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PHARMACY AND PREGNANCY: A REVIEW

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ABSTRACT

Pregnancy is a state of double danger i.e. any drug that a pregnant woman takes can easily cross placenta and can produce a teratogenic effects on fetus. It can interfere with normal embryonic or fetal development and induce abnormal post natal structure or function. Teratogens alter the genetic function of fetus. This review provides practitioners with summary of information regarding teratology risks for drugs, chemical exposure during pregnancy.

INTRODUCTION: Pregnancy is the term used to describe when a woman has a growing fetus inside of her. In most cases, the fetus grows in the uterus. Human pregnancy lasts about 40 weeks or just more than 9 months, from the start of the last menstrual period to childbirth. Each pregnancy is divided into three trimesters. These three trimesters have different emotional and physical happenings that make them unique.

- The First Trimester (Weeks 1-12)
- The Second Trimester (Weeks 13-27)
- The Third Trimester (Weeks 28-40)

A Double Danger: For a pregnant woman, drug abuse is doubly dangerous. First, drugs may harm her own health, interfering with her ability to support the pregnancy. Second, some drugs can directly impair prenatal development. Drugs taken by a pregnant woman reach the fetus primarily by crossing the placenta, the same route taken by oxygen and nutrients, which are needed for the fetus's growth and development.

Drugs that a Pregnant Woman takes during Pregnancy can affect the Fetus in several ways:

- They can act directly on the fetus, causing damage, abnormal development (leading to birth defects), or death.
- They can alter the function of the placenta, usually by causing blood vessels to narrow (constrict) and thus reducing the supply of oxygen and nutrients to the fetus from the mother. Sometimes the result is a baby that is underweight and underdeveloped.
- They can cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.

How Drugs Cross the Placenta: Some of the fetus's blood vessels are contained in tiny hair like projections (villi) of the placenta that extend into the wall of the uterus. The mother's blood passes through the space surrounding the villi (intervillous space). Only a thin membrane (placental membrane) separates the mother's blood in the intervillous space from the fetus's blood in the villi. Drugs in the mother's blood can cross this membrane into blood vessels in the villi and pass through the umbilical cord to the fetus [1].

Drug Metabolism in Pregnancy: During pregnancy, changes in drug absorption, metabolism, distribution, and elimination occur. Because of the dynamic nature of these changes, it is often difficult to predict which factors will have a significant impact on drug pharmacokinetics. Changes in gastrointestinal function that occur during pregnancy may affect the drug absorption [2]. Delayed gastric emptying may delay peak drug levels [3]. Prolonged intestinal transit time may increase the absorption of some relatively water-insoluble drugs or increase the metabolism of drugs by intestinal wall enzymes. Decreased gastric acid secretion may change the gastric pH and alter drug solubility.

Changes in body fluid compartments during pregnancy can profoundly affect drug distribution. Increases in maternal plasma volume and the enlarging fetal compartment increase the volume of distribution of many drugs, altering maternal plasma drug concentrations and elimination half-life. The progressive decrease in maternal albumin concentration causes a corresponding increase in unbound drug fraction.

Because pharmacological efficacy and toxicity are related primarily to the concentration of unbound drug, pregnancy-induced changes in protein binding may have important clinical implications, especially for acidic drugs that are highly protein-bound [3]. The 50% increase in the maternal glomerular filtration rate that occurs during pregnancy results in the increased elimination of renally excreted drugs. Drug levels of phenytoin (Dilantin) and carbamazepine (Tegretol) decrease in pregnancy, presumably because of increased P450 activity [4]. Progesterone induces certain cytochrome P450 enzymes and other mixed function oxidase enzymes. These hormone activities can have confounding effects on drug metabolism and make drug levels difficult to predict. Placental and fetal factors influence the effect of maternal medications on the developing fetus. Although most chemicals enter the fetal circulation by simple diffusion, some cross the placenta by facilitated or active transport processes [5]. The placenta contains enzymes capable of drug oxidation, reduction, hydrolysis, and conjugation.

Placental cytochrome P450 enzymes may play a role in fetal protection in the bio-oxidation of xenobiotics; including drugs [6]. Fetal tissues are also capable of metabolizing drugs. Although this contributes little to drug clearance, which is largely effected by maternal systems, it may contribute to fetal toxicity through the accumulation of toxic drug metabolites.

This mechanism may be particularly important for polar drugs, which do not readily cross the placenta back to the maternal circulation. Fetal albumin concentrations are below maternal levels early in pregnancy and then rise progressively. Early in pregnancy, fetal unbound drug concentrations may be high, even when maternal drug concentrations are low, resulting in toxicity to the fetus. This potential toxicity during the first trimester, the period of major organogenesis, underlies the recommendations for the conservative use of medications during early pregnancy.

Drugs and the Stages of Pregnancy: Some drugs can be harmful when used at any time during pregnancy; others, however, are particularly damaging at specific stages.

The stage of Organ Formation: Most of the body organs and systems of the baby-to-be are formed within the first ten weeks or so of pregnancy (calculated from the date of the last menstrual period). During this stage, some drugs and alcohol in particular can cause malformations of such parts of the developing fetus as the heart, the limbs, and the facial features.

The Stage of Prenatal Growth: After about the tenth week, the fetus should grow rapidly in weight and size. At this stage, certain drugs may damage organs that are still developing, such as the eyes, as well as the

nervous system. Continuing drug use also increases the risk of miscarriage and premature delivery. But the greatest danger drugs pose at this stage is their potential to interfere with normal growth. Intrauterine growth retardation (IUGR) is likely to result in a low-birth weight baby- a baby born too early, too small, or both.

The Stage of Birth: Some drugs can be especially harmful at the end of pregnancy. They may make delivery more difficult or dangerous, or they may create health problems for the newborn baby.

TERATOGEN: Teratogen is a substance, organism, physical agent, or deficiency state present during gestation that is capable of inducing abnormal postnatal structure or function (biochemical, physiologic or behavioral) by interfering with normal embryonic or fetal development if fetal exposure to these agents occurs during pregnancy. A child born with any kind of malformation or with any birth defect may create societal problems and therefore this subject needs concern [7].

FDA Rating System for the Teratogenic Effects of Drugs: FDA provides the most widely used system to grade the teratogenic effects of medications. The FDA assigns a safety category for medications by using a 5-letter system: A, B, C, D, and X. This safety category must be displayed on the labels of all drugs intended to be used during pregnancy [8]. The category & the labeling of drugs are summarized in **table 1**.

TABLE 1: SUMMARY AND LABELING ON DRUGS TO BE INTENDED DURING PREGNANCY

Category of drugs	Summary and labeling on drugs to be intended during pregnancy
A	Fetal risk not revealed in controlled studies in humans. Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Fetal risk not confirmed in studies in humans but has been shown in some studies in animals. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus. Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
D	Fetal risk shown in humans; use only if benefits outweigh risk to fetus. Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Contraindicated; benefit does not outweigh risk

Principles of Teratogenesis:

A. Susceptibility to a teratogenic agent is dependent upon the genotype of the embryo and the manner in which the agent interacts with environmental factors.

B. Susceptibility to teratogenic agents is dependent on the timing of the exposure and the developmental stage of the embryo.

C. Teratogenic agents act in specific ways on cells or tissues to cause pathogenesis.

D. The final manifestations of abnormal development are death, malformation, growth restriction and functional disorders.

E. Access to the embryo by environmental Teratogens depends on the nature of the agent.

F. As the dosage increases, manifestation of deviant development increases.

Drug Exposure in the Male Partner: Research is increasingly addressing the role of paternal exposure to medications before conception or during his partner's pregnancy. Certain exposures may alter the size, shape, performance, and production of sperm. This observation suggests that drug exposure in the male may put the fetus at risk. Animal studies have shown that paternal teratogenic exposure may lead to pregnancy loss or failure of the embryo to develop. However, unlike teratogenic agents affecting pregnant woman, teratogenic agents affecting the father do not seem to directly interfere with normal fetal development. Animal studies showing that paternal teratogenic exposure may lead to pregnancy loss or embryonic failure [9 10].

TABLE 2: LIST OF TERATOGENIC AGENTS AS PER FDA

S. NO	Name of the drug	Uses of the drug	Pregnancy category by FDA	Trimester of risk	Defects & Complications associated with the use of Drug
1	Acamprosate Calcium [11]	To Treat Alcohol Dependence	C	Unknown	Possible hydronephrosis, malformed iris, retinal dysplasia
2	ACE Inhibitors (Enalapril)	To treat heart failure, hypertension	C or D	First trimester (category C); second and third trimesters (category D)	IUGR premature labor, and fetal and neonatal renal failure, patent ductus arteriosus, respiratory distress syndrome
3	Acetohydroxamic acid	To treat chronic urinary infections	X	First, second, and third	Cardiac anomalies included atrial septal defects, ventricular septal defects. Skeletal anomalies
4	Acitretin [12]	Used to treat severe psoriasis	X	first	Severe limb defects, craniofacial anomalies
5	Aminocaproic Acid [13]	To treat excessive postoperative bleeding	C	First, second, and third	Possible fetal haemorrhage
6	Aminoglycoside [14] (streptomycin, gentamycin)	Used as antibiotics	D	Not consistent	Some neonates have had hearing defects, inner ear defect, and vestibular problems.
7	Amitriptyline [15]	Used in migraine, ankylosing spondylitis. As anti-depressant	C	First	Hydrocephaly, Abnormally small head ,heart defect, Jaw anomaly, foot deformities, extra digits, ambiquous genitalia, hypospadias, oral cleft, absent eyes
8	Anti-hypertensives (Candesartan)	Used in hypertension, diabetic neuropathy, congestive heart failure	D	First, second, and third	Hypotension, renal dysplasia, anuria or oliguria, IUGR, patent ductus arteriosus, incomplete ossification of the skull
9	Anti-convulsant (Lamotrigine)	To treat epilepsy as anticonvulsant, bipolar disorder	C	First, second, and third	Neural tube defects, hydrocephaly, pulmonary stenosis, wide set eyes, small jaw, extra digits , club foot, long thin fingers absent, ear canal opening
10	Atorvastatin [16]	Used to treat high cholesterol and high triglycerides	X	First, second, and third	spina bifida
11	Apomorphine [17]	Used to treat Parkinson's disease, erectile dysfunction, Alzheimer's disease	C	Unknown	Limb defects in chicken, birth defects in chicken
12	Aspirin [18]	NSAIDs	D	First, second, and third	Unclear; may be associated with an increased risk of gastroschisis
13	Atenolol [19]	Used to treat angina, high blood pressure, heart failure, migraine	D	First, second, and third	IUGR
14	Azacitidine [20]	Antineoplastic	D	First, second, and third	CNS anomalies, limb anomalies (e.g., micromelia, club foot, syndactyly, oligodactyly), and others (e.g., micrognathia, gastroschisis, oedema, rib abnormalities)
15	Azathioprine[21]	Immunosuppressant	D	First	Flattened back of skull, pulmonary stenosis, club foot, extra digits, Failure of bile ducts to develop, hypospadias,
16	temazepam, triazolam, flurazepam	Used to treat alcohol dependence, GAD, insomnia, seizures	X	The first, second, and third	Unclear; potential for isolated oral cleft
17	Bevacizumab [22]	Chemotherapeutic agent	C	Unknown	Decrease in maternal and fetal body weights, increased number of fetal resorptions
18	Birth control pills [23]	Oral contraceptives/ hormone replacement therapy	X	First, second, and third	Variable; inflammatory complications common

19	Bleomycin [24]	Used in treatment of cervical cancer, neck cancer ,skin cancer, testicular cancer, Hodgkin's disease	D	Second and third	Leucopoenia, neutropenia
20	Bromides [25]	Used to treat scrofula (as bromide of potassium), bromide ion is used as antiepileptic	D	First, second, and third	Polydactyl, GI anomalies, clubfoot, and congenital dislocation of the hip, IUGR
21	Busulfan [26]	Used to treat symptoms of leukaemia	D	First, second, and third	Mild anaemia, neutropenia, sterility in both male and female offspring.
22	Carbamazepine [27]	Used to treat epilepsy, neuralgia, bipolar disorder	D	First, second, and third	underdevelopment of the fingers, toes, and nails; developmental delay
23	Captopril [28]	Used to treat hypertension, congestive heart failure.	D	First	Decreased fetal limb contractures, hypoplastic lung development, IUGR, and patent ductus arteriosus
24	Cetuximab [29]	Used to treat cancer	C	Unknown	Unknown
25	Colchicine [30]	Anti-gout	C or D	unknown	Down syndrome
26	Cidofovir [31]	Treatment for CMV retinitis in AIDS patients, as broad-spectrum anti-viral, nucleoside analogue	C	Unknown	Possible external, soft tissue and skeletal anomalies (i.e., meningocele, short snout, short maxillary bones) of the foetus.
27	Cinacalcet [32]	Used to treat hyperparathyroidism	C	Unknown	Possible reduced postnatal maternal weight gain.
28	Clomiphene [33]	Used to treat infertility in women	X	First	Retinal aplasia ,Syndactyly, Clubfoot, Microcephaly, Cleft lip/palate, Down's syndrome
29	Clonazepam [34]	Used to treat anxiety , seizures	D	First	Neonatal withdrawal syndrome
30	Clorazepate [35]	Used to treat anxiety , seizures	D	First	Neonatal withdrawal syndrome
31	Cocaine [36]	Drug of abuse	X	First, second, third	Death, growth retardation, Premature labor and abruption placentae
32	Colchicine [37]	Used in arthritis and Mediterranean fever	C or D	Unknown	Down's syndrome, syndactly, cleft palate
33	Corticosteroids [38] (hydrocortisone, clobetasol propionate)	For inflammatory and autoimmune diseases	C	First	Reduced birth weight, preeclampsia, oral and lip clefts
34	Cyclophosphami-de [39]	Used to treat breast cancer, leukemia, ovarian cancer	D	First	Flattened nasal bridge, palate defect, Haemangioma, umbilical hernia, growth retarded
35	Cytarabine [40]	Used in treatment of leukemia	D	First and second	Bilateral microtia and atresia of external auditory canals, right hand lobster claw with three digits, bilateral lower limb defects
36	Danazol [41]	For endometriosis, angioedema	X	First, second, and third	virilisation of the external genital organs, Masculinisation of female foetus
37	Diazepam	Used in treatment of agitation, tremors, seizures, anxiety.	D	First	Neonatal withdrawal syndrome, neonatal apnea and hypotonia
38	Diethylstibestero-l [42]	Was used as a treatment for gonorrhoeal vaginitis, atrophic vaginitis and other symptoms of menopause, and to suppress postpartum lactation and prevent associated breast engorgement after childbirth	X	First, second and third	Structural uterine, cervical, or vaginal abnormalities in female offspring. Epididymal cysts, undescended testes, and small testes in male offspring. Still birth
39	Duloxetine [43]	For depression, GAD, diabetic neuropathy	C	First, second, and third	Variable
40	Ergotamine [44]	To treat migraine	X	First, second, and third	Low birth weight and preterm birth
41	Estradiol [45]	Used treatment of symptoms associated with menopause, prevention of bone fracture associated with osteoporosis, dysfunctional uterine bleeding	X	First, second, and third	Structural uterine, cervical abnormalities, Growth retardation
42	Ethanol [46]	Recreational Drug	D	First, second	growth retardation, Foetal alcohol

					syndrome
43	Etretinate [47]	Used to treat severe cases of psoriasis	X	First	cerebral abnormalities, including meningomyeloceles
44	Exenatide [48]	Used in treatment of renal failure, type 2 diabetes	C	Unknown	Possible skeletal effects
45	Finasteride [49]	Used in Male Pattern Baldness Treatment, Enlarged Prostate Treatment	X	First, second, and third	Abnormalities of the sex organs
46	Fluconazole [50]	Antifungal	C	Unknown	Craniofacial, skeletal, and cardiac effects
47	Fluoxetine [51]	To treat depression, bulimia, panic attacks, premenstrual disorder	D	First, second, and third	Variable; possible self-limited neonatal behavioural syndrome
48	Fluorouracil [52]	Used to treat precancerous and cancerous skin growth	D	First	radial aplasia; absent thumbs and three fingers; hypoplasia of lungs, aorta, thymus, and bile duct
49	Flurazepam [53]	Used as hypnotic to treat insomnia	X	First	Polydactyl, oral clefts, cardiovascular defects
50	Flutamide	Used to treat prostatic carcinoma	D	Third	Male pseudohermaphroditism
51	Folic acid antagonists [54] (Methotrexate, Aminopterin)	To treat megaloblastic anaemia	D in general	First, during normal closure of the fetal neural tube	Variable; neural tube defects
52	Hydroxyurea [55]	Used to treat melanoma, polycythemia, thrombocythemia	D	First	IUGR , hip dysplasia, unilateral renal dilatation and pilonidal sinus
53	Ibandronate [56]	To treat osteoporosis	C	Unknown	Unknown
54	Imipramine [57]	Used to treat symptoms of depression, childhood enuresis	D	First and third	Bilateral Amelia, dyspnoea, lethargy
55	Isotretinoin [58]	Used in treatment of severe , cystic acne	X	First	ear abnormalities (micropinna, small or absent external auditory canals); eye abnormalities (microphthalmia); facial dysmorphia; cleft palate, CNS abnormalities (hydrocephalus,
56	Kanamycin [59]	Used to treat bacterial infection, antibiotic	X	First	foetal eighth cranial nerve toxicity and hearing loss
57	Lithium carbonate [60]	Used in treatment of manic episodes of bipolar disorder	D	First	Cardiovascular defects (rudimentary left ventricle without inlet or outlet, aorta and pulmonary artery arising from right ventricle, patent ductus arteriosus, Mitral atresia) Ebstein's anomaly, spina bifida
58	Leflunomide [61]	To treat rheumatoid sarthritis	X	First	Microcephaly and mental retardation
59	Lenalidomide [62]	To treat myelodysplastic syndromes (MDS) and other cancers	X	First, second, and third	Possible reduction in fetal body weight and increase in post implantation losses and fetal variations
60	Leukotriene receptor antagonists [63] (prednisone, theophylline)	To treat asthma	C	Unknown	Unknown
61	Leuprolide [64]	Used to treat prostate cancer, uterus endometriosis	X	First	Spontaneous abortion, intrauterine growth retardation, low birth weight
62	Lithium [65]	To treat bipolar disorder	D	Unknown	Variable; possible cardiac effects
63	Medroxyprogest-erone	Used to treat abnormal bleeding from uterus, to restore normal menstrual period in females, to reduce risk cancer of uterus	D	First	ventricular septal defect and tricuspid Artesia
64	Mercaptopurine	Used to treat lymphocytic leukaemia, ulcerative colitis	D	First	Neural tube defects, oral clefts, heart defects, retarded foetal growth, small eyes
65	Methimazole[66]	To treat hyperthyroidism	D	First, possibly second, and third	scalp defects; possible choanal and oesophageal atresia
66	Methylene blue [67]	To treat malaria, cancer, resistant	C	Unknown	Intestinal Artesia's

		plaque psoriasis, cyanide poisoning, AIDS-related Kaposi's sarcoma			
67	Mifepristone [68]	To treat cancer, cushing syndrome, AIDS-related Kaposi's sarcoma	D	First	Unknown; possible sexual function
68	Minoxidil [69]	To treat hypertension, male pattern baldness	C	First, second, and third	Hypertrichosis of the back and extremities, dysmorphic facial features, uneven fat distribution, omphalocele
69	Misoprostol [70]	Reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs,) in induced gastric ulcers	X	First, second, and third	Mobius syndrome, Labor induction
70	Mycophenolate mofetil [71]	To treat autoimmune renal disease, and prevent organ transplant rejection	D	First	External ear and facial defects; cleft lip and palate; heart, oesophagus, kidney and distal limb defects
71	Mysoline [72]	To treat epilepsy	D	Unknown	Variable
72	Nalidixic acid	Used to treat urinary tract infections	C	First	Haemolysis in children with glucose-6-phosphate deficiency
73	Natalizumab [73]	To treat multiple sclerosis	C	Unknown	Unknown
74	Nelarabine	To treat T-cell acute lymphoblastic leukemia	D	First, second, and third	Variable; disrupting DNA synthesis in rapidly diving cells
75	Nicotine [74]	(for smoking) Depression, anxiety, schizophrenia	D	First	Death, growth retardation, musculoskeletal malformations
76	Norethisterone [75]	used to treat premenstrual syndrome, painful periods, abnormal heavy bleeding, irregular periods, menopausal syndrome	X	First	Masculinisation of female infant
77	Pegaptanib [76]	For recurrent and non-clearing vitreous haemorrhage in proliferative diabetic retinopathy	B	Unknown	Unknown
78	Pemetrexed [77]	Used as chemotherapy drug	C	Unknown	Unknown
79	Penicillamine [78]	To treat Wilson's disease, cystinuria, scleroderma, rheumatoid arthritis	D	Unknown	Variable; possible connective-tissue defects, cerebral palsy, hydrocephalus, skeletal defects, cleft palates, and fetal toxicity
80	Phencyclidine	Used as veterinary anaesthetic	X	Third	Triangular-shaped face with pointed chin, antimon- goloid slanted eyes, nystagmus
81	Phenobarbital [79]	To treat epilepsy hypnotics	D	Third	cleft palate or lip and congenital heart disease, can cause fetal addiction and newborn withdrawal symptoms
82	Phensuximide [80]	Used to treat epilepsy and other seizure disorders	D	Third	Ambiguous genitalia, inguinal hernia, pyloric stenosis
83	Phenytoin [81]	To treat epilepsy	D	Unknown	Finger like thumbs, clubfoot, abnormal palmar creases and nail hypoplasia or aplasia. hirsutism, microcephaly,mild micrognathia,foetal hydantoin syndrome
84	Potassium iodide [82]	To treat thyroid cancer, used as an expectorant	D	Unknown	Hypoplasia, goitre
85	Povidone-iodine [83]	Used to treat wounds, infections, as antiseptic, in mouthwashes, gargles	D	First	Enlarged heart, goitre, foetal growth retardation
86	Progesterones [84]	To treat menstrual problems, lowers the risk of estrogens-related cancer of the uterus	D or X	First, second, and third	Possible cardiovascular defects, hypospadias
87	Propylthiouracil [85]	Used to treat hyperthyroidism	D	Second and third	Hypothyroidism, neonatal goitre
88	Quinine [86]	Used to treat malaria, fever, also acts as analgesic	X	First	Hydrocephaly, dysmelia, auditory defects, optic nerve damage
89	Ramelteon	To treat insomnia	C	Unknown	Unknown

90	Retinoids [87] (arotinoids RO 13-7410, RO 13-6298, RO 15-1570)	To treat acne, psoriasis, skin cancers, inflammatory skin disorders, photo aging	X	The first, second, and third trimesters are times of risk. The critical window of exposure is at 3-5 weeks of pregnancy.	hydrocephalus; microcephalusf, cleft palate,thymic aplasia; psychological impairments; absent or defective ears; small jaw
91	Ribavirin [88]	Used for treatment of hepatitis C, cirrhosis	X	First	Stillbirth, abortion
92	Rifaximin [89]	To treat traveller's diarrhoea, also as antibiotic	C	Unknown	cleft palate, agnathia, jaw-shortening, haemorrhage, eyes partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae
93	Simvastatin [90]	It is used to control hypercholesterolemia (elevated cholesterol levels) and to prevent cardiovascular disease	X	First	Extra digits, clubfoot, duodenal atresia ,Pyeloureteral junction constriction, cleft lip, retarded fetal growth, fetal death
94	Sodium iodide (I-131, I-125) [90]	Used to treat and cure iodine deficiency, goitre	X	First	hydrocephaly, cardiopathy, genital hypotrophy, limb deformity, congenital hypothyroidism
95	Solifenacin succinate [91]	To treat the symptoms of an overactive bladder, such as frequent urination, leaking accidents, and urinary urgency	C	Unknown	Unknown
96	Sorafenib [92]	Used to treat hepatocellular carcinoma, renal cell carcinoma	D	First, second, and third	Variable
97	Streptomycin [93]	Used in treatment of tuberculosis, plague, respiratory, endocardial, and meningeal infection	D	First, Second and third	Ototoxicity, deafness
98	Sulfasalazine [94]	To treat inflammatory bowel disease	B	First	Microcephaly, ventricular septal defect and coarctation of the aorta, cleft palate
99	Tamoxifen [95]	Used to treat breast cancer, infertility, gynecomastia, bipolar disorder.	D	First	craniofacial anomalies include facial asymmetry, microtia, micrognatha and U-shaped cleft of the secondary palate
100	Telithromycin [96]	To treat wide variety of bacterial infections.	C	Unknown	Variable; potential liver failure and liver damage in the mother
101	Temazepam	used as hypnotic, used in in insomnia therapy	X	First	Neonatal withdrawal syndrome
102	Tetracyclines [97] (Achromycin, doxycyclin)	To treat bacterial infections	D	Second and third	Dental staining
103	Thalidomide [98]	Was used as tranquilizer and painkiller, for morning sickness.	X	First, second, and third	Malformed intestines, hearing defects, absent ears, and/or ocular and renal anomalies, phocomelia
104	Thioguanine [99]	Used in treatment of non lymphocytic leukemia	D	First and second	Generalized oedema, cranial defects, general skeletal hypoplasia, hydrocephalus, ventral hernia
105	Tinidazole [100]	To treat giardiasis, trichomoniasis	C	First, second, and third	Variable
106	Tiotropium bromide [101]	To treat chronic obstructive pulmonary disease (COPD)	C	Unknown	Unknown
107	Tobramycin	used to treat eye infection, intra abdominal infections, meningitis	C	First and second	Hearing problem to off spring, neural tube defect, cleft lip, cleft palate

108	Toluene	Solvent Sniffing	D		Growth retardation
109	Triazolam	Used in treatment of insomnia	X	First	Neonatal withdrawal syndrome, oral clefts, extra digits, heart defects, hydrocephaly, retarded fetal growth.
110	Trimethadione [102]	To treat seizure disorders	D	First, second, and third	Malformed ears, cleft palate, cardiac defects, urogenital malformations, and skeletal abnormalities; delayed mental and physical development also observe
111	Trospium chloride [103]	To treat Overactive Bladder	C	Unknown	Unknown
112	Valproic acid [104]	To treat epilepsy, bipolar disorder	D	First, second, and third	Spina bifida with meningomyelocele or meningocele, often accompanied by midfacial hypoplasia, deficient orbital ridge
113	Vinblastine [105]	Used in treatment of Lymphocytic lymphoma, Advanced carcinoma of the testis	D	First	Olygodactyly, respiratory distress syndrome
114	Vincristine [106]	Used in treatment of Acute Lymphoid Leukemia, Diffuse Large B-Cell Lymphoma.	D	First, second, third	Fetal death. Increased incidence of skeletal and eye defects, spina bifida, exencephaly, syndactyly
115	Warfarin [107]	To treat the risk of pulmonary embolism	X	First, second, and third	Deformities of the axial and appendicular skeleton; also, a hypoplastic nose, eye abnormalities, mental retardation, brachydactyly, and scoliosis.

Drugs Withdrawn From Market Because Of Their Teratogenic Effects:

Diethylstilbestrol (DES): It is a synthetic nonsteroidal estrogen that was first synthesized in 1938. Human exposure to DES occurred through diverse sources, such as dietary ingestion from supplemented cattle feed and medical treatment for certain conditions, including breast and prostate cancers. From about 1940 to 1970, DES was given to pregnant women under the mistaken belief it would reduce the risk of pregnancy complications and losses. In 1971, DES was shown to cause a rare vaginal tumor in girls and young women who had been exposed to this drug in uterus [108]. The US FDA subsequently withdrew DES from use in pregnant women.

Thalidomide: Thalidomide is an immunomodulatory agent used for the acute treatment of erythema, nodosum leprosum, a cutaneous manifestation of Hansen's disease (leprosy). Thalidomide was introduced into clinical medicine in West Germany in 1956.

Although a wide range of indications was promoted for the drug; it was used as hypnotic and sedative. Thalidomide was one of the first drugs that was clearly shown to be a human teratogen and probably has caused more known severe malformations in humans than any other drug [109].

Several reviews have described the various human systems affected by thalidomide-induced embryopathy. One of these reviews presented the pregnancy history of two children (twins), born in the United States, who had very different severity of thalidomide embryopathy The first twin, a 2211-g female, was born with duodenal atresia, a rectoperineal fistula, and hypoplastic, dislocated thumbs (right thumb worse than left). The other twin, a 2240-g male, had phocomelia of both upper extremities and a midline hemangioma on the forehead. Missing or hypoplastic digits were noted on both hands.

Because of the concern over birth defects, thalidomide was withdrawn from the market in most countries in late 1961.

Teratogenic Counseling: In counseling the pregnant patient exposed to a potential human teratogen, it is important to emphasize the significance of exposure to the patient [109]. Ascertaining the clinical facts regarding the nature of the exposure: the length, dosage, and

timing of exposure during pregnancy, as well as other exposures of concern about which the patient may not ask (e.g., alcohol, cigarette smoking). All available current data regarding the agent are then collected, and conclusions regarding the risks of exposures are drawn.

Counseling should include the background human baseline risk for major malformations, whether the fetus is at increased risk, which anomaly has been associated with the agent in question, a risk assessment, methods of prenatal detection, when available, limitations in our knowledge, and limitations of prenatal diagnostic capabilities. Additional aspects include the potential risk of the medical condition for which a drug is prescribed, known interactions (in both directions) between the disease state and the pregnancy and preventive measures, when applicable (e.g., folic acid supplementation in the case of carbamazepine exposure).

Because more than 50% of pregnancies in North America are unplanned, teratogenic risk assessment should be started prior to pregnancy.

CONCLUSION: There are no absolute teratogens; however, many agents can exhibit teratogenic effects under certain circumstances. The dose and the time of exposure to a particular agent often determine the severity of the damage and the type of defect that occurs. The dose response is obvious: the greater the dose, the greater the effect. The time of exposure is another important concept, as certain stages of embryonic and fetal development are more vulnerable than others.

In general, the embryonic stage (first trimester) is more vulnerable than the fetal period (second and third trimesters). Thalidomide provides a classic example. The critical period of exposure is during organogenesis (the formation of the organs) from the 35th-48th day after the last menstrual period. The specificity of the malformations is linked to the time of exposure: 35-37 days, no ears; 39-41 days, no arms; 41-43 days, no uterus; 45-47 days, no tibia; and 47-49 days, triphalangeal thumbs. The types or severity of abnormalities caused by a teratogenic agent is also dependent on the genotype of the pregnant woman and the genotype of the fetus (genetic susceptibility).

For example, variation in maternal metabolism of a particular drug will determine what metabolites the fetus is exposed to and the duration of exposure. Differences in placental membranes, placental transport and biotransformation all affect fetal exposure. The genetic susceptibility of the fetus to a particular teratogenic agent will also have an effect on the final outcome.

It is therefore advised to go for the genetic counseling before conceiving the baby**.**

1. The use of teratogenic drugs should be avoided during pregnancy in less severe (non life-threatening) diseases such as acne and psoriasis.

2. It is necessary to select non-teratogenic drugs instead of teratogenic drugs during pregnancy if possible and not harmful for pregnant women. The best example for this strategy is to replace coumarin derivative with heparin in early pregnancy.

3. The necessary use of teratogenic drugs may have to be continued in severe maternal diseases such as epilepsy and cancer if the discontinuation of treatment causes worsening of the disease and pregnant women agree with it.

4. Teratogenic drugs cannot cause CAs if the exposure is in the first month of gestation and in general after the third month of pregnancy. However, the fetotoxic effect of some drugs should be considered in the second part of pregnancy.

5. Recent effective ultrasound scanning can detect major fetal defects about the 18th-20th week of gestation with a high degree of efficacy. Thus we have a chance to evaluate the risk after the inadvertent or necessary use of teratogenic drugs during pregnancy. If serious fetal defects are detected, the couple can then be given information to help them decide whether to terminate their pregnancy or not.

REFERENCES:

1. Ambudkar SV, Dey S, Ramachandra M, Pastan I, Gottesman M M: Biochemical, cellular, and pharmacological aspects of the multidrug transporter. Annual Review of Pharmacology and Toxicology 1999; 39: 361–398.

2. Jeffries WS, Bochner F: The effect of pregnancy on drug pharmacokinetics. The Medical Journal of Australia 1988; 149: 675.
3. Mucklow JC: The fate of drugs in pregnancy. Clinical Obstetrics and Gynecology 1986; 13:161.
4. Harris RZ, Benet LZ, and Schwartz JB: Gender effects in pharmacokinetics and pharmacodynamics. Drugs 1995; 50: 222.
5. Chow AW, Jewesson PJ: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Review of Infectious Diseases 1985; 7: 287.
6. Schuetz JD, Kauma S, Guzelian PS: Identification of the fetal liver cytochrome CYP3A7 in human endometrium and placenta, Journal of Clinical Investigations 1993; 92: 1018.
7. Blackburn ST: Pharmacology and Pharmacokinetics during the Perinatal Period. Maternal, Fetal & Neonatal Physiology- A clinical Perspective 2007; 3: 199.
8. Boothby LA, Doering PL: FDA labeling system for drugs in pregnancy, The Annals of Pharmacotherapy 35: 1485-1489.
9. Austin SM, Robaire B, Hales BF, and Kelly SM: Paternal cyclophosphamide exposure causes decreased cell proliferation in cleavage-stage embryos. Biology of Reproduction 1994; 50(1): 55-64.
10. Chatenoud L, Parazzini F, Zanconato G, Benzi G, Bortolus R: Paternal and maternal smoking habits before conception and during the first trimester: relation to spontaneous abortion. Annals of Epidemiology 1998; 8(8): 520-526.
11. Ochoa R, Hunter K: Acamprosate (Campral) for Treatment of Alcoholism. American Family Physician 2006; 74(4): 645-646.
12. Williams KJ, Willhite C: Teratogenic Dose-Response Relationships of Etretinate in the Golden Hamster. Toxicological Sciences 1984; 4(6): 977-982.
13. Gorman PJ: Hereditary angioedema and pregnancy. Canadian Family Physician 2008; 54(3): 365 – 366.
14. Mulheran M, Knox AJ, Smyth AR: Aminoglycoside Prescribing and Surveillance in Cystic Fibrosis. American Journal of Respiratory and Critical Care Medicine 2003; 167: 819-823.
15. Guze BH, Guze PA: Psychotropic medication use during pregnancy. Western Journal of Medicine 1989; 151(3): 296–298.
16. Gibb H, Scialli AR: Statin drugs and congenital anomalies. American Journal of Medical Genetics Part A 2005; 135: 230–231.
17. Ance P, Scheinre H: The teratogenic capacity of certain chemical substances and in particular that of apomorphine. Archives d' anatomie d'histologie et d'embryologie 1951; 34(1-8): 19-21.
18. Leonhardt A, Bernert S, Watzer B, Ziegler GS, Hannsjorg W: Low Dose Aspirin in Pregnancy: Maternal and Neonatal Aspirin Concentrations and Neonatal Prostanoid Formation. Pediartics 2003; 111(1): 77-81.
19. Butters L, Kennedy S, and Rubin PC: Atenolol in essential hypertension during pregnancy. British Medical Journal 1990; 301: 587–589.
20. Rosen MB, House HS, Franci BM, Chernoff N: Teratogenicity of 5-azacytidine in the Sprague-Dawley rat. Journal of Toxicology and Environmental Health 1990; 29(2): 201 – 210.
21. Gillibrand PN: Systemic lupus erythematosus in pregnancy treated with azathioprine. Proceedings of the Royal Society of Medicine 1966; 59(9): 834.
22. Miklovich L: An evaluation of the teratogenicity of certain antinauseant drugs. American Journal of Obstetrics And Gynecology 1976; 125: 244–248.
23. Wild J, Schorah CJ, Smithells RW: Vitamin A, pregnancy, and oral contraceptives. British Medical Journal 1974; 1(5897): 57–59.
24. Ocampo AN, Kim TJ, Shim JK, and Park CT: Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases. Reproductive Toxicology 2005; 19(4): 557-561.
25. Dumoulin JG: Tetraethylammonium Bromide in Toxaemia of Pregnancy. Obstetrical & Gynecological Survey 1952; 5(1): 56.
26. Sherman JL, Robert VL: Use of Busulfan in Myelogenous Leukemia during Pregnancy. The New England Journal of Medicine 1958; 259: 288-289.
27. Jones KL, Lacro RV, Johnson KA, and Adams J: Pattern of Malformation in the children of women treated with carbamazepine during pregnancy. The New England Journal of Medicine 1989; 320: 1661-1666.
28. Moura RD, Lopes MA: Effects of captopril on the human foetal placental circulation: an interaction with bradykinin and angiotensin I. British Journal of Clinical Pharmacology 1995; 39(5): 497–501.
29. Langford S, Fradgley S, Evans M, Blamks C: Assessing the Risk of Handling Monoclonal Antibodies. Hospital Pharmacist 2008; 15: 60-64.
30. Michael O, Goldman RD, Koren G: Safety of colchicine therapy during pregnancy. Canadian Family Physician 2003; 49: 967–969.
31. Ferdinand I, Frederik GD: Side-effects of cidofovir in the treatment of recurrent respiratory papillomatosis. European Archives of Oto- rhino -laryngoly 2008; 265(8): 871–879.
32. Sugie O, Kimata N, Miwa N, Nitta K: Successful cinacalcet treatment of refractory secondary hyperparathyroidism due to multiple lung parathyroid adenomas. Oxford Journals, Medicine, NDT Plus 1997; 3(1): 60-63.
33. Mishell DR: Clomiphene (Clomid®): Is it Teratogenic? Western Journal of Medicine 1975; 123(5): 385.
34. Sullivan FM, McElhatton PR: A comparison of the teratogenic activity of the antiepileptic drugs carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and primidone in mice. Toxicology and Applied Pharmacology 1977; 40(2): 365-378.
35. Handler A, Kistin N, Davis F, Ferré C: Cocaine Use during Pregnancy: Perinatal Outcomes. American Journal of Epidemiology 133(8): 818-825.
36. Ghozlan R, Pras M, Bettoun A: Periodic arthralgia: teratogenicity of colchicine and its influence on pregnancy and sterility. Ann Med Interne (Paris) 1981; 132(7): 493-495.
37. Oren D, Nulman L, Makhija M, Ito S, Koren G: Using corticosteroids during pregnancy. Are topical, inhaled, or systemic agents associated with risk? Canadian Family Physician 2004; 50:1083–1085.
38. Durodola JI: Administration of Cyclophosphamide during Late Pregnancy and Early Lactation: A Case Report. The Journal National Medical Association 1979; 71(2):165–166.
39. Newcomb M, Balducci L, Thigpen TJ, Morrison FS: Acute Leukemia in Pregnancy: Successful Delivery after Cytarabine and Doxorubicin. The Journal of American Medical Association 1978; 239(25): 2691-2692.
40. Varghese L, Viswabandya A, Mathew AJ: Dapsone, danazol, and intrapartum splenectomy in refractory ITP complicating pregnancy. Indian Journal of Medical Sciences 2008; 62: 452-455.

41. Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, and McLachlan JA: Proliferative lesions and reproductive tract tumors in male descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 2000; 21(7): 1355-1363.
42. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR: Prevalence of depression during pregnancy: systematic review. Obstetrics and Gynecology 2004; 103(4): 698-709.
43. Czeizel A: Teratogenicity of ergotamine. Journal of Medical Genetics 1989; 26(1): 69–70.
44. Sawaki M, Noda S, Muroi T, Takakura S, Sakamoto S, Yamasaki K: In Utero through Lactational Exposure to Ethinyl Estradiol Induces Cleft Phallus and Delayed Ovarian Dysfunction in the Offspring. Toxicological Sciences 2003; 75 (2): 402-411.
45. Marbury MC, Linn S, Monson R, Schoenbaum S, Stubblefield PG, Ryan KJ: The association of alcohol consumption with outcome of pregnancy. American Journal of Public Health 73(10): 1165-1168.
46. Rosa FW: Teratogenicity of isotretinoin. Lancet 1983; 2(8348): 513.
47. Williams J, Pomeroy N, Lash R, Douyon L: Exenatide Use during Pregnancy. Endocrinologist 19(3):119-121.
48. Sallout B, Wadi K: Aphalangia possibly linked to unintended use of finasteride during early pregnancy. Annals Of Saudi Medicine 2009; 29(2): 155.
49. Nogaard M, Pedersen L, Gislum M: Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. Journal of Antimicrobial Chemotherapy 2008; 62(1): 172-176.
50. [50]Chambers C, Johnson K, Jones K: Birth Outcomes in Pregnant Women Taking Fluoxetine. The New England Journal of Medicine 1996; 335: 1010-1015.
51. Stadler HE, Knowles J: Fluorouracil in Pregnancy: Effect on the Neonate. The Journal of American Medical Association 1971; 217(2): 214-215.
52. Eros E, Czeizel AE, Rockenbauer M: A population-based case-control teratologic study of nitrazepam, medazepam, tofisopam, alprazolam and clonazepam treatment during pregnancy. European Journal of Obstetrics and Gynecology and Reproductive Biology 2002; 101:147–154.
53. Berry R, Bailey L: Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. American Journal of Clinical Nutrition 2005; 81(5): 1213S-1217S.
54. Italia KY, Jijina FF, Chandrakala S, Nadkarni AH, Sawant P, Ghosh K, Colah RB: Exposure to Hydroxyurea During Pregnancy in Sickle-β Thalassemia: A Report of 2 Cases. The Journal of Clinical Pharmacology 2010; 50: 231-234.
55. Bergner R, Dill K, Boerner D: Elimination of intravenously administeredibandronate in patients on haemodialysis: a monocentre open study. Nephrol Dial Transplant 2002; 17: 1281-1285.
56. Guze BH, Guze PA: Psychotropic medication use during pregnancy. Western Journal of Medicine 1989; 151(3): 296–298.
57. Chang SY, Soong YK: Unexpected pregnancies exposed to leuprolide acetate administered after the mid-luteal phase for ovarian stimulation. Human Reproduction 1995; 10(1): 204-206.
58. Uziel A, Romand R, Maro M: Electrophysiological study of the ototoxicity of kanamycin during development in guinea pigs. Hearing Research 1979; 1(3): 203-211.
59. Vacaflor L, Lehmann HE, Ban T: A.,Side Effects and Teratogenicity of Lithium Carbonate Treatment. Journal of Clinical Pharmacology 1970;10(6): 387-389.
60. Brent RL: Teratogen Update: Reproductive Risks of Leflunomide (Arava™); A PyrimidineSynthesis Inhibitor: Counseling WomenTaking Leflunomide Before or During Pregnancy and Men Taking Leflunomide WhoAre Contemplating Fathering a Child. Teratology 2001; 63:106–112.
61. Anderson KC: Lenalidomide and thalidomide: mechanisms of action—similarities and differences. Seminars in Hematology 2005; 42(4): S3–S8.
62. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD: Safety of leukotriene receptor antagonists in pregnancy The Journal of Allergy and Clinical Immunology 2007; 119(3): 618-625.
63. Chang SY, Soong YK: Unexpected pregnancies exposed to leuprolide acetate administered after the mid-luteal phase for ovarian stimulation. Human Reproduction 1995; 10(1), 204-206.
64. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D: Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. The Lancet 1992; 339(8792), 530-533.
65. Karlsson FA, Axelsson O, Melhus H: Severe Embryopathy and Exposure to Methimazole in Early Pregnancy. The Journal of Clinical Endocrinology & Metabolism, 87(2), 947-948.
66. Cowett RM, Hakanson DO, Kocon RW: Untoward neonatal effect of intraamniotic administration of methylene blue. Obstetrics and Gynecology 1976; 48, 74S5S.
67. Beischer NA, Sen TC, Wein P: Norethisterone and Gestational Diabetes, Australian and New Zealand Journal of Obstetrics and Gynaecology 1992; 32(3), 233–238.
68. Gilani SH, Fallon E, Kozam G: The effects of minoxidil on the development of the chick embryo. Life Sciences 1989. 45(22), 2157-2161.
69. Pottie, K: Is misoprostol teratogenic? Misoprostol use during early pregnancy and its association with Mobius' syndrome,Canadian Family Physician 1999. 45, 315–316.
70. Pergola, PE, Kancharla, A, Riley, DJ. Kidney Transplantation during the First Trimester of Prenancy: Immunosuppression with Mycophenolate Mofetil, Tacrolimus, and Prednisone. Transplantation 2001; 71(7), 994-997.
71. Sullivan, FM, McElhatton, PR. Teratogenic activity of the antiepileptic drugs phenobarbital, phenytoin, and primidone in mice. Toxicology and Applied Pharmacology 1975; 34(2), 271-282.
72. Wehner, NG, Shopp G, Rocca MS, Clarke J: Effects of natalizumab, a α4 integrin inhibitor, on the development of Hartley guinea pigs. Birth Defects Research Part B: Developmental and Reproductive Toxicology 2009; 86(2): 98–107.
73. Werler MM, Mitchell AA, Shapiro S: The Relation of Aspirin Use during the First Trimester of Pregnancy to Congenital Cardiac Defects, the New England Journal of Medicine 1989; 321: 1639-1642.
74. Beischer NA, Sen TC, Wein P: Norethisterone and Gestational Diabetes. Australian and New Zealand Journal of Obstetrics and Gynaecology 1992; 32(3): 233–238.
75. Giuliari GP, Banda RM, Guel DA: Intravitreal injection of pegaptanib sodium for proliferative diabetic retinopathy. British Journal of Ophthalmology 2009; 93: 1474-1478.
76. Bajetta L, Celio L, Buzzoni R, Ferrari L, Marchianò A, Becerra C: Phase II study of pemetrexed disodium (Alimta®) administered

with oral folic acid in patients with advanced gastric cancer. Annals of Oncology 14(10): 1543-1548.
77. Corcoran R, Castles WJ: Penicillamine therapy and teratogenesis. British Medicinal Journal 1977; 1(6064): 838.
78. Aksamija A, Habek D, Stanojevi M, Ujev B: Fetal Malformations Associated with the Use of Methylphenobarbital and Carbamazepine during Pregnancy. Fetal Diagnosis And Therapy 2009; 25: 79-82.
79. Rankin G, Wang R, Brown P: Urinary tract effects of phensuximide in the Sprague-Dawley and Fischer 344 rat. Journal of Applied Toxicology 6 (5): 349–356.
80. Monson RR, Rosenberg L, Hartz SC, Shapiro S, Heinonen OP, Slone D: Diphenylhydantoin and Selected Congenital Malformations. The New England Journal of Medicine 1973; 289: 1049-1052.
81. Escobar DM, Obregon MJ: Maternal thyroid hormones early in pregnancy and fetal brain development, Best Practice and Research. Clinical Endocrinology and Metabolism 2004; 18: 225-48.
82. Danziger Y, Pertzelan A, Mimouni M: Transient congenital hypothyroidism after topical iodine in pregnancy and lactation. Archives of Disease In Childhood 1987; 62:295-296.
83. Zarutskiea PW, Phillips JA: Re-analysis of vaginal progesterone as luteal phase support (LPS) in assisted reproduction (ART) cycles. Fertility and Sterility 2007; 88 (1): S113.
84. Karlsson FA, Axelsson O, Melhus H: Severe Embryopathy and Exposure to Methimazole in Early Pregnancy. The Journal of Clinical Endocrinology & Metabolism 87(2): 947-948.
85. Phillips RE, Looareesuwan S, White NJ, Silamut K, Kietinun S, Warrell DA: Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. British Journal of Clinical Pharmacoogy 1986; 21(6): 677–683.
86. Lammer EJ, Chen DT, Hoar R, Agnish ND, Benke PJ, Braun JT: Retinoic Acid Embryopathy. The New England Journal of Medicine 1985; 313: 837-841.
87. Roberts SS: Assessing Ribavirin Exposure During Pregnancy: The Ribavirin Pregnancy Registry. Gastroenterology Nursing 2008; 31(6): 413 – 417.
88. Bertoli D, Borelli G: Teratogenic action of Rifaximin in the rat and rabbit and its effect on perinatal development in the rat. Bollettino-Societa Italiana Biologia Sperimentale 1984; 60(5): 1079-1085.
89. Ulku C, Kesim M, Kalyoncu NI:Normal pregnancy outcome following inadvertent exposure to rosiglitazone, gliclazide, and atorvastatin in a diabetic and hypertensive woman. Reproductive Toxicology 2004; 18(4): 619-621.
90. Kanamoto Y, Che LJ, Taki K, Moatamed f, Schultz JJ, Brent GA, Kogai T: Systemic Retinoic Acid Treatment Induces Sodium/Iodide Symporter Expression and Radioiodide Uptake in Mouse Breast Cancer Models. Cancer Research 2004; 64:415.
91. Epstein BJ, Gums JG, Molina E: Newer agents for the management of overactive bladder. American Family Physician 2006; 74(12): 2061-2068.
92. Mousa AB: Sorafenib in the Treatment of Advanced Hepatocellular Carcinoma. The Saudi Journal Of Gastroenterology 2008; 14(1): 40–42.
93. Conway N: Streptomycin in Pregnancy: Effect on the Foetal Ear. British Medical Journal 1965; 2(5456): 260–263.
94. [94]Donaldson RM: Management of Medical Problems in Pregnancy — Inflammatory Bowel Disease. The New England Journal of Medicine 1985; 312: 1616-1619.
95. Gateley CA, Barthelmes L: Tamoxifen and pregnancy. The Breast 2004; 13 (6): 446-451.
96. Kim YS, Lee HJ, Chang M, Son SK, Rhee YE, and Shim SK: Scrub typhus during pregnancy and its treatment: A case study and review of the literature. American Journal Of Tropical Medicine And Hygiene 2006; 75: 955-95.
97. Lodi KB, Carvalho VAP, Rocha RF: Rational use of antimicrobials in dentistry during pregnancy. Medicina Oral, Patologia Oral Y Cirugia Bucal 2009; 14 (1): E9-E15.
98. Gordon GB, Spielberg SP, Blake DA, Balasubramanian V: Thalidomide teratogenesis: evidence for a toxic arene oxide metabolite. Proceedings of National Academy of Sciences, USA 1981; 78(4): 2545–2548.
99. Wilhelm AJ, Remmink AJ, Mulder CJJ, Bodegraven AV: 6-Thioguanine for Crohn's disease during pregnancy: Thiopurine metabolite measurements in both mother and child. Scandinavian Journal of Gastroenterology 2005; 40(1): 1374 – 1377.
100. Karhunen M: Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. British Journal of Clinical Pharmacology 1984; 18(2): 254–257.
101. Kapoor AS, Olsen SR, Puttagunta L, Vethanayagam D: The efficacy of tiotropium as a steroid-sparing agent in severe asthma. Canadian Respiratory Journal 2009; 16(3): 99–101.
102. Brown NA, Shull G, Fabro S: Assessment of the teratogenic potential of trimethadione in the CD-1 mouse. Toxicology and Applied Pharmacology 1979; 51(1): 59-71.
103. Burnakis T: Trospium Chloride Treatment of Overactive Bladder, The Annals of Pharmacotherapy 43(2): 283-295.
104. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK: Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. The New England Journal of Medicine 2010; 362: 2185-2193.
105. Ferm VH: Congenital Malformations in Hamster Embryos after Treatment with Vinblastine and Vincristine. Science 1963; 141(3579): 426.
106. Abadi S, Einarson A, Koren G: Use of warfarin during pregnancy. Canadian Family Physician 2002; 48: 695–697.
107. Gabriel RO, Rohmer A, Clavert J, Schneegans E: Teratogenic and lethal actions of diethylstilbestrol on the mouse embryo. Archives Francaises De Pediatrie 1972; 29(2): 149-154.
108. Larsen V: The teratogenic effects of thalidomide, imipramine HCI and imipramine-N-oxide HC1 on white Danish rabbits. Acta Pharmacologica *et* Toxicologica 1963; 20:186-203.
109. Schwarz EB, Santucci A, Borrero S, Akers A, Nikolajski C: Perspectives of primary care clinicians on teratogenic risk counseling. Birth Defects Research Part A : Clinical And Molecular. Teratology 2009; 85(10): 858–863.

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