HUMAN TERATOGENESIS: GENE–ENVIRONMENT INTERACTION AND FOUNDATIONS FOR PREVENTION

TERATOGÊNESE HUMANA: INTERAÇÃO GENÉTICO-AMBIENTAL E BASES PARA A PREVENÇÃO

TERATOGÉNESIS HUMANA: INTERACCIÓN GENÉTICO-AMBIENTAL Y BASES PARA LA PREVENCIÓN

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ABSTRACT

Human teratogenesis is a complex process resulting from the interaction between environmental factors and maternal–fetal genetic susceptibility, capable of altering embryofetal development and producing structural, functional, and neurodevelopmental anomalies. The vulnerability of the embryo and fetus depends on the timing of exposure, with organogenesis (weeks 3–8) being the period of highest risk for major malformations, whereas in later stages functional and growth alterations predominate. The principles of teratology, described by Wilson, establish that the teratogenic effect is conditioned by dose, duration of exposure, genetic susceptibility, and the pathogenic mechanisms involved, such as oxidative stress, DNA damage, altered cell proliferation, and disruption of angiogenesis. Teratogenic agents are classified as biological, physical, chemical, and maternal factors, all with convergent mechanisms that affect fetal development. Biological teratogens include congenital infections that cause damage through direct invasion and inflammation. Physical agents, such as ionizing radiation and hyperthermia, produce cellular and structural alterations. Chemical agents, including drugs, alcohol, tobacco, and environmental pollutants, interfere with key molecular processes and represent a frequent cause of preventable fetal damage. Maternal factors, such as diabetes, phenylketonuria, and

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nutritional deficiencies, modify the intrauterine environment. Early recognition of risk exposures and the implementation of preventive strategies are essential to reduce the incidence of congenital anomalies and improve perinatal outcomes.

Keywords: Teratogenesis. Embryofetal Development. Environmental Factors. Maternal Factors. Congenital Infections. Teratogenic Drugs.

RESUMO

A teratogênese humana é um processo complexo que resulta da interação entre fatores ambientais e a suscetibilidade genética materno-fetal, capaz de alterar o desenvolvimento embriofetal e produzir anomalias estruturais, funcionais e do neurodesenvolvimento. A vulnerabilidade do embrião e do feto depende do momento da exposição, sendo a organogênese (semanas 3–8) o período de maior risco para malformações maiores, enquanto nas fases posteriores predominam alterações funcionais e do crescimento. Os princípios da teratologia, descritos por Wilson, estabelecem que o efeito teratogênico é condicionado pela dose, duração da exposição, suscetibilidade genética e pelos mecanismos patogênicos envolvidos, como o estresse oxidativo, o dano ao DNA, a alteração da proliferação celular e a disrupção da angiogênese. Os agentes teratogênicos são classificados em biológicos, físicos, químicos e fatores maternos, todos com mecanismos convergentes que afetam o desenvolvimento fetal. Os teratógenos biológicos incluem infecções congênitas que causam dano por invasão direta e inflamação. Os agentes físicos, como a radiação ionizante e a hipertermia, produzem alterações celulares e estruturais. Os agentes químicos, incluindo fármacos, álcool, tabaco e poluentes ambientais, interferem em processos moleculares-chave e representam uma causa frequente de dano fetal prevenível. Os fatores maternos, como diabetes, fenilcetonúria e deficiências nutricionais, modificam o ambiente intrauterino. O reconhecimento precoce de exposições de risco e a implementação de estratégias preventivas são essenciais para reduzir a incidência de anomalias congênitas e melhorar os desfechos perinatais.

Palavras-chave: Teratogênese. Desenvolvimento Embriofetal. Fatores Ambientais. Fatores Maternos. Infecções Congênitas. Fármacos Teratogênicos.

RESUMEN

La teratogénesis humana es un proceso complejo que resulta de la interacción entre factores ambientales y la susceptibilidad genética materno-fetal, capaz de alterar el desarrollo embriofetal y producir anomalías estructurales, funcionales y del neurodesarrollo. La vulnerabilidad del embrión y del feto depende del momento de la exposición, siendo la organogénesis (semanas 3–8) el periodo de mayor riesgo para malformaciones mayores, mientras que en etapas posteriores predominan alteraciones funcionales y del crecimiento. Los principios de la teratología, descritos por Wilson, establecen que el efecto teratogénico está condicionado por la dosis, la duración de la exposición, la susceptibilidad genética y los mecanismos patogénicos implicados, como el estrés oxidativo, el daño al ADN, la alteración de la proliferación celular y la disrupción de la angiogénesis. Los agentes teratogénicos se clasifican en biológicos, físicos, químicos y factores maternos, todos con mecanismos convergentes que afectan el desarrollo fetal. Los teratógenos biológicos incluyen infecciones congénitas que causan daño por invasión directa e inflamación. Los agentes físicos, como la radiación ionizante y la hipertermia, generan alteraciones celulares y estructurales. Los agentes químicos, incluyendo fármacos, alcohol, tabaco y contaminantes ambientales, interfieren con procesos moleculares clave y representan una causa frecuente de daño fetal prevenible. Los factores maternos, como diabetes, fenilcetonuria y deficiencias nutricionales, modifican el ambiente intrauterino. El reconocimiento temprano de exposiciones de riesgo y la implementación de estrategias preventivas son esenciales para reducir la incidencia de anomalías congénitas y mejorar los resultados perinatales.

Palabras clave: Teratogénesis. Desarrollo Embriofetal. Factores Ambientales. Factores Maternos. Infecciones Congénitas. Fármacos Teratogénicos.

1 OVERVIEW OF TERATOGENESIS

Teratogenesis is a complex biological process by which various environmental factors, in interaction with the genetic susceptibility of the embryo and the mother, alter the normal development of the product of conception, generating structural, functional, metabolic or behavioral abnormalities. This phenomenon does not depend exclusively on the causative agent, but on a dynamic relationship between the time of exposure, the dose, the duration and the biological conditions of the host.

During embryo-fetal development, vulnerability to teratogenic agents is not uniform. In the embryonic period, particularly between the third and eighth week of gestation, organogenesis occurs, a critical stage in which the primordia of the main organs are established. Exposure to harmful agents in this range is more frequently associated with major birth defects. In contrast, during the fetal period, which extends from the ninth week until birth, growth and functional maturation processes predominate, so aggressions usually result in alterations in functional development, especially of the central nervous system.

The central nervous system is a particularly susceptible target, since its development extends from early stages of gestation to the first years of postnatal life. For this reason, many teratogenic exposures do not generate morphological abnormalities evident at birth, but manifest later as neurodevelopmental disorders, cognitive deficits, behavioral alterations or psychiatric diseases.

From a clinical perspective, the identification of teratogenic factors is an essential component of prenatal care. A targeted anamnesis, recognition of risk exposures (pharmacological, infectious, environmental or occupational) and a comprehensive assessment of the maternal context allow effective preventive strategies to be established. In this sense, the classification of teratogens into physical, chemical, biological, environmental and maternal factors facilitates the understanding of fetal risk and guides evidence-based clinical decision-making.

2 FUNDAMENTAL PRINCIPLES OF TERATOLOGY

Teratology is the discipline that studies the causes, mechanisms, and consequences of congenital anomalies induced by environmental or genetic factors, or their interaction. Its conceptual development was consolidated with the principles proposed by James G. Wilson in 1959, which continue to be the fundamental theoretical framework for understanding the action of teratogens.

2.1 CONCEPT OF TERATOGEN

A teratogen is any external agent capable of interfering with normal embryo-fetal development, producing structural, functional, growth or behavioral alterations. These agents include physical, chemical, biological, environmental factors and conditions of the maternal state.

2.2 WILSON'S PRINCIPLES APPLIED TO TERATOGENESIS

1. Dependence on the time of exposure

The susceptibility of the embryo or fetus varies according to the stage of development:

- **Preimplantation period (0–2 weeks):** "all or nothing" phenomenon.
- **Embryonic period (3–8 weeks):** maximum susceptibility to structural malformations.
- **Fetal period (≥9 weeks):** functional and growth alterations predominate.

2. Genetic variability of susceptibility

The response to a teratogen depends on the maternal and fetal genotype. Factors such as polymorphisms in metabolizing enzymes, detoxification mechanisms, and DNA repair capacity influence the extent of damage.

3. Dose–response relationship

There is a direct correlation between the intensity/duration of exposure and the likelihood of harm:

- Some teratogens have **a threshold effect**.
- Others can induce harm even with brief but intense exposures.

4. Specific pathogenic mechanisms

Teratogens act through defined biological pathways, including:

- Alteration of cell proliferation, migration and differentiation
- Oxidative stress and DNA damage
- Interference with angiogenesis and uteroplacental flow
- Induction of apoptosis or cell necrosis

5. Spectrum of manifestations

Teratogenic damage can be expressed as:

- Embryonic or fetal death
- Major or minor birth defects
- Intrauterine growth restriction
- Functional or neurodevelopmental alterations

6. Influence of the biological model and the environment

The results observed in animal models cannot always be extrapolated to humans. In addition, environmental, social, and nutritional factors modulate the clinical expression of teratogenic damage.

2.3 CLASSIFICATION OF TERATOGENIC AGENTS

Teratogenic agents are classified as: (Fig. 1)

- **Physical:** ionizing radiation, hyperthermia
- **Chemicals:** drugs (e.g. retinoids, anticonvulsants), alcohol, heavy metals
- **Biologics:** congenital infections (TORCH and others)
- **Environmental and social:** malnutrition, hypoxia, occupational exposure, stress
- **Maternal:** chronic diseases such as diabetes, phenylketonuria, or lupus

Figure 1

The image presents a graphic diagram entitled "Classification of teratogens", the purpose of which is to illustrate the main factors capable of producing congenital malformations or alterations in fetal development during pregnancy. Vargas, 2026

2.4 TERATOGENICITY CRITERIA IN HUMANS

Identifying an agent as a teratogen in humans requires consistent evidence based on:

- Temporal association between exposure and effect
- Presence of a specific pattern of malformations
- Dose–response relationship
- Biological plausibility

- Reproducibility across studies and populations
- Exclusion of alternative causes

The evidence comes mainly from epidemiological studies (cohorts and case-controls), exposure registries and, in a complementary way, experimental models.

2.5 TERATOGENIC RISK ASSESSMENT

Risk assessment involves determining the likelihood of fetal harm by considering:

- Exposure period (critical window)
- Dosage and duration of the agent
- Maternal-fetal genetic susceptibility

Historically, the FDA classification (categories A, B, C, D, and X) was used as clinical guidance; however, this system has been replaced by the **PLLR (Pregnancy and Lactation Labeling Rule)** narrative model, which provides more detailed and contextualized information on fetal risks, clinical considerations, and surveillance data. (Fig. 2)

Figure 2

The image shows a stepwise scheme of the classification of drugs according to their risk during pregnancy, corresponding to the FDA (Food and Drug Administration) classification traditionally used to evaluate the teratogenic potential of drugs. Vargas, 2026

2.6 PREVENTION AND COUNSELLING

The prevention of teratogenesis is based on:

- Preconception planning
- Review of potentially teratogenic drugs
- Folic acid supplementation
- Maternal Disease Management
- Pre-pregnancy vaccination
- Environmental and occupational hazard education

2.7 INTEGRATIVE CONCLUSION

Teratogenesis is the result of a complex interaction between environmental and biological factors that act on a highly vulnerable developing organism. Knowledge of the fundamental principles of teratology makes it possible to understand the variability of teratogenic effects, improve risk assessment and strengthen prevention strategies. In clinical practice, a comprehensive, individualized, evidence-based approach is the most effective tool to reduce the incidence of avoidable birth defects and their long-term consequences.

Biological teratogens

1. Introduction

Biological agents are one of the most relevant causes of teratogenesis, particularly in the context of maternal infections acquired during pregnancy. These include viruses, bacteria and parasites with the ability to cross the placental barrier and infect the embryo or fetus, generating structural, functional and neurodevelopmental alterations.

Fetal susceptibility depends on multiple factors, including gestational age at the time of infection, virulence of the pathogen, infectious burden, and maternal immune response. During the embryonic period (weeks 3–8), exposure is mainly associated with major congenital malformations, while in fetal stages functional alterations, intrauterine growth restriction (IUGR), and long-term neurological sequelae predominate.

From a clinical point of view, congenital infections represent a preventable cause of perinatal morbidity and mortality, which underscores the importance of prenatal screening, vaccination and primary prevention measures.

2. Classification of biological agents

Biological teratogens are classified as:

- Viruses
- Bacteria
- Parasites

Traditionally, these agents are grouped within the **TORCH** complex (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes simplex), to which emerging pathogens such as Zika virus and parvovirus B19 are now added.

3. Pathophysiological mechanisms of infectious teratogenesis

Infectious agents exert their teratogenic effect through multiple mechanisms:

- Direct cytotoxicity and cell lysis
- Interference with cell proliferation, differentiation, and migration
- Disruption of angiogenesis and placental perfusion
- Induction of chronic inflammation (placentitis)
- Activation of apoptosis and DNA damage
- Aberrant fetal immune response

These mechanisms critically affect organogenesis and the development of the central nervous system, explaining the high frequency of neurological alterations in congenital infections.

4. Main teratogenic biological agents

4.1 Viral infections

Viruses are the main biological teratogens due to their high cellular tropism and capacity for intracellular replication.

Rubella virus

Responsible for congenital rubella syndrome, characterized by the classic triad:

- Congenital heart disease
- Cataracts
- Sensorineural hearing loss

The risk of fetal harm is highest during the first trimester, reaching up to 90% in early infections.

Cytomegalovirus (CMV)

It is the most common cause of congenital infection worldwide.

Demonstrations:

- Microcephaly
- Periventricular calcifications
- Chorioretinitis
- Hearing and cognitive deficit

CMV presents marked neurotropism and can produce sequelae even in asymptomatic newborns.

Herpes simplex virus (HSV)

It is mainly transmitted during childbirth.

Demonstrations:

- Neonatal encephalitis
- Cutaneous-mucosal lesions
- Disseminated disease

Intrauterine infection is rare but serious.

Varicella-zoster virus

Associated with congenital chickenpox syndrome:

- Hypoplasia of the extremities
- Skin scars
- Neurological and ocular alterations

Increased risk between 8–20 weeks of gestation.

Virus del Zika

Emerging agent with high neurotropism.

Manifestations of congenital Zika syndrome:

- Severe microcephaly
- Cortical alterations
- Intracranial calcifications
- Arthrogryposis

It represents a paradigm of modern viral teratogenesis.

Parvovirus B19

It produces severe fetal anemia due to destruction of erythroblasts.

Complications:

- Non-immunological hydrops fetalis
- Fetal heart failure
- Intrauterine death

HIV and hepatitis B/C

They are not direct teratogens, but they can alter the fetal environment and be associated with vertical transmission with systemic consequences.

4.2 Bacterial infections

Treponema pallidum (syphilis)

It causes congenital syphilis, with manifestations such as:

- Hydrops fetalis
- Anemia
- Hepatosplenomegaly

- Bone and neurological alterations

In late stages:

- Hutchinson's Triad (teeth, deafness, keratitis)

Listeria monocytogenes

Associated with:

- Miscarriage
- Preterm delivery
- Neonatal sepsis

The damage is related to placental invasion and inflammatory response.

4.3 Parasitic infections

Toxoplasma gondii

Intracellular protozoan with high clinical relevance.

Classical triad:

- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications

Transmission increases with gestational age, but severity is greater in early infections.

Trypanosoma cruzi (Chagas disease)

It causes congenital infection with:

- Heart disease
- Hepatosplenomegaly
- Neurological involvement

Important in endemic regions of Latin America.

5. Clinical manifestations

Congenital infections have a broad spectrum:

- Structural malformations
- Microcephaly
- Intrauterine growth restriction
- Hepatosplenomegaly
- Hematological alterations
- Neurological and cognitive deficit
  - Long-term sequelae

Many infections can be subclinical at birth and manifest later.

6. Prenatal diagnosis

Diagnosis is based on a combination of tools:

- **Maternal Serology:** IgM, IgG, Avidity Tests
- **Molecular biology:** PCR in blood or amniotic fluid
- **Fetal ultrasound:** ventriculomegaly, calcifications, hydrops
- **Fetal MRI:** Advanced Neurological Evaluation
- **Amniocentesis:** etiological confirmation

Early diagnosis allows for timely intervention and better prognosis.

7. Prevention

Preventive strategies include:

- Routine prenatal screening
- Preconception vaccination (rubella, chickenpox, hepatitis B)
- Hygienic-dietary measures (toxoplasmosis, CMV)
- Sexual and reproductive health education
- Maternal Disease Management
- Surveillance in high-risk pregnancies

8. Fetal and neonatal follow-up

- Serial ultrasound and fetal Doppler
- Assessment of fetal growth and well-being
- Intrauterine molecular diagnosis
- Comprehensive postnatal evaluation
- Neurological, auditory and visual monitoring

9. Conclusion

Biological agents represent a significant and largely preventable cause of teratogenesis. Its impact on embryo-fetal development depends on the interaction between the pathogen, the timing of infection, and the host's response. Early recognition, systematic screening and prevention strategies are fundamental pillars to reduce perinatal morbidity and mortality and long-term sequelae.

Table 1

Main teratogenic biological agents

Agent	Type	Demonstrations	Mechanism
Rubella	Viruses	Heart disease, cataracts	Mitotic inhibition
CMV	Viruses	Microcephaly, calcifications	Neurotropism
HSV	Viruses	Encephalitis	Cytotoxicity
Zika	Viruses	Severe microcephaly	Neuronal alteration
T. pallidum	Bacteria	Hydrops, anemia	Inflammation
Listeria	Bacteria	Neonatal sepsis	Placental invasion
Toxoplasma	Parasite	Chorioretinitis	Tissue necrosis

T. cruzi	Parasite	Heart disease	Chronic inflammation

Figure 3

Pathogenesis schematic (to be designed)

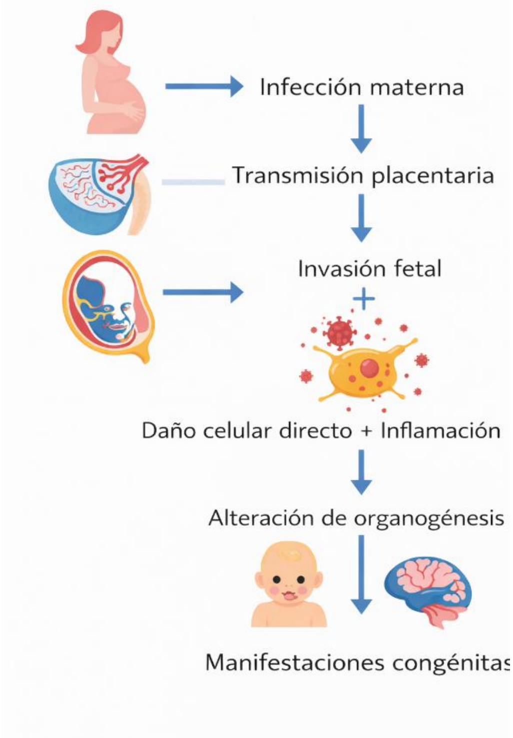

Fig. 3. Maternal infection → Placental transmission → Fetal invasion →Direct cell damage + Inflammation → Alteration of organogenesis → Congenital manifestations.

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Physical teratogens

3.1 Introduction

Physical agents constitute a relevant group of teratogens that exert their effect through direct cell damage, DNA alterations, interference in cell proliferation and modifications of the intrauterine environment. Unlike biological and chemical agents, their impact depends fundamentally on quantifiable variables such as the intensity, duration and time of exposure during pregnancy.

The susceptibility of the embryo and fetus varies according to the stage of development. During organogenesis (weeks 3–8), physical agents can induce major structural malformations. In later stages, the effects are mainly related to growth disturbances, functional maturation and neurological damage.

3.2 Ionizing radiation

Ionizing radiation is the best characterized teratogenic physical agent. Its biological effect derives from the transfer of energy at the molecular level, producing direct and indirect damage to DNA.

Mechanisms of action

- DNA strand breaks and mutations
- Generation of free radicals (oxidative stress)
- Induction of cell apoptosis

- Alterations in tissue differentiation
- Vascular and placental damage

The **Bergonié-Tribondeau** principle states that immature cells with a high proliferative rate (such as embryonic cells) are more sensitive to radiation.

Critical period and effects

- Preimplantation (0–2 weeks): all-or-nothing effect
- Organogenesis (3–8 weeks): structural malformations
- Fetal period (8–25 weeks): neurological and cognitive damage

Demonstrations:

- Microcephaly
- Intrauterine growth restriction (IUGR)
- Intellectual disability
- Neurobehavioral alterations
- Increased risk of childhood cancer

Dosage and risk

- **<50 mGy:** no significant increase in malformations
- **100–150 mGy:** increased teratogenic risk
- **>300 mGy:** High risk of severe neurological damage

Routine diagnostic exposures (plain X-rays, CT scans with standard protocols) are generally below the risk threshold.

Sources of exposure

- X-rays: <1 mGy
- CT scan: 10–50 mGy
- Radiation therapy or nuclear accidents: >100 mGy

Prevention

- Rational use of radiological studies
- Abdominal shield protection
- Preference for non-radiation methods (ultrasound, MRI)

3.3 Non-ionizing radiation

Ultraviolet (UV) radiation

UV radiation is not considered a potent direct teratogen, but it can induce indirect effects:

- Decrease in maternal folic acid
- Oxidative stress
- Metabolic alterations

This can increase the risk of neural tube defects with prolonged exposures.

Diagnostic Ultrasound

Ultrasound uses high-frequency mechanical waves (2–10 MHz) and not ionizing radiation, so it is considered safe in clinical practice.

Theoretical mechanisms

- Thermal effect (minimal temperature rise)
- Cavitation (not demonstrated in humans)

Safety principle

- **ALARA (As Low As Reasonably Achievable)**

There is no conclusive evidence of teratogenicity when used medically.

Electromagnetic Fields (EMFs)

They include:

- Mobile phones
- Wi-Fi
- Power lines
- MRI

The current evidence is **inconclusive**, with no clear demonstration of teratogenicity in humans at normal environmental levels. MRI is considered safe, especially from the second trimester onwards.

3.4 Maternal hyperthermia

Hyperthermia (maternal temperature ≥39 °C) is a relevant physical teratogen, especially in the first trimester.

Mechanisms

- Protein denaturation
- Alteration of DNA replication
- Interference in cell migration
- Induction of apoptosis

Associated malformations

- Neural tube defects
- Cleft lip and palate
- Congenital heart disease
- Microphthalmia
- Neurodevelopmental alterations

The risk is greatest during neural tube closure (weeks 3–6).

Sources

- Prolonged maternal fever
- Infections
- Saunas, jacuzzis
- Extreme Environmental Exposure

Prevention

- Early fever control
- Avoid exposure to extreme heat
- Adequate hydration

3.5 Mechanical factors

Mechanical factors affect fetal development through physical restraint or intrauterine compression.

Main causes

- Oligohydramnios
- Uterine malformations
- Multiple pregnancy
- Amniotic bands

Demonstrations

- Positional deformities (clubfoot, plagiocephaly)
- Congenital hip dislocation
- Pulmonary hypoplasia
- Fetal amputations (amniotic bands)

These effects are more related to morphomechanical alterations than to direct cellular damage.

3.6 Noise, vibration and mechanical trauma

Loud noise (>85 dB)

- Risk of fetal hearing loss
- Low birth weight
- Preterm birth
- Maternal stress (cortisol axis)

Vibration

- Decreased uteroplacental flow
- IUGR
- Miscarriage

Abdominal trauma

- Placental abruption

- Fetal hypoxia
- Stillbirth
- Direct fetal injury

3.7 General pathophysiological mechanisms

Physical agents induce teratogenesis by:

- Direct DNA damage
- Oxidative stress
- Alteration of cell proliferation
- Apoptosis
- Interference in organogenesis
- Fetal mechanical compression

3.8 Clinical manifestations

- Congenital malformations
- Microcephaly
- Intrauterine growth restriction
- Neurocognitive deficit
- Musculoskeletal deformities

3.9 Prevention and management

- Rational use of medical radiation
- Radiation protection
- Maternal fever control
- Avoid extreme physical exposures
- Prenatal surveillance with ultrasound
- Early identification of mechanical factors

Table 2

Teratogenic physical agents

Agent	Mechanism	Critical period	Demonstrations	Agent
Ionizing radiation	DNA damage	3–15 weeks	Microcephaly, IUGR	Ionizing radiation
Hyperthermia	Protein alteration	3–6 weeks	NTDs, heart disease	Hyperthermia
Oligohydramnios	Fetal compression	2nd–3rd trimester	Pulmonary hypoplasia	Oligohydramnios
Amniotic bands	Mechanical restraint	Variable	Amputations	Amniotic bands
Vibration	Hypoperfusion	Variable	IUGR, Prematurity	Vibration
Loud noise	Neuroendocrine stress	Variable	Hearing loss	Loud noise

Figure 4

Teratogenesis by physical agents

Fig. 4. Teratogenesis by physical agents → Cell damage / mechanical compression → Alteration of proliferation and differentiation → Failure in organogenesis → **Congenital manifestations.**

3.10 Conclusion

Physical agents represent a heterogeneous group of teratogens whose impact depends on the nature of exposure and gestational timing. Ionizing radiation is the best-established risk, while other factors such as hyperthermia and mechanical mechanisms can also cause significant damage. Most of these effects are preventable through appropriate protection, education, and prenatal care strategies, highlighting the importance of a preventive approach in clinical practice.

4. Chemical factors

4.1 Introduction

Chemical agents constitute one of the broadest, most complex and clinically relevant groups of teratogens, due to their high prevalence of exposure and the diversity of mechanisms by which they can interfere with embryo-fetal development. They include drugs, consumer substances, heavy metals, environmental pollutants, and industrial compounds, many of which cross the placenta by passive diffusion or by specific transporters, reaching fetal concentrations comparable to or higher than maternal concentrations [1,2].

The teratogenic potential depends on multiple factors, including:

- Dose and duration of exposure
- Liposolubility and molecular weight of the compound
- Plasma protein binding
- Maternal-fetal biotransformation capacity
- Time of exposure during pregnancy

The period of greatest susceptibility corresponds to organogenesis (weeks 3–8), during which major structural malformations may occur. In later stages, functional, growth, and neurodevelopmental alterations predominate [1,3].

4.2 Drugs

Drugs represent the most studied cause of chemical teratogenesis. Its effect is related to interference in fundamental processes such as DNA synthesis, cell proliferation, angiogenesis, and molecular signaling [4].

Main teratogenic drugs

- **ThalidomideA potent antiangiogenic agent associated with phocomelia, microtia and visceral malformations. It constitutes the historical paradigm of pharmacological teratogenicity.**
- **Isotretinoin (retinoids)**

It causes fetal retinoid syndrome: craniofacial, cardiac, CNS, and thymus abnormalities. There is no safe dose.

- **Valproic acid**

High risk of neural tube defects, facial dysmorphisms, and neurocognitive impairments. Risk of major malformations ~10%.

- **WarfarinCharacteristic embryopathy: nasal hypoplasia, punctate epiphyses, and neurological abnormalities (6–12 weeks).**
- **Methotrexate and chemotherapy**

They inhibit cell proliferation → abortions, multiple malformations and growth restriction.

- **ACE and ARA II**

Especially in 2nd–3rd trimester: oligohydramnios, renal dysplasia, pulmonary hypoplasia.

- **MisoprostolAssociated with fetal vascular disruption → Möbius syndrome, arthrogryposis and limb defects.**
- **LithiumIncreased risk of congenital heart disease (especially Ebstein's anomaly).**

Risk Classification

The classic FDA classification **(A, B, C, D, X)** has been replaced by the **PLLR (Pregnancy and Lactation Labeling Rule)** system, which emphasizes individualized risk-benefit assessment based on clinical evidence [5].

Drugs with a proven teratogenic effect (Table 3)

Table 3

Main drugs with high teratogenic risk in humans

Pharmacological group	Drug(s)	Critical exposure period	Main teratogenic effects	Level of evidence
Systemic retinoids	Isotretinoin, Acitretin, Etretinate	3rd–8th week	Craniofacial, cardiac, CNS malformations, thymic aplasia, microtia	High
Antiepileptics	Valproic Acid, Carbamazepine, Phenytoin, Topiramate	4th–10th week	Neural tube defects, heart disease, cleft lip/palate, cognitive delay	High
Oral anticoagulants	Warfarin	6th–12th week	Nasal hypoplasia, punctate epiphyses, growth retardation, fetal hemorrhage	High
Antimetabolites	Methotrexate	6th–8th week	Miscarriages, neural tube defects, craniosynostosis, limb abnormalities	High
Alkylating agents	Cyclophosphamide, Busulfan, Chlorambucil	First trimester	Multiple malformations, growth restriction, stillbirth	High
Hormone modulators	Diethylstilbestrol (DES), Danazol	First trimester	Genital tract abnormalities, vaginal adenocarcinoma (DES), virilization	High
5-α-reductase inhibitors	Finasteride, Dutasteride	8th–12th week	Genital ambiguity, hypospadias	Moderate
Antihypertensives	ACE, ARA II	2nd–3rd trimester	Oligohydramnios, renal dysplasia, pulmonary	High

			hypoplasia, neonatal death	
Anti-infectives	Thalidomide, Misoprostol, Ribavirin, Tetracyclines	Variable (mainly 1.er quarter)	Phocomelia, cranial defects, multiple embryopathy, dental disorders	High
Psychotropic	Lithium, Paroxetine	2nd–8th week	Ebstein's anomaly, congenital heart disease	Moderate–High

The level of evidence is based on observational studies, pregnancy registries, and meta-analyses. Thus, some drugs (retinoids, valproate, thalidomide) do not have a known safe dose. Preconceptional exposure is particularly relevant in acitretin and etretinate.

4.3 Substances of consumption and drugs of abuse

Alcohol

Alcohol is the most common teratogen and the leading preventable cause of fetal nerve damage.

Mechanisms:

- Oxidative stress
- Alteration of neuronal migration
- Disruption of synaptogenesis

Main consequence:

- Fetal alcohol spectrum disorders (FASDs), including fetal alcohol syndrome (FAS)

Demonstrations:

- Cognitive deficit
- Characteristic facial features
- Failure to thrive
- Behavioral alterations

There is no safe level of consumption during pregnancy [6,7].

Tobacco

Tobacco exerts its effect mainly by nicotine and carbon monoxide.

Mechanisms:

- Uteroplacental vasoconstriction
- Chronic fetal hypoxia
- Oxidative stress

Consequences:

- Low birth weight
- Prematurity
- Intrauterine growth restriction
- Sudden infant death [8,9]

Cocaine

It produces intense vasoconstriction → fetal hypoxia.

Effects:

- Placental abruption
- Fetal infarctions
- Vascular malformations
- IUGR

Cannabis and methamphetamines

The evidence is variable, but they have been associated with:

- Neurodevelopmental alterations
- Cognitive and behavioral deficits
- Low birth weight

4.4 Heavy metals

Heavy metals are potent neuroteratogens that accumulate in fetal tissues.

- **Lead**
  - Decreased IQ
  - Behavioral disorders
  - ADHD
- **Mercury (methylmercury)**
  - Microcephaly
  - Cerebral palsy
  - Sensory and motor deficits

Mechanism:

- Alteration of synaptogenesis
- Interference with myelination
- Direct neurotoxicity [10,11]

4.5 Environmental pollutants and endocrine disruptors

Environmental pollutants represent an emerging public health problem.

Main agents

- Bisphenol A (BPA)
- Phthalates
- Dioxins
- PCBs

Mechanisms

- Endocrine disruption

- Impaired hormone signaling
- Abnormal metabolic programming

Effects

- Reproductive alterations
- Metabolic disorders
- Neurodevelopmental disorders [12]

4.6 Occupational and Industrial Exposure

Includes:

- Pesticides (organophosphates, carbamates)
- Organic solvents
- Hydrocarbons

Effects:

- Miscarriages
- CNS malformations
- Heart defects
- IUGR

4.7 Pathophysiological mechanisms

Chemical agents induce teratogenesis in multiple ways:

- Alteration of DNA synthesis and repair
- Oxidative stress
- Interference in cell signaling
- Endocrine disruption
- Inhibition of angiogenesis
- Direct toxicity to fetal tissues [1,4]

4.8 Clinical manifestations

The manifestations depend on the agent and the time of exposure:

- Structural congenital malformations
- Neurocognitive deficits
- Intrauterine growth restriction
- Behavioral disorders
- Endocrine and metabolic disruptions [6,10]

4.9 Prevention and management

Preventive strategies include:

- Rigorous evaluation of drug use during pregnancy
- Preconception counseling

- Suspension of known teratogenic substances
- Avoid alcohol, tobacco, and drug use
- Reduction of environmental and occupational exposure
- Use of teratological databases (TERIS, LactMed)
- Strict prenatal care [3,5]

Table 4

Main teratogenic chemical agents

Agent	Type	Mechanism	Demonstrations	Agent
Thalidomide	Drug	Antiangiogenesis	Focomelia	Thalidomide
Isotretinoin	Drug	Gene alteration	Craniofacial defects	Isotretinoin
Valproate	Drug	Folate Alteration	DTN	Valproate
Alcohol	Substance	Neurotoxicity	SAF	Alcohol
Tobacco	Substance	Hypoxia	Low weight	Tobacco
Lead	Metal	Neurotoxicity	Cognitive deficit	Lead
Mercury	Metal	Neuronal damage	Motor alterations	Mercury
BPA	Environmental	Endocrine disruption	Hormonal alterations	BPA

Figure 5

Schematic of teratogenesis by chemical agents

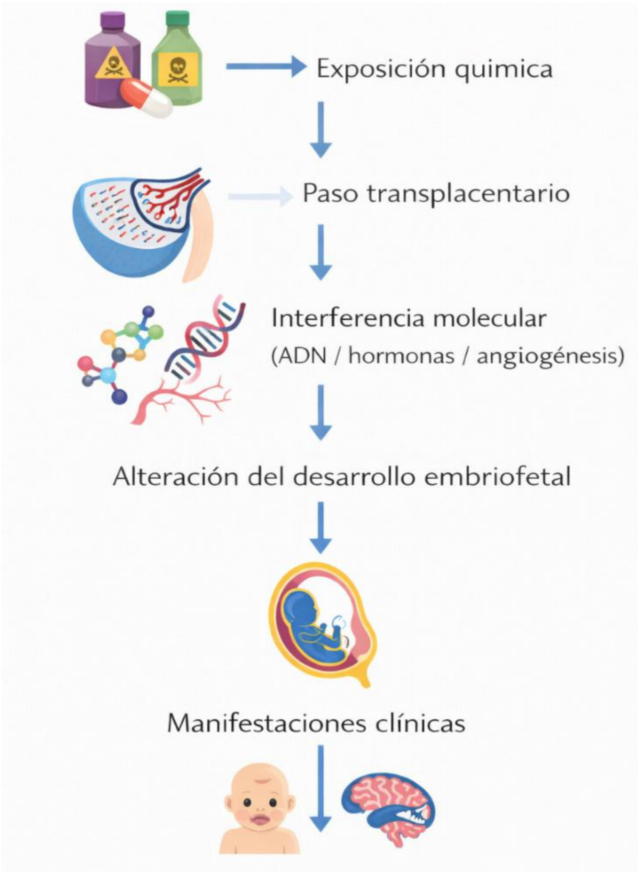

Fig. 5 Chemical exposure → Transplacental passage →Molecular interference (DNA/hormones/angiogenesis) →Impaired embryofetal development → Clinical manifestations

5. Maternal factors as endogenous teratogens

5.1 Introduction

Maternal factors constitute a group of endogenous teratogens in which fetal damage results from alterations in the intrauterine environment secondary to the mother's own conditions. These conditions modify the supply of oxygen, nutrients, hormones, and metabolic signals essential for embryo-fetal development [1,2]. (Table 5)

Unlike exogenous agents, maternal factors exert a continuous effect during pregnancy. Its impact depends on the degree of clinical control of the disease, the time of exposure, and the interaction with other environmental or genetic factors [3].

5.2 Pregestational diabetes mellitus

Pregestational diabetes mellitus is one of the best-established models of maternal teratogenesis. Exposure of the embryo to hyperglycemia during the period of organogenesis (weeks 3–8) significantly increases the risk of congenital malformations [4].

Main manifestations

- Congenital heart disease (VSD, TGA, tetralogy of Fallot)
- Neural tube defects
- Caudal regression syndrome (specific marker)
- Renal and gastrointestinal abnormalities

Pathophysiological mechanisms

- Hyperglycemia-induced oxidative stress
- Alteration of embryonic energy metabolism
- Disruption of gene expression and cell signaling
- Fetal hyperinsulinism (anabolic and dysmorphogenic effect)

Key clinical aspect

There is a direct relationship between elevated HbA1c levels in the periconceptional period and the risk of malformations. Adequate glycemic control prior to pregnancy significantly reduces this risk.

Clinical differentiation

- **Pregestational diabetes** → structural malformations
- **Gestational diabetes** → macrosomia and neonatal metabolic disorders

5.3 Maternal Phenylketonuria (PKU)

Uncontrolled maternal phenylketonuria is a classic example of metabolic teratogenesis. The accumulation of phenylalanine in maternal blood crosses the placenta and exerts a direct neurotoxic effect on the fetus [6].

Demonstrations

- Microcephaly
- Intellectual disability
- Congenital heart disease
- Intrauterine growth restriction

Key features

- Damage occurs regardless of fetal genotype
- There is a dose-dependent relationship with phenylalanine levels
- It is a highly preventable condition

Prevention

Strict diet low in phenylalanine started before conception and maintained throughout gestation.

5.4 Nutritional deficiencies

Maternal nutritional deficiencies affect critical processes such as DNA synthesis, cell proliferation, and tissue differentiation.

Main deficiencies

- **Folic acid** → neural tube defects (anencephaly, spina bifida)
- **Iodine** → congenital hypothyroidism and neurodevelopmental disorders

These findings support universal folic acid supplementation and adequate micronutrient intake during pregnancy [7,8].

5.5 Maternal hypoxia

Conditions that generate maternal hypoxia (severe anemia, respiratory or heart disease) decrease the oxygen supply to the fetus, affecting growth and development [3].

Consequences

- Intrauterine growth restriction (IUGR)
- Low birth weight
- Perinatal complications

Mechanism

Alteration of placental angiogenesis and fetal metabolism, with redistribution of blood flow (Fig. 6).

5.6 Maternal thyroid disorders

Maternal thyroid hormones are essential for fetal neurodevelopment, especially in the first trimester.

Untreated hypothyroidism

- Cognitive deficit
- Psychomotor delay
- Increased risk of neurodevelopmental disorders

Clinical significance

It is not a classic structural teratogen, but it is a powerful **disruptor of neurodevelopment**.

5.7 Autoimmune Diseases: Systemic Lupus Erythematosus

Maternal systemic lupus erythematosus (SLE) can affect the fetus through the transplacental passage of autoantibodies.

Main effects

- Congenital heart block
- Neonatal lupus
- Intrauterine growth restriction
- Preterm birth

Important Consideration

Teratogenic risk is often associated with the **drugs used** (e.g., immunosuppressants), rather than with the disease itself.

5.8 Maternal obesity

Maternal obesity is associated with a pro-inflammatory state and metabolic alterations that increase the risk of:

- Neural tube defects
- Heart malformations
- Fetal macrosomia
- Obstetric complications

5.9 Maternal psychological stress

Severe maternal stress acts as a functional teratogen by activating the hypothalamic–pituitary–adrenal axis.

Mechanisms

- Elevated fetal cortisol
- Oxidative stress
- Uteroplacental vasoconstriction

Consequences

- Prematurity
- Low birth weight
- Neurodevelopmental alterations

5.10 Global pathophysiological mechanisms

Maternal factors induce teratogenesis through convergent mechanisms:

- Metabolic alterations
- Oxidative stress
- Fetal hypoxia
- Endocrine disruption
- Nutritional deficiencies
- Alteration of the intrauterine environment

5.11 Clinical manifestations

Clinical consequences are variable and include:

- Structural congenital malformations
- Microcephaly
- Intrauterine growth restriction
- Neurocognitive deficits
- Neonatal metabolic disorders

5.12 Prevention and management

Key strategies include:

- Preconception control of maternal diseases
- Metabolic optimization (especially in diabetes)
- Folic acid and iodine supplementation
- Strict prenatal follow-up
- Maternal education and multidisciplinary counseling

Table 5

Main examples of maternal teratogens

Maternal condition	Mechanism	Effects on the fetus
Poorly controlled diabetes mellitus	Oxidative stress	Heart malformations, neural tube defects, fetal macrosomia, stillbirth
Phenylketonuria (PKU) without diet	Neurotoxicity	Microcephaly, mental retardation, heart defects, IUGR
Untreated hypothyroidism	Thyroid disruption	Mental retardation, low weight, alterations in brain development
Systemic lupus erythematosus (SLE)	Endothelial and placental alteration	Congenital heart block, preterm birth, fetal growth restriction
Chronic kidney disease		IUGR, preterm birth, oligohydramnios
Severe obesity	Inflammation	Risk of neural tube defects, macrosomia, preeclampsia, stillbirth

Maternal Infections (TORCH)	Inflammation	Deafness, microcephaly, hydrocephalus, chorioretinitis, brain calcifications
Severe maternal malnutrition	DNA alteration	IUGR, neurological abnormalities, low birth weight
Chronic hypoxia (severe asthma, COPD)	↓ Fetal O_2	IUGR, chronic fetal distress, preterm birth
Severe psychological stress or trauma	Hormonal and placental alterations	Hormonal alterations that affect fetal growth and neurodevelopment
Thyroid disorders (hyperthyroidism)	Thyroid disruption	Malformations, fetal loss, preterm birth

Figure 6

Maternal teratogenesis scheme

Fig. 6. Maternal condition → Alteration of the intrauterine environment →Deficit of oxygen/nutrients/signals →Alteration of embryo-fetal development → Clinical manifestations

5.13 Conclusion

Maternal factors represent a fundamental and potentially preventable cause of teratogenesis. Its impact depends to a large extent on clinical control and preconceptional management. Early identification and timely intervention can significantly reduce fetal morbidity, highlighting the importance of a comprehensive approach to prenatal care.

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ANNEX 1

GLOBAL FIGURE. Comparative classification of teratogens and mechanisms of embryo-fetal damage

INTEGRATED SCHEME

TERATOGENIC EXPOSURE

── 1. BIOLOGICAL TERATOGENS

(Viruses, bacteria, parasites) │ ├─ Examples: TORCH, Zika, syphilis ├─ Mechanism: │ • Direct fetal infection │ • Intrauterine inflammation │ • Tissue necrosis │ └─ Manifestations: • Microcephaly • Brain calcifications • Deafness, chorioretinitis

── 2. PHYSICAL TERATOGENS

(Radiation, hyperthermia, trauma) │ ├─ Examples: ionizing radiation, maternal fever ├─ Mechanism: │ • Direct DNA damage │ • Cellular apoptosis │ • Alteration of cell proliferation │ └─ Manifestations: • Structural malformations • Growth restriction • Neurological alterations

── 3. CHEMICAL TERATOGENS

(Drugs, toxicants, pollutants) │ ├─ Examples: │ • Drugs: thalidomide, valproate │ • Substances: alcohol, tobacco │ • Metals: lead, mercury │ • Endocrine disruptors: BPA │ ├─ Mechanism: │ • Oxidative stress │ • DNA alteration │ • Endocrine disruption │ • Antiangiogenesis │

└─ Manifestations: • Congenital malformations • Neurocognitive deficit • IUGR

── 4. MATERNAL FACTORS

(Maternal Internal Conditions) │ ├─ Examples: │ • Diabetes │ • PKU │ • Hypothyroidism │ • Obesity │ • Hypoxia │ ├─ Mechanism: │ • Metabolic Disorders │ • Fetal Hypoxia │ • Nutritional Deficiencies │ • Hormonal Disruption │ └─ Manifestations: • Congenital Heart Disease • Neural Tube Defects • Microcephaly • IUGR

COMMON PATHOPHYSIOLOGICAL AXIS

Teratogenic agent ↓Transplacental passage / Maternal alteration ↓Molecular interference (DNA, cell signaling, hormones, angiogenesis) ↓Alteration of embryo-fetal development ↓Clinical manifestations (malformations, IUGR, neurodevelopment)

Table 6

Global comparison table

Type of teratogen	Source	Main mechanism	Critical moment	Key example	Typical manifestation	Type of teratogen
Biological	Exogenous	Direct infection	1st trimester	TORCH	Microcephaly	Biological
Physical	Exogenous	DNA damage	Organogenesis	Radiation	Malformations	Physical
Chemical	Exogenous	Oxidative stress/disruption	Variable	Valproate	DTN	Chemical
Maternal	Endogenous	Metabolic Alteration	Continuous	Diabetes	Heart Disease	Maternal

KEYS FOR DISCUSSION

This outline allows you to highlight strengths in your chapter:

1. Pathophysiological convergence

Although the agents are different, they all converge in:

Molecular damage

Alteration of cell development

Disruption of the fetal microenvironment

2. Importance of exposure time

Preimplantation → embryonic death

Organogenesis (3–8 weeks) → structural malformations

Fetal period → functional alterations

3. Multifactorial interaction

Fetal genetics

Maternal status

Combined environmental exposure