Selected agents with potential adverse fetal effects

Reproductive toxin	Alleged fetal effects	Timing of exposure
Drugs		
Androgens	Masculinization of the developing female fetus can occur from androgens and high doses of some male-derived progestins.	First trimester for labial fusion; second and third trimesters for clitoral hypertrophy
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Fetal hypotension resulting in fetal kidney hypoperfusion and anuria, oligohydramnios, pulmonary hypoplasia, cranial bone hypoplasia, fetal growth restriction and demise. Neonatal oliguria, anuria, hypotension, and renal tubular dysgenesis.	Second and third trimesters
Antiseizure medications		
▪ Carbamazepine	Increases the risk of facial dysmorphology, neural tube defects, cardiovascular defects, and urinary tract defects.	First trimester
▪ Phenytoin	Increases the risk of fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, ventricular septal defect, and growth and intellectual disability.	18 to 60 days postconception (organogenesis)
▪ Trimethadione and paramethadione	Increases the risk of characteristic facial dysmorphology, intellectual disability, V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, and severe developmental delay.	First trimester
▪ Valproic acid	Increases the risk of spina bifida, facial dysmorphology, autism, atrial septal defect, cleft palate, hypospadias,	18 to 60 days postconception (organogenesis)

	polydactyly, craniosynostosis, and limb abnormalities.	
Antidepressants	Publications have implicated some of the SSRIs administered in the last trimester with postnatal neurobehavioral effects that are transient and whose long-term effects have not been determined. First trimester exposures to some SSRIs have been reported to increase the risk of some congenital malformations, predominantly congenital heart disease. The results have not been consistent, but warnings have been issued. However, other developmental toxicities have been associated with SSRIs including spontaneous abortions, low birth weight, prematurity, neonatal serotonin syndrome, neonatal behavioral syndrome (withdrawal), and persistent pulmonary hypertension of the newborn.	First and third trimesters
Antituberculous therapy	Isoniazid does not appear to cause congenital anomalies; paraaminosalicylic acid may cause an increased risk of ear and limb defects and hypospadias.	First trimester and possibly second trimester
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive agents (eg, cyclosporine, leflunomide)	Many chemotherapeutic agents used to treat cancer have a theoretical risk for producing malformations in the fetus when administered to pregnant women, especially because most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword. Cyclophosphamide causes congenital defects when used during organogenesis, and fetal bone marrow suppression may occur when exposure occurs later in pregnancy.	First trimester for malformations; second and third trimesters possibly associated with fetal growth restriction and pancytopenia
Diethylstilbestrol	Administration during pregnancy produces genital abnormalities, adenosis, and clear cell adenocarcinoma of vagina in adolescents. The last has a risk of 1:1000 to 1:10,000, but the other effects, such as adenosis, can be quite high.	First and second trimesters

Dolutegravir	Preliminary results from an observational study suggest that serious cases of neural tube congenital anomalies involving the brain, spine, and spinal cord may occur in babies of women with HIV treated with this drug.[1]	Fetuses with exposure at the time of conception or early in the first trimester appear to be at higher risk for these defects
Ethanol	Fetal alcohol syndrome consists of microcephaly, intellectual disability, growth restriction, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.	First trimester for fetal alcohol syndrome or fetal alcohol-related congenital anomalies; second and third trimesters for fetal alcohol neurodevelopmental disorders
Glucocorticoids	High exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiologic studies are not consistent.	First trimester
Insulin shock therapy	Microcephaly and intellectual disability.	First trimester
Lithium therapy	Chronic usage for the treatment of bipolar disorder has an increased risk for Ebstein anomaly and other malformations, but the risk seems to be very low.	First trimester
Macrolides (eg, azithromycin, clarithromycin, erythromycin)	Increased incidence in congenital malformations, in particular cardiovascular effects. Increased incidence in genital malformations.	First trimester for congenital malformations; first, second, and third trimesters for genital malformations
Minoxidil	Promotion of hair growth in the fetus and hirsutism in newborns.	First trimester
Methimazole	Aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy.* Other anomalies have been reported and include tracheoesophageal fistulas, patent vitellointestinal duct, choanal atresia, omphalocele, and omphalomesenteric duct anomaly.	First trimester; especially weeks 6 to 10

Methotrexate	Pregnancy loss, growth restriction, microcephaly, meningomyelocele, intellectual disability, decreased ossification of the calvarium, hypoplastic supraorbital ridges, small low-set ears, micrognathia, and limb defects.	18 to 60 days postconception (organogenesis)
Methylene blue intra-amniotic instillation	Fetal intestinal atresia, hemolytic anemia, and jaundice in the neonatal period. This procedure is no longer used to identify one twin.	18 to 60 days postconception (organogenesis)
Misoprostol	A low incidence of vascular disruptive phenomenon, such as limb-reduction defects and Mobius syndrome, has been reported in pregnancies in which this drug was used to induce an abortion.	First and second trimesters
Mycophenolate mofetil	First trimester exposure associated with miscarriage, abnormalities of the brain, ears, eyes, distal limbs, heart, esophagus, kidney, and cleft lip/palate.	First trimester
Penicillamine (D-penicillamine)	This drug results in the physical effects referred to as "lathyrism," the results of poisoning by the seeds of the genus *Lathyrus*. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition seems to be reversible, and the risk is low.	Timing associated with the occurrence of these anomalies is not clear
Progestin therapy	Very high doses of androgen hormone-derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of these drugs have the potential for producing nongenital malformations.	Third trimester
Propylthiouracil	This drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter.	Throughout gestation
Retinoids	Systemic retinoic acid, isotretinoin, and etretinate can cause increased risk of CNS, cardioaortic, ear, and clefting defects such as microtia, anotia, thymic aplasia, other branchial arch and aortic arch	First trimester

	abnormalities, and certain congenital heart malformations.	
Retinoids, topical	Topical administration is very unlikely to have teratogenic potential because teratogenic serum levels cannot be attained by topical exposure to retinoids.	
Streptomycin	Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low-risk phenomenon. Children are less sensitive than adults to the ototoxic effects of these drugs. However, deafness in newborns can occur.	Throughout gestation
Sulfa drugs and vitamin K	These drugs can produce hemolysis in some subpopulations of fetuses. Sulfa drugs can cross the placenta and bind proteins displacing bilirubin and trigger kernicterus at low bilirubin levels.	Second and third trimesters
Tetracycline	This drug produces bone and teeth staining; it does not increase the risk of any other malformations.	Second and third trimesters
Thalidomide	Multiple defects in the following systems: limbs, other skeleton, craniofacial, major organs (lungs, cardiovascular, gastrointestinal, and genitourinary), and inguinal hernia.	22 to 36 days postconception
Trimethoprim	Has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels, which has resulted in neurologic symptoms in adults taking this drug. It is also associated with cardiovascular defects and possibly oral clefts.	First trimester
Vitamin A	Although still controversial, the malformations reported with the retinoids have been reported with very high doses of vitamin A (retinol). Doses to produce congenital anomalies would have to be in excess of 25,000 to 50,000 units/day. Other gravida exposed to high doses of vitamin have had normal pregnancies.	Possibly during the first trimester

Warfarin and warfarin derivatives	Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth restriction. CNS malformations can occur in late pregnancy exposure because of bleeding.	First trimester
Radiation		
Ionizing radiation	Radiation exposure above a threshold of 20 rad (0.2 Gy) can increase the risk for some fetal effects such as microcephaly or growth retardation, but the threshold for intellectual disability is higher.	First trimester
Radioactive isotopes	Tissue- and organ-specific damage depends on the radioisotope element and distribution (ie, high doses of Iodine-131 administered to a pregnant woman can cause fetal thyroid hypoplasia after the eighth week of development).	After eighth week
Chemicals		
Carbon monoxide	CNS damage has been reported with very high exposures (carbon monoxide poisoning), but the risk seems to be low.*	
Lead	Very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 microgram/percent in the serum of pregnant mothers.	Potential risk throughout pregnancy
Gasoline	Facial dysmorphology, intellectual disability, embryopathy from exposure due to gasoline addiction.	Throughout the pregnancy
Methyl mercury	Minamata disease consists of cerebral palsy, microcephaly, intellectual disability, blindness, and cerebellum hypoplasia. Other epidemics have occurred from adulteration of wheat with mercury-containing chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely to represent a teratogenic risk, but reducing or limiting the consumption of carnivorous fish has been suggested to avoid exceeding the maximum permissible exposure recommended by the	Throughout the pregnancy

	Environmental Protection Agency, an exposure level far below the level at which the toxic effects of mercury are seen.	
Polychlorinated biphenyls	Poisoning has occurred from adulteration of food products ("Cola-colored babies," CNS effects, pigmentation of gums, nails, teeth, and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures.	Throughout the pregnancy
Toluene	Facial dysmorphology, intellectual disability, embryopathy from exposure due to toluene addiction.	
Embryonic and fetal infections		
Cytomegalovirus infection	Retinopathy, CNS calcification, microcephaly, intellectual disability. Occurs in 30 to 50% of primary infections.	First 6 months of pregnancy
Rubella	Deafness, congenital heart disease, microcephaly, cataracts, intellectual disability. Occurs in up to 80% of fetuses with a primary infections.	Up to 16 weeks although more significant in the first 2 months of pregnancy
Herpes simplex	Fetal infection, liver disease, death.	Throughout the pregnancy
HIV	Perinatal HIV infection.	Throughout the pregnancy
Parvovirus infection, B19	Stillbirth, hydrops.	Up to 20 weeks gestation
Syphilis	Maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis.	Throughout the pregnancy
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis, intellectual disability.	Throughout the pregnancy
Varicella zoster	Skin and muscle defects; intrauterine growth retardation; limb reduction defects, CNS damage (very low increased risk).	First trimester
Venezuelan equine encephalitis	Hydranencephaly; microphthalmia; destructive CNS lesions; luxation of hip.	First trimester

Zika virus	Microcephaly, intracranial calcifications, intellectual disability.	Up to 20 weeks gestation
Maternal disease states		
Corticosteroid-secreting endocrinopathy	Mothers who have Cushing's disease can have infants with hyperadrenocorticism, but anatomic malformations do not seem to be increased.	
Iodine deficiency	Can result in embryonic goiter and intellectual disability.	
Intrauterine problems of constraint and vascular disruption	These defects are more common in multiple-birth pregnancies, pregnancies with anatomic defects of the uterus, placental emboli, or amniotic bands. Possible congenital anomalies include club feet, limb-reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia, cleft lip, omphalocele, and encephalocele.	
Maternal androgen endocrinopathy (adrenal tumors)	Masculinization of female fetuses.	
Maternal diabetes with poor glycemic control	Increases the risk of a wide variety of congenital anomalies; cardiac abnormalities are most common.	
Maternal folic acid in reduced amounts	An increased incidence of neural tube defects.	
Maternal phenylketonuria	Abortion, microcephaly, and intellectual disability; very high risk in untreated patients.	
Maternal starvation	Intrauterine growth restriction, abortion, neural tube defects (Dutch famine experience).	
Tobacco smoking	Fetal growth restriction and stillbirth. Although the risk of defects is small (approximately twofold), they can involve the heart and great vessels, limbs, skull, genitourinary system, feet, abdominal wall, small bowel, and muscles.	
Zinc deficiency*	Neural tube defects.*	

CNS: central nervous system; SSRI: selective serotonin reuptake inhibitor; HIV: human immunodeficiency virus.

* Controversial.

Reference:

1. *FDA drug safety communication: FDA to evaluate potential risk of neural tube congenital anomalies with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq), May 18, 2018. https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm (Accessed on May 30, 2018).*

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