Drugs in Pregnancy

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Pregnancy is a unique period in a woman's life. Many changes are happening to her body that may affect the pharmacology of medications. During pregnancy, a woman's gastric pH is increased and gastric motility is reduced which may interfere with the rate and extent of medication absorption. Maternal plasma volume is increased leading to changes in the volume of distribution. In addition, increases in progesterone and estradiol levels may affect the hepatic metabolism of some medications. Glomerular filtration rate is increased due to increase renal blood flow which may affect renally cleared medications. Despite the changes, the pharmacology of most medications is not altered enough to require dosing changes.[1]

The placenta is an organ of exchange allowing the mother to pass nutrients and medications to the fetus; therefore, medications administered to pregnant women have the potential to affect the growing fetus. The fetus is generally at the greatest risk of developing teratogenic effects from medications during the first trimester, but it is drug specific. The use of medications in pregnancy should be evaluated for the benefits and risks to both the mother and fetus. Upon evaluation, some medications may be used sparingly during some trimesters and contraindicated in others. [2] All efforts should be made to optimize the risk benefit ratio.

Drugs with low molecular weight, low maternal protein binding, low ionization, and high lipophilicity are more likely to cross the placenta and cause pharmacologic affects.[1] The developing fetus's body systems are not mature; therefore, the fetus may lack the ability to metabolize medications causing teratogenic effects. [2]

The FDA has categorized the potential teratogenic risk of medications by an A, B, C, D, X system.

Category A: Controlled studies in women have failed to demonstrate a risk to the fetus in the first trimester and there is no evidence of risk in later trimesters. The possibility of fetal harm appears remote. Medications in this class are considered safe to use in pregnancy. Examples of medications in this class are vitamins and levothyroxine.

Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have demonstrated risk to the fetus that was not confirmed in controlled studies in pregnant women in the first trimester and there is no evidence of a risk in later trimesters. Medications in this class are generally considered safe. Examples of medications in this class are acetaminophen and amoxicillin.

Category C: Studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs from this class can be given to pregnant women if the benefit to the mother outweighs the risk to the fetus. Examples of medications in this class are diltiazem and spironolactone.

Category D: Evidence of human fetal risk has been documented, but the benefits to the mother may be acceptable despite the risk to the fetus. Drugs in this class may be used in pregnancy if the benefits to the mother outweigh the risk to the fetus (i.e. a life threatening situation or a serious disease for which safer medication cannot be used or are not efficacious). Examples of medications in this class are phenytoin and valproic acid.

Category X: Studies in animals or humans have demonstrated teratogenic effects. The risk to the fetus clearly outweighs any potential benefit to the mother. Drugs in this category are contraindicated in pregnancy. Examples of medications in this class are thalidomide and warfarin.[2]

Antibiotics

Generic (Brand)	Pregnancy Category	Crosses placenta	Reported adverse effects to mom or baby from use in pregnancy	Place in therapy
Nitrofurantoin (Macrobid)	B	Yes	Fetus: Hemolytic anemia	
Sulfamethoxazole (SMX)/ trimethoprim (TMP) (Bactrim DS/ Septra DS)	C	SMX: Unknown TMP: Yes	Fetus: SMX: jaundice, hemolytic anemia, and possibly kernicterus TMP: neural tube defects (NTD), oral clefts, cardiac defects, and urinary tract defects	Not recommended in pregnancy
Metronidazole (Flagyl) Topical-(Metrogel)	B	Yes	Fetus: Low birth weight babies, spontaneous abortions, and carcinogenic possibilities Not mutagenic or teratogenic	Safe for use only in 2nd and 3rd trimester Contraindicated in 1st trimester
Clindamycin (Cleocin, Clindagel, Cleocin-T)	B	Yes	Fetus: Increase in neonatal infection and low birth weight seen with vaginal preparation[1,12]	For BV as oral alternative, but not the topical Group B strep. disease in patients with penicillin allergy
Tetracyclines	D	Yes	Fetus: Hypospadia(1st trimester only), inguinal hernia, limb hypoplasia, teeth discoloration(2nd,3rd) cataracts, cleft palates, spina bifida, polydactyly Maternal: liver toxicity, irreversible shock	Not recommended in pregnancy
Cephalosporins	B	Yes	None reported	Generally considered safe in pregnancy unless penicillin allergic
Penicillins +/- Beta-lactamase inhibitor	B	Yes	None reported	Safest class of abx in pregnancy if not allergic Tx of choice for syphilis (desensitize if penicillin allergic)
Macrolides	Azithro, Erythro: B Claritro: C	Yes	Fetus: Cardiovascular abnormalities and cleft palate with Clarithromycin.	
Fluoroquinolones	C	Yes	Erosion of weight-bearing cartilage in rats and dogs, but no human reports	Not recommended in pregnancy
Aminoglycosides (Amikacin, Gentamicin, and Tobramycin)	D	Yes	Fetus: ototoxicity/deafness (damage of 8th CN) Neuromuscular weakness, respiratory depression with concomitant gentamicin and Mag sulfate	Do not use in pregnancy not unless the benefit outweighs the risk to the fetus.

Antiepileptic Drugs (AEDs)

Generic (Brand)	Pregnancy category	Crosses placenta	Reported adverse effects to mom or baby from use in pregnancy	Place in therapy
Carbamazepine (Tegretol)	D	Yes: levels 50-80% of maternal, highest in fetal liver and kidneys	Fetus: dysmorphic facial features, cranial defects, cardiac defects, spina bifuda, fingernail hypoplasia, developmental delay, mild mental retardation, neural tube defects	Compatible – Maternal Benefit >> Embryo/Fetal Risk If drug is required during pregnancy it should not be withheld because the benefits of preventing seizures outweigh potential fetal harm
Ethosuximide (Zarontin)	C	Unknown	Fetus: spontaneous hemorrhage, patent ductus arteriosus, cleft lip/palate, mongoloid facies, short neck, altered palmar crease and accessory nipple, hydrocephalus	Limited human data. Probably compatible. Succinamide anticonvulsants: DOC for tx of petit mal epilepsy in 1st trimester
Felbamate (Felbatol)	C	Unknown	Fetus: mental retardation. Maternal: aplastic anemia, acute liver failure	Limited Human Data – Animal Data Suggest Moderate Risk. Drug crosses placenta in animals, not yet described in humans. But should occur because of LMW
Phenytoin (Dilantin)	D Dose-related teratogenic effect	Unknown	Fetus: congenital abnormlaities, hemorrhage at birth, neurodevelopment abnormalities Maternal: folic acid deficiency	Compatible – Maternal Benefit >> Embryo/Fetal Risk Significant Risks: major/minor congenital abnormalities, hemorrhage at birth, neurodevelopment Maintain lowest level required to prevent seizures in order to lessen risk of fetal anomalies
Fosphenytoin (Cerebyx)	D	Unknown	Fetus: congenital malformations, orofacial clefts, cardiac defects, minor anomalies, mental deficiency Maternal: An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics	Benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffected)
Gabapentin (Neurontin)	C	Unknown	Limited human data does not allow an assessment as to the safety of gabapentin	Limited Evidence: If required, benefits appear > fetal risks
Lamotrigine (Lamictal)	C	Yes	Fetus: frequency of major defects among 1st trimester monotherapy exposure was 2.9% (12 of 414)	Human Data Suggest Low Risk; Adjust dose to maintain clinical response
Levetiracetam (Keppra)	C	Unknown	Risk to human fetus/embryo unknown	Risk to human embryo/fetus is unknown
Oxcarbamazepine (Trileptal)	C	Yes	Fetus: no major congenital malformations reported, mild facial defects observed in one case	No epoxide metabolites: lower risk of teratogenicity compared to other agents, Supplement with folic acid
Phenobarbital (Luminal Sodium)	D	Yes	Fetus: congenital defects, hemorrhage at birth, addiction, AE of neurobehavioral development Maternal: Benefit > Risk	Benefits >Risk during at lowest effective level
Pregabalin (Lyrica)	C	Unknown	Animal studies – fetal abnormalities, skeletal malformations, male-mediated teratogenicity No human studies	Use only if maternal benefit>fetal risk
Tiagabine (Gabitril)	C	Unknown	Fetus: one incidence with unspecified malformations, otherwise unknown	Safest course: Avoid in 1st trimester ; later trimesters unknown,
Primidone (Mysoline)	D	Unknown	Newborn: neurologic manifestations (overactivity /tumor); mechanism for hemorrhagic effects is due to suppression of VitK-dependent clotting factors, recommend administration of VitK to infant immediately after birth	If benefits > risks (e.g., drug needed in life-threatening situation or serious disease with no safer drug)
Topiramate (Topamax)	C	Yes	Hypospadias in males (relationship not established); Data too limited to assess embryo/fetus risk	Avoid if possible in 1st trimester

Valproic Acid (Depakene)	D	Yes	Fetus: neural tube defects, minor facial defects, defects of the head, face, digits, urogenital tract, mental and physical growth	Benefits > Risks (e.g., drug needed in life-threatening situation or serious disease with no safer drug)
Zonisamide (Zonegran)	C	Unknown	Congenital anomalies possible	Avoid if possible in 1st trimester
Trimethadione	D	Unknown	Fetus: mental retardation, craniofacial defects, genitourinary defects, malformed hands, clubfoot	Contraindicated in 1st trimester[1]
Clonazepam (Klonopin)	D	Unknown	Human data suggest low risk; fetal and neonatal toxicity has been reported	Safest course is to avoid during the 1st trimester; however, if indicated, it should not be withheld because of pregnancy
Lorazepam (Ativan)	D	Yes	Fetus: high IV doses may cause "floppy infant" syndrome, higher incidence of respiratory distress	Benefits > Risks (e.g., drug needed in life-threatening situation or serious disease with no safer drug)
Carbamazepine (Tegretol)	D	Yes	Fetus: minor craniofacial defects, fingernail hypoplasia, developmental delay, mild mental retardation	If required, Benefits > risks

Cough and Cold

Generic (Brand)	Class	Pregnancy Category	Crosses placenta	Reported adverse effects to mom or baby from use in pregnancy	Place in therapy
Diphenhydramine (Benadryl)	Antihistamine	B	Yes	1st trimester – cleft palate, cardiovascular defects, oral clefts, spina bifida, polydacytly, limb reduction defects and hypospadias. Maternal: premature labor	DOC if parenteral antihistamines are indicated Meclizine and cyclizine: viable alternatives
Chlorpheniramine (Chlorphen, Aller-Chlor)	Antihistamine	B	Unknown	Fetal: polydactyly, GI defects, eye and ear defects, inguinal hernia, hydrocephaly, congenital dislocation of the hip and malformation of the female genitalia.	Meclizine and cyclizine do not require a restriction on use in pregnant women and would be viable alternatives
Fexofenadine (Allegra)	Antihistamine	C	Unknown	No well-controlled studies published; avoid in first trimester	Consider diphenhydramine or chlorpheneramine
Loratadine (Alavert, Claritin)	Antihistamine	C B in 2nd/3rd	Unknown	Fetal: Cleft palate, microtia, microphthalmia, deafness, triscuspid dysplia, diaphragmatic hernia.	Consider diphenhydramine or chlorpheneramine Not recommended in 1st trimester
Cetirizine (Zyrtec)	Antihistamine	C B in 2nd and 3rd	Unknown	1st trimester – spontaneous abortion, ectopic kidney, undescended testes Exposure too low assess potential risks	Consider diphenhydramine or chlorpheneramine Not recommended in the 1st trimester
Dextromethorphan (Robitussin, Pediacare)	Anti-tussive	C	Unknown	generally safe based on observation	DOC for cough during pregnancy; combination products containing alcohol should be avoided during pregnancy; avoid liquid alcohol containing preparations
Benzonatate (Tessalon Perles)	Anti-tussive	C	Unknown	There has not been sufficient clinical experience to establish the safety of benzonatate in general during pregnancy	If possible, use of benzonatate during pregnancy should be avoided
Codeine / Hydrocodone rx cough syrups	Anti-tussive	C; D at higher doses for longer time	Unknown	1st trimester – physical dependence, withdrawal, growth retardation, respiratory depression, cleft lip/palate, dislocated hip, musculoskeletal defects. 2nd trimester – alimentary tract defects	Use only if clearly needed
Guaifenesin (Mucinex , Humibid)	Expectorant	C	Unknown	1st trimester –increase frequency of inguinal hernias and cardiovascular defects	Use only if Benefits > Risks
Saline Nasal Spray		A	Unknown	No known adverse effects	Safe to use during all trimesters in pregnancy.
Phenylephrine (Tannate)	Sympathomimetic	C	Unknown	1st trimester – ear/eye malformation, syndactyly, preauricular skin tag, club foot, inguinal hernia. Congenital hip dislocation, musculoskeletal defects, umbilical hernia Maternal: uterine vessel vasoconstriction and reduced blood flow results in fetal hypoxia	Until more information is available, use of phenylephrine should be avoided during pregnancy
Pseudoephedrine (Sudafed, Dimetapp)	Sympathomimetic	C	Unknown	1st trimester – inguinal hernia,club foot. May result in fetal hypoxia. Teratogenic is some animal species	
Nasal Steroids Budesonide (Rhinocort) Fluticasone (Flonase) Mometasone (Nasonex) Triamcinolone (Nasacort)	Cortico-steroid	C Budes: B Triamcin: D in 1st trimester)	Unknown	1st trimester - orofacial clefts, conotruncal defects, neural tubal defects and limb abnormalities. Congenital malformations, premature birth, low birth weight, C-section, stillbirth multiple births. Budenoside: no increased risk of these AE. Triamcinolone: in animals cleft palate, umbilical hernia, undescended testes, reduced ossification, growth retardation.	The benefits of treatment must be carefully weighed against the potential risks of therapy. Of the nasal corticosteroids, budesonide is the best choice. It is the only inhaled corticosteroid that is category B

Diabetes Mellitus

Generic (Brand)	Class	Pregnancy Category	Crosses placenta	Reported adverse effects to mom or baby from use in pregnancy	Place in therapy
Glyburide (Diabeta, Micronase, Glynase)	Sulfonylurea	C	Yes	Possible ear defects in 1st trimester, fetal hypoglycemia	Insulin is recommended first line by the ADA; ACOG recommends use of this agent in D2 or GDM
Glipizide (Glucotrol)	Sulfonylurea	C	Yes	Possible ear defects in 1st trimester, no teratogenicity in animal studies	Not recommended; limited human data
Glimepiride (Amaryl)	Sulfonylurea	C	Unknown	Skeletal malformation in high doses	Not recommended; No human data
Metformin (Glucophage, Fortamet, Glumetza)	Biguanide	B	Unknown	Neural tube defects in animals at high doses. Few abnormalities in humans at normal doses and likely due to poor BG control	Insulin is recommended first line by the ADA; ACOG recommends use of this agent in D2 or GDM
Sitagliptin (Januvia)	Dipeptidyl peptidase IV inhibitor	B	Unknown	No good studies in humans; animal studies show no defects/complication at high doses	Possible; No human data
Pioglitazone (Actos)	TZD	C	Unknown	Developmental delay, decreased fetal weight in animals	Not recommended
Rosiglitazone (Avandia)	TZD	C	Yes	Fetal death/retardation was seen in animal studies	Not recommended
Exenatide (Byetta)	Incretin mimetic	C	Unknown	Decreased fetal growth, skeletal malformations in animal studies	Not recommended
Pramlintide (Symlin)	Amylino-mimetic	C	Unknown	Animals: neural tube defects, cleft palate at high doses	Not recommended
Regular insulin (Humulin R, Novolin R)	Short acting insulin	B	No	None reported	Drug of choice
Lispro insulin (Humalog)	Rapid acting insulin	B	No	Case reports: sudden neonatal death, growth retardation; controlled studies: as efficacious as regular insulin	Recommended
Glulisine insulin (Apidra)	Rapid acting insulin	C	Unknown	No available studies	Not recommended unless benefits > risks
NPH insulin (Humulin N, Novolin N)	Intermediate acting insulin	B	No	None reported	Recommended
Glargine insulin (Lantus)	Long acting insulin	C	Unknown	No available studies	Not recommended unless benefits > risks
Detemir insulin (Levemir)	Intermediate-long acting insulin	C	Unknown	Visceral abnormalities were seen in animals	Not recommended

Analgesics

Generic (Brand)	Class	Pregnancy Category	Crosses placenta	Reported adverse effects to maternal or fetus from use in pregnancy	Place in therapy
Aspirin (Bufferin, Ecotrin)	NSAID	C	Yes	Fetal: increased perinatal mortaility, teratogenic effects, pulmonary HTN, bleeding risk, premature ductus arteriosis closure Maternal: anemia, ante/post partum hemorrhage, prolonged labor	Should not be used in pregnancy, consider acetaminophen
Ibuprofen (Advil, Midol,)	NSAID	B D in 3rd trimester	Unknown	Fetal: ductus arteriosis constriction, pulmonary HTN in 3rd trimester Maternal: prolonged labor, spontaneous abortion	Should be avoided when possible and completely avoided during the 3rd trimester. Consider acetaminophen.
Naproxen (Aleve, Anaprox, Midol, Naprosyn, Pamprin)	NSAID	B; D in 3rd trimester	Yes	Fetal: ductus arteriosis constriction, intracranial hemorrhage, primary pulmonary HTN	Should be avoided when possible and completely avoided during the 3rd trimester. Consider acetaminophen.
Acetaminophen	Analgesic antipyretic	B	Yes	Fetal: overdose can lead to liver toxicity Maternal: overdose can lead to liver toxicity	Drug of choice for analgesia and fever during pregnancy
Butorphanol (Stadol)	Narcotic analgesic	C D if prolonged use	Yes	Fetal: sinusoidal fetal heart rate pattern, addiction, respiratory depression Maternal - addiction	Used for analgesia during labor
Morphine (Duramorph, Kadian, MS Contin, Oramorph SR, Roxanol)	Narcotic analgesic	C; D if prolonged use	Yes	Fetal: addiction, possible relation to inguinal hernia and respiratory depression Maternal: addiction	Should only be used when analgesia or anesthetic is clearly indicated
Fentanyl (Actiq, Duragesic)	Narcotic analgesic	C; D if prolonged use	Yes	Fetal: respiratory depression, dependence and loss of fetal heart rate variability without hypoxia	Only use when benefits > risks
Hydromorphone (Dilaudid)	Narcotic analgesic	C D if prolonged use	Yes	Fetal: respiratory depression	Only use when benefits > risks Manufacturer recommended CI in pregnancy
Meperidine (Demerol, Meperitab)	Narcotic analgesic	C; D if prolonged use	Yes	Fetal: respiratory depression (time, dose dependant), addiction, inguinal hernia Mom: metabolite build up that can cause seizures	
Hydrocodone	Narcotic analgesic	C; D if prolonged use	Yes	Fetal: addiction, respiratory depression	
Oxycodone (OxyContin, OxyFast, OxyIR, Roxicodone)	Narcotic analgesic	B; D if prolonged use	Yes	Fetal: addiction, respiratory depression	
Tramadol (Ultram)	Central analgesic	C	Yes	Fetal: dose related fetal toxicity in animals, respiratory depression and addiction	Should be avoided until further evidence concerning the dose related fetal toxicity is available
Ergotamine (Ergomar)	Sympatholytic	X	Yes	Fetal: increase uterine tone leading to fetal hypoxia, teratogenic and fetal toxicity	Do not use in pregnancy

Immunizations

Generic (Brand)	Class	Pregnancy Category	Crosses placenta	Reported adverse effects to mom or baby from use in pregnancy	Place in therapy
Human Papillomavirus (Gardasil)	Inactivated vaccine	B	Unknown	Currently under study	Do not use during pregnancy
Hepatitis B (Engerix-B, Recombivax HB)	Inactivevaccine		Unknown	No risk to the mom or baby have been reported	Give if indicated ACOG recommends that vaccine should be given pre- or post exposure in women at risk for infection
Influenza (injection) (Afluria, Fluarix, FluLaval, Fluvirin, Fluzone)	Inactivated vaccine	C	Unknown	Studies of immunization of over 2000 women showed no fetal adverse effects associated with vaccination	ACOG recommends the vaccine be given to pregnant women in the 2nd and 3rd trimesters during flu season. All at risk for pulmonary complications should be vaccinated, regardless of trimester
Influenza (nasal) (FluMist)	Live vaccine	C	Unknown	Fetal infection with live attenuated virus may occur	Do not use during pregnancy
Meningococcal (Menomune-A/C/Y/W-135, Menactra)	Inactivated vaccine	C	Unknown	Risks to the fetus are unknown.	Use if indicated
MMR (M-M-R II)	Live vaccine	C	Unknown	Fetal infection with live attenuated virus may occur	Do not use during pregnancy; Avoid pregnancy for 12 weeks after injection
Pneumococcal Vaccine (Pneumovax)	Inactivated vaccine	C	Maternal Ab yes[2]	Risk to the fetus in the 1st trimester is unknown. No adverse events reported [2]	Use if indicated in high risk patients
Td (Decavac)	Toxoid	C	Unknown	No evidence of teratogenicity	Use if indicated
TdP (Adacel, Boostrix)	Toxoid	C	Maternal Ab yes	Antibodies may also interfere with the infant's immune response to infant doses of DTaP, so infant may not be protected.	Use if at high risk for pertussis
Varicella Vaccine (Varivax)	Live vaccine	C	Unknown	Fetal infection may occur	Do not use in pregnancy

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