cardiac abnormalities, but in other studies, no relationship was found [75, 76].

2.4.6 Retinoids

1. Acitretin is a retinoid, used to treat skin diseases such as psoriasis. Acitretin has been shown to be teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3, and 15 mg/kg, respectively.

These doses are approximately 0.2, 0.3, and 3 times the maximum therapeutic dose recommended. Major human fetal abnormalities associated with acitretin administration have been reported including meningomyelocele, multiple synostoses, facial dysmorphia; syndactyly, absence of terminal phalanges, malformations of hip, ankle, and forearm, low-set ears; high palate; decreased cranial volume; and cardiovascular malformation and alterations of the skull and cervical vertebrae [77–79].

2.4.7 Heavy Metals

1. Methylmercury is a hazardous substance found in contaminated water and food. Children born to pregnant women who ate food that was heavily contaminated with methylmercury are affected by cerebral palsy and mental retardation with associated abnormalities of development, coordination, gait, speech, and swallowing. Spasticity, abnormal reflexes, involuntary movements, seizures, microcephaly, hearing loss, strabismus, and poor postnatal growth are also common. In experimental animals, neurotoxicity has been reported with measured levels of total mercury in the brain as low as 1800 parts ppb [51, 80–86].
2. Inorganic lead (Pb) salts have a strong correlation with teratogenesis in several animal species. Lead acetate is teratogenic in rats, hamsters, and primates, but not in sheep, cows, mice, rabbits, and guinea pigs. Lead carbonate is teratogenic in mice but not in rabbits. Lead nitrate is teratogenic in rats, mice and hamsters but not guinea pigs. In humans, there is evidence associating inorganic lead salts with intrauterine growth retardation, spontaneous abortion, problems with neural development and mental retardation, depending upon the level and timing of exposure [15, 87].
3. Lithium salts are used to treat several psychiatric disorders even during early pregnancy. It has been associated with an increased risk of cardiovascular malformations, particularly Ebstein's anomaly of the tricuspid valve. The magnitude of this teratogenic risk is small, probably no more than a few percent. High rates of relapse have been described in women with psychiatric disorders who have discontinued medical treatment prior to or during pregnancy. Lithium salts within the human therapeutic range have also elicited teratogenesis in mice and rats [51, 88–90].

2.4.8 Other Drugs

1. Acetazolamide is a carbonic anhydrase inhibitor that is used to treat idiopathic intracranial hypertension, glaucoma, and epilepsy. Congenital malformations, such as ectrodactyly, syndactyly, oligodontia, cleft lip and palate, and retarded incisor teeth development, were reported in experimental animals of rats, mice, and hamsters [91, 92].

2. Misoprostol is an analogue of prostaglandin, used therapeutically in the treatment of peptic ulcer disease, in the induction of labor, and as an abortifacient. Misoprostol is teratogen in human, rats, and rabbits, and associated with a wide range of birth defects. An association has been observed between maternal unsuccessful use of misoprostol to induce abortion early in pregnancy and the subsequent birth of a child with congenital anomalies such as Moebius anomaly, terminal transverse limb reduction defects, arthrogryposis multiplex congenita, talipes equinovarus, and gastroschisis. These anomalies are thought to result from vascular disruption induced in the embryo or fetus by misoprostol [79, 93–95].
3. Quinine is used in small doses to treat leg cramps, in higher doses as an antimalarial, and at very large doses as a postcoital contraceptive and abortifacient. In humans, there is a strong association between high doses of quinine administered in the first trimester of pregnancy with fetal death or major congenital anomalies (central nervous system, cleft lip and/or palate, heart defects, musculoskeletal defects and other) [96]. Quinine is teratogenic in rats, guinea pigs, and chinchillas. No teratogenic effect was found in rats, mice, dogs, or primates [97].
4. Thalidomide is a sedative, prescribed to pregnant women in the 1950s to control nervousness and nausea, and has become the most notorious teratogen known to man. Various characteristic malformations, particularly limb-reduction defects, were associated with its use during the fifth and sixth weeks of pregnancy in 20% of cases, even with low doses. Later investigations in pregnant animals were performed in the early 1960s using pregnant mice, rats, and guinea pigs, but revealed no malformations in their offspring. Eventually, one particular strain of rabbit (New Zealand) was found to be teratologically sensitive to thalidomide during a specific 2-day window of pregnancy. Subsequent extensive investigations have demonstrated extreme variability in species susceptibility. Several species of primate have shown sensitivity to thalidomide including baboons, macaques, and green monkeys. The thalidomide tragedy caused an increasing interest in drug exposure during pregnancy and the mechanism of action of teratogenic agents on abnormal embryo–fetal development [79].
5. Warfarin is used for the treatment of a variety of thromboembolic disorders. It has gained notoriety for teratogenesis in humans, being associated with characteristic defects known as “fetal warfarin syndrome.” These defects are predominantly skeletal, ocular, and central nervous system oriented when exposure is in the first trimester of pregnancy. Exposure during the second or third trimesters induces neuronal problems. Maternal warfarin use late in pregnancy has been associated

with fetal, placental, and neonatal hemorrhage. Warfarin depresses synthesis of vitamin K-dependent clotting factors. Similar congenital anomalies in infants with prenatal vitamin K deficiencies whose mothers did not take warfarin during pregnancy suggest vitamin K deficiency as a possible pathogenic mechanism of warfarin [51, 98–100].

6. Polychlorinated biphenyls (PCBs) are a family of more than 200 compounds that are widely used in industry. Children born to women who ate food contaminated with high levels of PCBs during pregnancy may have reduced birth weight and length, developmental delay, ectodermal defects, and dark skin, gingiva, and nails [51, 101–103].
7. Methylene blue is a dye, and also is used to treat methemoglobinemia. Several studies have found an association between the occurrence of intestinal atresia and the instillation of methylene blue into the amniotic sac during midtrimester. The risk of intestinal atresia in an infant born after this procedure is about 20%. Neither oral nor topical administration of methylene blue to the mother has been associated with a similar teratogenic risk, emphasizing the importance of direct intra-amniotic injection in this effect [51, 104–106].
8. Caffeine from coffee, but not from other sources such as chocolate or tea, was associated with slightly increased gestational length. Total caffeine and caffeine from all different sources studied was associated with decreased body weight at birth. However, caffeine does not induce teratogenic effects in humans. Instead, caffeine induced malformations in mice, rat, and monkey offspring when the daily dose is equivalent to 5–10 cups of coffee [107, 108].
9. Cigarette smoking during pregnancy has been associated with miscarriage, low birth weight, cryptorchidism, hypospadias, but most epidemiological studies have not found an increased risk for major congenital anomalies. The adverse effect of maternal smoking on birth weight is reduced in women who stop smoking early in pregnancy [51, 109–111].
10. Alcohol is widely consumed as a recreational drug, and has long been strongly associated with human birth defects. Prenatal ethanol exposure affects the developing brain and causes neural impairment, cognitive and behavioral effects, characteristic facial features, and organ malformations, collectively known as “fetal alcohol spectrum disorders” (FASD) or the “fetal alcohol syndrome” (FAS). This disorder has a characteristic set of abnormalities (and characteristic face morphology) present in up to one in three children of alcoholic mothers. These abnormalities are generally similar to those in the many animal species that have been the subject of teratology testing

with human equivalent doses of ethanol, including rats, mice, rabbits, ferrets, guinea pigs, sheep, pigs, dogs, and nonhuman primates [112, 113].

11. Solvent inhalation regularly abused during pregnancy may have an unusual pattern of congenital anomalies that resembles the fetal alcohol syndrome. Features include central nervous system dysfunction, developmental delay, attention deficit disorder, microcephaly, growth deficiency, short palpebral fissures, deep-set eyes, micrognathia, abnormal auricles, and small fingernails. Occupational exposure to toluene at levels below regulatory threshold limits has not been associated with an increased risk of congenital anomalies [51, 114].
12. Oxidative damage to cellular macromolecules such as lipids, proteins, DNA, and RNA is caused by reactive oxygen species (ROS), which provide oxidation–reduction reactions. Exogenous ROS sources include ultraviolet light, UVA and UVB radiation, ionizing radiation, and chemical agents, while endogenous sources are related to cellular metabolism and oxidase enzymes and most are related to inflammatory process. Some of these agents are called proteratogens, and can be bioactivated by embryonic cytochrome P450 enzymes. Their teratogenic effect will depend on the intracellular balance between proteratogen bioactivation, molecular target damage, maternal proteratogen elimination, and repair of damaged cells. Among drugs that induce oxidative stress are thalidomide, valproic acid, phenytoin, alcohol, and anticancer drugs [57, 79, 115–118], and their teratological effects have been previously described.

2.5 Biological Agents

Several infectious agents can cross the placenta and enter the fetal blood stream affecting the fetus with a variety of lethal or birth defects. Infectious agents during pregnancy may lead to direct cytotoxic effect, mitotic inhibition, or vascular disruption events in the embryo or fetus. However, a repair process may result in scarring or calcification, which causes further damage by interfering with histogenesis. Usually, the ToRCH group of infections (Toxoplasmosis, Rubella virus, Cytomegalovirus, and Herpes/varicella virus infections) is screened for in the case of permanent cerebral impairment in the neonate [119]. Moreover, infections with human immunodeficiency virus (HIV) and other agents may lead to permanent fetal injury. Microcephaly, hydrocephalus, hydranencephaly, and cerebral calcifications are the sequelae most often found in the ToRCH group of infections, and lead to developmental delay, psychomotor retardation, and others. Microphthalmia is often a consequence of prenatal toxoplasmosis, rubella, and HIV infection [120, 121]. Ultimately, these infections can lead to destruction of cerebral tissue with formation of cystic in the brain. In all instances, the

nature and the degree of disturbances are correlated to the gestation time of the infection. Early infections may lead to intrauterine death; lissencephaly may result from cytomegalovirus onset between 16 and 18 weeks of gestation, whereas polymicrogyria may be due to onset of infection between 18 and 24 weeks of gestation. If the fetus aborts early, the lesions may be restricted to foci of macrophages around glial or neuronal cells with classical intranuclear viral inclusions [79, 122, 123].

2.5.1 Parasites

1. *Toxoplasma gondii*, one of the most prevalent parasites worldwide is the causal agent of toxoplasmosis. This is due to the fact that the parasite is able to chronically infect all warm-blooded animals including humans. Furthermore, its lifelong persistence in the host increases the chance of transmission. Definitive hosts are members of the *Felidae* family, which eventually shed environmentally resistant oocysts that are taken up by new intermediate or aberrant hosts (e.g., mice, pigs, or humans) via soil, food, or water [124, 125]. Women who contract toxoplasma infections before pregnancy usually do not transmit it to their fetuses (which are immunologically protected). If a mother becomes infected during pregnancy, this pathogen will be transmitted to the fetus through the placenta. Clinical manifestations of toxoplasmosis in fetuses and neonates vary greatly (with the gestation period). Risk of congenital toxoplasmosis is low if infection occurs during the first trimester (10–25%) than if it occurs during the third trimester (60–90%) [122]. However, the severity of congenital anomalies is substantially higher after infections during the first trimester. Typical anomalies include hydrocephalus or microcephalus, chorioretinitis, intracranial calcifications, skin rash, purpura, jaundice, hepatosplenomegaly, and extramedullary hematopoiesis [3, 124, 126]. Because most pregnant women are infected during the third trimester, about two-thirds of newborns present the subclinical form of infection. In these cases, neonates are asymptomatic at birth on routine pediatric examination, but later in their lives, deafness, mental retardation, and learning difficulties will be detected [3, 127].

2.5.2 Virus

1. Rubella: Although maternal infection with the rubella virus can affect any fetal organ, deafness is the most common consequence, but heart disease, mental retardation, thrombocytopenia, and encephalitis also occur frequently [128, 129]. If the infection occurs in the first 12 weeks of gestation, about 80% of the fetuses will be born with congenital anomalies, such as heart defects, deafness, and cataracts. If maternal infection occurs between 12 and 16 weeks, about 50% of fetuses are affected. Infection after 16 or 17 weeks, the most common finding is deafness, and the risk of malformations is significantly lower

[52, 123, 130, 131]. Near 8% of rubella virus infections can lead to spontaneous abortion. Stillborn show hepatosplenomegaly, thickening of the intima of the aorta, and severe problems in the thymus such as hypoplasia and Hassall corpuscles absent, cystic, or calcified. Other changes include hepatocyte swelling and deep changes in liver histology [3, 52, 129].

2. Cytomegalovirus (CMV) causes the most common viral infection of the fetus. Infection of the early embryo during the first trimester most commonly results in spontaneous abortion. Exposure later during the second trimester of pregnancy results in intrauterine growth retardation, fetal growth restriction, amniotic fluid abnormalities (oligohydramnios or polyhydramnios), disorders of brain development (calcifications and enlarged ventricles), micromelia, chorioretinitis, blindness, microcephaly, mental retardation, and hepatosplenomegaly [132–135]. Ultimately, these infections can lead to formation of brain cysts in the brain, which are formed by dysplastic cortex such as polymicrogyria [136]. Hearing loss from congenital cytomegalovirus infection can be either unilateral or bilateral and varies from mild to profound, in terms of degree. Children with congenital CMV infection have varying degrees of delayed psychomotor and cognitive development that usually remain unrecognized until the first or second year of life. On the other hand, some asymptomatic children present lower IQs [120, 123, 137, 138].
3. Varicella-zoster virus is responsible for both varicella or chickenpox and herpes zoster. Varicella is a highly infectious disease, and usually more than 80% of children have chickenpox during childhood. When the varicella infection occurs between 8 and 20 week of pregnancy, the virus is most likely to damage neural tissues [139, 140]. In these situations, there is a 2% chance of a group of defects called “Congenital Varicella Syndrome” that includes scars, defects of muscle and bone, malformed and paralyzed limbs, cataract, microphthalmia, chorioretinitis, microcephaly, dysfunction of the bowel or bladder sphincter, and mental and psychomotor retardation. This syndrome is rare when the infection occurs after 20 weeks of pregnancy [3, 52, 141–144].
4. Parvovirus B19 is associated with fetal abnormalities that may result from injuries to different fetal organs including the brain, and as a result, may also cause neurodevelopmental problems. Fetal anemia and cardiac failure may also be an important factor in the etiology of developmental disorders, especially if infection occurs during the first 20 weeks of gestation. All in all, there seems to be sufficient data to conclude that parvovirus B19 is not a significant teratogen in man, but the possible effects on the brain and on development need further evaluation [143, 145, 146].

5. Influenza virus infection during pregnancy conduces to symptoms that include cough, fever, malaise, rhinitis, myalgias, headache, chills, and sore throat. Less common symptoms include nausea and vomiting, otitis, and conjunctival burning. Pregnant women are at high risk for severe complications of influenza during seasonal influenza periods and pandemics [123]. Influenza virus infection conduces to spontaneous abortion, fetal death, birth defects, and anomalies of the central nervous system [147]. Experimental teratology in mice demonstrated that prenatal influenza infection is associated with histopathologic changes in the brain and behavioral alterations. Concerning this virus, there are gaps in the literature including insufficient evidence on seasonal influenza disease and gestational timing of influenza disease [123, 147, 148].
6. Zika virus (ZIKV) is associated with severe neurological complications in consequence to its high neurotropism, promoting inflammation, apoptosis, and cell death. Microcephaly is one abnormally associated with virus in utero infection, as low birth weight and small at birth time. Other abnormalities described associated to microcephaly were ventriculomegaly, calcifications, and lissencephaly [149–151].
7. Schmallemberg virus is a novel Orthobunyavirus that affect ruminants. The malformations described in these animals borne by mothers infected with this virus are diverse congenital malformations such as severe torticollis, scoliosis, kyphosis and arthrogryposis of several joints, brachygnathia inferior, severe muscle atrophy and hypoplasia of the lungs, micromyelia and in some cases, the lumbar spinal cord was duplicated (diplomyelia). The central nervous system shows diverse deformities like hydranencephaly, and hypoplasia of the cerebrum and of the cerebellum [152, 153]. The critical period of infection of this virus that is related to the malformation observed is the second month of gestation for sheep and after the second month until the sixth month for cattle [154].

2.5.3 Bacteria

1. Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum*, and little is known about its mechanism of action. The fetus cannot be infected with syphilis early in pregnancy because the cytotrophoblastic layer of cells in the chorionic villi of the placenta prevents the spirochete from passing from the maternal to the fetal blood. This cell layer disappears at the sixth month. Since the spirochete usually does not reach the conceptus during the first trimester, it is usually not a cause of abortion [15, 155, 156]. However, syphilitic untreated women can develop endometritis leading to abortion during the first trimester, early fetal loss, prematurity, low birth weight, neonatal and infant death, and congenital disease among newborn babies [157].

In untreated maternal syphilis in the primary or secondary stages, 50% are stillborn or die within 4 weeks after birth. In untreated maternal syphilis in the early part of the tertiary stage, 20–60% of infants are normal, 40% have congenital syphilis, 20% are born prematurely, and 16% are stillborn or die within 4 weeks after birth. In untreated syphilis in the late part of the tertiary stage, 75% of babies are unaffected, 10% have congenital syphilis, 9% are born prematurely, 10% are stillborn, and 1% die within 4 weeks after birth [15, 158].

Sixty to eighty percent of newborns could manifest "pseudoparalysis of Parrot" (periostitis that mostly affects the metaphysis of long bones generally in the upper limbs) and other skeletal malformations, developed after syphilis infection in the last term of gestation [159].

2. Chlamydiosis is a disease caused by *Chlamydia trachomatis*. Maternal infection with this agent is associated with a congenital defect of the abdominal wall (gastroschisis) [160] that has been documented over the past several decades among young mothers' offspring. A study from the National Birth Defects Prevention Study reported that women delivering an infant with gastroschisis were four times more likely to report a genitourinary infection (i.e., urinary and sexually transmitted infections) during the periconceptional period than control mothers [5, 161–163].

3 Conclusion

Teratology is a complex science that deals with the abnormalities of the newborn. Several factors are implicated in these anomalies, since the genome of the germ cells (maternal or paternal one), the genome of the conceptus, and the time at which the extrinsic (environmental, alimentary, biological) factors can act over the embryo.

In some cases, these factors act inducing problems in the fetus, causing minor defects or even no problems. In other cases, similar factors cause so severe abnormalities that, depending on the embryo age, cause fetal resorption, abortion, or very severe malformation, some compatible with survival, but others causing death.

The importance of the laboratory animal science in this field has a crescent importance, since every day new factors and products are related with anomalies of the newborn. In future, it is aimed to predict these factors, making pregnancy a calm, happy, and trouble-free period that ends with the birth of a healthy child.

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