

Table S1 - Main teratogen categories and respective embryo-fetal effects during pregnancy.

Categories	Teratogen	Characteristic	Effects	Reference
Category I: Drugs and substances	Alcohol	The enzyme alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde, which inhibits DNA synthesis, amino acid transport from placenta to the fetus, besides interfering in brain development. The susceptibility is related to the amount of ADH, which have variations in their expression due to genetic differences in ADH alleles.	Deficiency in intrauterine growth and postnatal growth, cognitive abnormalities, leading to a set of characteristics called fetal alcohol syndrome (FAS), characterized by: alterations in facial appearance (small palpebral fissures, large epicanthal folds, small head, small upper jaw, smooth philtrum, thin upper lip), decreased muscle tone, poor coordination, heart defects (ventricular and atrial septal defects), late reasoning, speech, movement and social skills development. FAS is the main cause of intellectual disability.	(Rostand <i>et al.</i> , 1990; Sampson <i>et al.</i> , 1997)
	Tobacco	Nicotine is a vasoconstrictor interfering in intrauterine growth due to decreased perfusion fetal tissues, which may lead to placental abruption. Carbon monoxide present in the smoke of the cigarette also crosses the placenta, producing an increase in carboxyhemoglobin in blood.	Oral clefts, low birth weight, intrauterine growth retardation, spontaneous abortion, premature birth.	(Werler 1997; Nicoletti <i>et al.</i> , 2014)
	Marijuana	It is extracted from the <i>cannabis sativa</i> plant. Liposoluble active compound 8, 9-tetrahydrocannabinol crosses the placenta easily, reaching the fetus. This compound binds to cannabinoid receptors, acting on the analgesia route, as well as the anxiolytic route and immunological system.	Intrauterine growth restriction, cognitive and neurobehavioral imbalance, respiratory and hormonal disorders.	(Kuczkowski 2004)

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	LSD	LSD (lysergic acid diethylamide) produces a series of distortions in the functioning of the brain, changing the psychic, circulatory and thermal functions.	Brain damage, abnormalities in the lower jaw, modification of facial contours, defects in the limbs and eyes, joint problems and miscarriage.	(McGlothlin <i>et al.</i> , 1970)
	Cocaine	Cocaine has vasoconstrictor activity, which may result in an interruption of blood flow to the fetus.	Placental abruption, intrauterine growth retardation, limb defects, vascular disorders, prematurity, respiratory problems, ileal atresia, defects in brain growth and central nervous system (CNS), neurobehavioral disorders.	(Rizk <i>et al.</i> , 1996; Behnke <i>et al.</i> , 2001)
	Thalidomide	(S) enantiomer of thalidomide is an angiogenesis inhibitor, affecting the following pathway: growth factor I (IGF-I), and fibroblast growth factor 2 (FGF-2). Stimulation of integrin subunit B3 genes transcription, which are responsible for stimulation of angiogenesis in the developing limb buds, which promotes the growth from the root	Phocomelia of upper and lower limbs, pre-axial polydactyly, trifalangeal thumb, facial hemangiomas, esophageal and duodenal atresia, cardiac defects, renal agenesis, urinary tract anomalies, genital defects, dental anomalies, ear anomalies, facial palsy, ophthalmoplegia, anophthalmia and microphthalmia.	(Stephens <i>et al.</i> , 2000; Kim and Scialli 2011)
	Antagonists of folic acid and folic acid deficiency	Folic acid has an important role in nucleic acid synthesis. It acts as a coenzyme in various cellular reactions. It is included in cellular division process, due to the role in biosynthesis of purines and pyrimidines, in the transfer of carbon in the metabolism of amino acids and nucleic acids. A deficiency of folic acid or the use of antagonistic drugs can impair cell growth and replication of the fetus	Neural tube defects, heart defects (ventricular septum), cleft lip, cleft palate and anencephaly.	(Scholl and Johnson 2000; Hernández-Díaz <i>et al.</i> , 2001)
	Sedatives	Especially drugs containing benzodiazepine, which	Cleft lip, cleft palate, congenital heart disease, intrauterine growth	(Eger 1991; Leppée <i>et al.</i> ,

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		acts selectively on polysynaptic pathways of the CNS. They have an anti-anxiety and calming effect.	restriction, as well as changes in facial appearance, similar to FAS.	2010)
	Isotretinoin	It is a retinoic acid, which acts in the induction and control of epithelial differentiation, in mucus-secreting tissue or keratinizing, in the production of prostaglandin E2, of collagen. Also acts in controlling the proliferation of certain skin microorganisms.	Cleft palate, webbed neck, microphthalmia and absent external ears, cardiovascular defects (aortic arch interruption, defect in the atrial and ventricular septum), hydrocephalus, absence of cerebellar vermis, defects in cranial nerves.	(Hansen and Pearl 1985)
	Caffeine	Caffeine is a xanthine alkaloid, which readily crosses the human placenta, entering the fetal circulation during its development. Drug effect occurs on the CNS stimulation, such as increased motor activity, catecholamine release, adrenaline and noradrenaline release, serotonin turnover in selected areas, inhibition of phosphodiesterase activity.	CNS defects, orofacial clefts, structural skeletal defects, cardiovascular malformations, adactyly and absence of thumbs.	(Al-Hachim 1989; Collier <i>et al.</i> , 2009)
	Ergotamine	It is a natural alkaloid, which acts on smooth muscle contraction, producing fetal vasoconstriction.	Neural tube defects, cardiovascular malformation, polydactyly, intrauterine growth retardation and jejunal atresia.	(Czeizel 1989)
	Phenytoin (Hydantoin)	It is an antiepileptic drug that decreases the neuronal excitation. It stabilizes the neuronal membrane by inhibiting the sodium channel, interfering in the psychomotor performance.	Delayed mental development, craniofacial dysmorphism, hypoplasia of the distal phalanges, cardiac, skeletal and eye defects, imbalance in the immune system. Can cause a number of disruptions, known as the fetal hydantoin syndrome.	(Hansen and Billings 1985; Singh and Shah 1989; Hill <i>et al.</i> , 2010)

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	Dimethadione and trimethadione	Anticonvulsants oxazolindiones that have action in the thalamus region by repetitive stimulation, acting on Ca ²⁺ currents.	Spontaneous abortions, microphthalmia, anophthalmia, microcephaly, celosomia, absence of toe, developmental delay, facial alterations (brachycephaly, V-shaped eyebrows, broad nasal bridge, cleft palate, mal-positioned ears), cardiovascular defects (globular heart), renal malformations, ventral hernia, hypospadias and intellectual disabilities.	(Rifkind 1974)
	Warfarin	It is an anticoagulant, which readily crosses the placenta. It has an action in the coagulation cascade by reducing hepatic synthesis of factors II, VII, IX and X, besides the inhibition of vitamin K formation.	Spontaneous abortions; can cause the fetal warfarin syndrome (skeletal abnormalities, nasal hypoplasia, narrow nasal bridge, scoliosis, spinal calcifications, femur and heel bone calcifications, low birth weight, and developmental disabilities.	(Baillie <i>et al.</i> , 1980; Starling <i>et al.</i> , 2012)
	Angiotensin-converting enzyme (ACE) inhibitors	It is an antihypertensive that has an action in ACE inhibition, which is an enzyme responsible for converting angiotensin I to angiotensin II, acting on the renin angiotensin aldosterone system.	Small formation of amniotic fluid (oligohydramnios), spontaneous abortions, intrauterine and neonatal deaths, neonatal respiratory distress, central nervous system and limb defects, calcarial hypoplasia and renal disorders (intrauterine renal failure, renal tubular dysplasia).	(Barr 1994)
	Statins	Statins are used for reducing the serum levels of cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG - CoA) altering the kinetics of formation of cholesterol.	Spontaneous abortion, CNS defects, skeletal abnormalities, hypospadias, duodenal atresia, cleft lip and scars on the skin.	(Godfrey <i>et al.</i> , 2012)
	Misoprostol	It is a synthetic prostaglandin E1 (PGE1) used for stomach disorders, activating the	Neurological disorders (Moebius syndrome), malformations of limbs	(da Silva Dal Pizzol <i>et al.</i> , 2006; Allen and O'Brien

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		production of protective mucus, as well as increasing blood flow. However, it can cause strong uterine contractions and is used as an illegal abortion method.	and miscarriage.	2009)
	Tetracycline	A broad-spectrum action antibiotic, bacteriostatic, which has an action in the bacterial protein synthesis inhibition by binding the 30S subunit of the bacterial ribosome. When used in late pregnancy, it causes antibiotic deposition in the calcification of teeth.	Modification in dental enamel with yellow-brown discoloration, and calcification of deciduous teeth	(Demers <i>et al.</i> , 1968)
	Lithium	Used in bipolar disorder treatment, crossing the placenta freely and affecting the vascular formation of the fetus, showing greater teratogenic potential in the first quarter of pregnancy.	Cardiac anomalies are more common, such as Epstein's anomaly, dextrocardia, coarctation of the aorta, as well as hypotonia, respiratory distress syndrome, cyanosis, muscle weakness and lethargy.	(Gentile 2012)
Category II: Physical agents	Radiation	Ionizing radiation can cause cellular death, gene mutation, and change in the mitosis pattern, which leads to serious damage to embryonic development.	Spontaneous abortion, intrauterine growth retardation, microcephaly, intellectual disabilities.	(Brent 1980; De Santis <i>et al.</i> , 2005)
Category III: Environmental agents	Lead	Accumulates in maternal bone tissue; It is released slowly, crossing the placenta between the 12 th -14 th weeks, accumulating in fetal tissue.	Spontaneous abortion, vertebral alterations and anal defects, cardiovascular defects, polydactyly, clubfoot, tracheoesophageal fistula, renal defects and abnormalities of limbs.	(Bellinger 2005)
	Mercury	Organic forms are more toxic than inorganic forms. Methylmercury (MeHg) readily crosses the placenta and the hematoencephalic barriers; In addition to being highly toxic, it is selective to the CNS, leading to inhibition of the neuronal cell, such as the	CNS defects, neurobehavioral disorders. The best known syndromic alteration is Minamata disease that includes sensory disturbances in the hands and feet, ocular and hearing disorders, weakness and paralysis	(Myers <i>et al.</i> , 2003; Bose-O'Reilly <i>et al.</i> , 2010; Sagiv <i>et al.</i> , 2014)

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		division and migration. The contamination normally occurs by ingestion of poisoned food, such as fish.	of limbs.	
	Toluene	Toluene (methylbenzene) is a liposoluble aromatic hydrocarbon, which is used as a solvent, capable of easily crossing placental barrier, causing metabolic acidosis and hypoxia, which will lead to fetal hypoperfusion and ischemia	Prematurity, failure to thrive, microcephaly, anencephaly, developmental delay, renal disorders and craniofacial anomalies.	(Donald <i>et al.</i> , 1991; Wilkins-Haug 1997)
	Polychlorinated and polybrominated byphenyls (PCBs)	(PCBs) are synthetic hydrocarbons. They are chemical pollutants that have lipophilic characteristics, and may cross the placenta, reaching the fetus directly or be transferred via breast milk, accumulating mainly in the skin.	Hyperpigmentation and facial acne, nail alterations, and behavioral deficits intellectual disabilities.	(Jacobson and Jacobson 1997; Cohn <i>et al.</i> , 2011)
	Chromium	Chromium is used for biological applications and industrial processes. This chemical agent may reach the circulatory system and cross the placental barrier, reaching the fetus and transferring chromium from the mother to the bones of the developing fetus	Skeletal abnormalities, sub-dermal hemorrhagic patches and abortion	(Kanojia <i>et al.</i> , 1996)
Category IV: Maternal infections	Varicella	Caused by the <i>varicella-zoster</i> virus (VZV), which is able to cross the placenta and infect the fetus.	Skin lesions such as scars are more common, miscarriage, premature birth, muscular and skeletal malformations, defects in the CNS, calcifications, blindness, growth retardation and intellectual disabilities.	(Sauerbrei 2010)
	Mumps	Caused by the <i>paramyxovirus</i> virus RNA, which can reach the fetus in cases of acute maternal viremia. Malformative effects during	The effects observed are postnatal, causing inflammation of the parotid, submaxillary and sublingual glands.	(Ornoy and Tenenbaum 2006; Lozo <i>et al.</i> , 2012)

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		pregnancy are unknown.		
	Influenza	Caused by influenza A, B and C, typically occurring during the winter, associated with periods of fever and secondary bacterial infections of the respiratory system. The influenza virus infection appears to have no significant effects in the fetal development.	The effects observed are postnatal periods which include fever and respiratory problems.	(Acs <i>et al.</i> , 2005)
	Cytomegalovirus	Caused by viruses of the family <i>Herpesviridae</i> , reaching the fetus in phases of acute viremia in the different embryonic stages.	Microcephaly, intellectual disabilities, unilateral or bilateral deafness, neuromuscular diseases, chorioretinitis, hepatosplenomegaly, cerebral calcifications, and cortical / subcortical abnormalities.	(Pass <i>et al.</i> , 1980; Pascual-Castroviejo <i>et al.</i> , 2012)
	Parvovirus	Caused by the human Parvovirus B-19. It is able to cross the placenta and infect the liver of the fetus, which is the main hematopoietic source of the embryo. This virus has affinity for dividing cells, in particular the erythropoietic tissues.	Spontaneous abortion, fetal hydrops, fetal anemia, myocarditis, liver failure, CNS defects, craniofacial and eye abnormalities.	(Ergaz and Ornoy 2006)
	Syphilis	Caused by the <i>Treponema pallidum</i> , which is a spirochete capable of crossing the placental barrier and infecting the fetus near 14 th week of gestation. Placental infection and reduced blood flow to the fetus are the causes of fetal death.	Spontaneous abortion, prematurity, low birth weight, hepatosplenomegaly, hematological disorders.	(Genc and Ledger 2000; De Santis <i>et al.</i> , 2012)
	Toxoplasmosis	Caused by the protozoan <i>Toxoplasma gondii</i> , the most common infection in pregnancy. Transmission in adults occurs through the consumption of undercooked meat or contact with the feces of infected cats. The parasite crosses from the placenta	Seizures, intellectual disability, cerebral palsy, deafness and blindness.	(Yokota 1995; Rorman <i>et al.</i> , 2006)

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		to infect the fetus.		
	Herpes	Herpes simplex virus (HSV) type 1/2 and Epstein - Barr virus (EBV) belong to human herpes virus. Genital HSV can cause intrauterine infection or during childbirth. Transplacental transmission of the EBV is rare, but can occur.	Effects caused by HSV include spontaneous abortion, skin manifestations, chorioretinitis, microphthalmia and neurological damage. EBV affects the heart, liver and eyes.	(Avgil and Ornoy 2006; Malm and Forsgren 2009)
	Genitourinary infections	The most common infections are bacterial vaginosis (<i>Gardnerella vaginalis</i> , <i>Bacteroides spp.</i> , <i>Mycoplasma hominis</i> , <i>Mobiluncus spp.</i>) and candidiasis (<i>Candida albicans</i>); they may infect the fetus during childbirth.	Skin infections, dermatological alterations and ophthalmological problems.	(Hay 2005)
	*Zika virus	Zika virus (ZIKV) is a flavivirus of the same family as yellow fever, dengue, West Nile, and Japanese encephalitis viruses. The transmission occurs through the bite of the <i>Aedes spp.</i> mosquitoes, including <i>Ae. africanus</i> , <i>Ae. luteocephalus</i> , <i>Ae. hensilli</i> , <i>Ae. Aegypti</i> , well as with potential sexual transmission. It leads to symptoms such as rash, arthralgia, and conjunctivitis. It is suspected to cause microcephaly in babies born from women that contracted the virus during pregnancy.	Microcephaly, neurological and ophthalmic anomalies	(Hayes 2009; Campos <i>et al.</i> , 2015; Musso <i>et al.</i> , 2015; Atkinson <i>et al.</i> , 2016; D'Ortenzio <i>et al.</i> , 2016; Freitas <i>et al.</i> , 2016; Mlakar <i>et al.</i> , 2016; Rasmussen <i>et al.</i> , 2016; Schuler-Faccini <i>et al.</i> , 2016; Ventura <i>et al.</i> , 2016)
Category V: Maternal conditions	Obesity	Excessive weight gain during pregnancy may impair intrauterine life, as well as maternal life, leading to serious complications such as preeclampsia and gestational diabetes.	Macrosomia and cardiovascular defects are more common. Obesity can also increase the risk of neural tube defects, orofacial clefts, hydrocephalus, anal atresia, hypospadias, renal abnormalities, omphalocele, and	(Stothard <i>et al.</i> , 2009; Blomberg and Källén 2010)

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			diaphragmatic hernia.	
	Diabetes mellitus	Hyperglycemic state leads to an increase in the formation of glycated hemoglobin, in addition to increasing oxidative stress in embryos, inhibiting the expression of specific genes, such as Pax3, which encodes a transcription factor for neural tubes.	Spontaneous abortion, macrosomia, neural tube defects, CNS disorders, cardiovascular defects.	(Ray <i>et al.</i> , 2001; Loeken 2006)
	Hypothyroidism	Deficiency of thyroid stimulating hormone (TSH) can be caused by a problem in the development of the thyroid gland (dysgenesis) due to a mutation in the transcription factor of the thyroid 2 (TTF-2) or by a biosynthesis thyroid hormone disorder (dyshormonogenesis), having an effect on the neurological development of the fetus.	Choanal atresia, cleft palate, prolonged jaundice, difficulty feeding, lethargy, umbilical hernia, macroglossia constipation, blotchy skin, hypotonia.	(Bamforth <i>et al.</i> , 1986; Källén and Wikner 2014)
	Hyperthyroidism	Caused mainly by autoimmune diseases, such as Grave's disease, or in combination with other maternal biochemical disturbances. Antibodies and antithyroid medication given to the mother can cross the placenta and affect the fetal thyroid gland	Malformation of the ear lobes, omphalocele, imperforate anus, anencephaly, cleft lip, growth retardation, accelerated bone maturation, goiter and policactilia.	(Momotani <i>et al.</i> , 1984; Alamdari <i>et al.</i> , 2013)
	Hypoparathyroidism	The parathyroid dysfunction is caused by parathyroid hormone deficiency, which leads to hypocalcemia and hyperphosphatemia	Prematurity, bone demineralization, craniofacial uncovered, microcephaly, deep-set eyes, thin lips, micrognathia, flattened nasal bridge, anomalies in the outer ear, hand and feet small, micropenis and intellectual disabilities.	(Sanjad <i>et al.</i> , 1991)
	Iodine deficiency	During pregnancy, iodine intake should be increased by almost 50%. Iodine	Spontaneous abortion, stillbirth, genital abnormalities, hearing	(Hetzel and Mano 1989; Zimmermann

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		deficiency during pregnancy can cause fetal hypothyroidism and impair neurological development of the fetus	disorders, brain function impaired, the most common being cretinism, which is an intellectual impairment, as well as the strabismus.	2009; Zimmermann 2012)
	Phenylketonuria	Characterized by decreased activity of the enzyme phenylalanine hydroxylase, which is responsible for transforming phenylalanine to tyrosine, which leads to accumulation of phenylalanine in the fetus	Intrauterine growth retardation, microcephaly, cardiovascular defects, intellectual disabilities.	(Levy and Ghavami 1996; Matalon <i>et al.</i> , 2003)
	Hypoglycemia	Stages of hypoglycemia during pregnancy stop the power supply to the fetus, as well as induced hypoxia.	Spontaneous abortion, intrauterine growth retardation.	(Zamudio <i>et al.</i> , 2010)
	Hyperthermia	Maternal body temperature above 39 ° C can lead to cell death or delay of the proliferation of neuroblasts. It can also lead to fetal vascular disruption.	Anencephaly, microphthalmia, arthrogyrosis, abdominal wall defects, abnormalities of the distal limbs, midface hypoplasia and intellectual disabilities.	(Isaacs and Gericke 1990; Graham <i>et al.</i> , 1998; Edwards 2006)

*Zika virus was confirmed to cause an outbreak of microcephaly in newborns of women that contracted the virus during pregnancy (Rasmussen *et al.*, 2016). Here we present this virus as a new teratogenic agent. Shepard's criteria have already been contemplated (Rasmussen *et al.*, 2016), more epidemiological studies are being performed to establish the teratogenic potential and spectrum of malformations.

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