SUMMARY

Treatment with drugs during pregnancy has been a reason for concern because many pregnant women take a prescribed or over-the-counter drug preparation daily .

1.THE HUMAN PLACENTA

The human placenta provides a link between the circulations of two distinct individuals but also acts as a barrier to protect the foetus from xenobiotics in the maternal blood**.**However , the impression that the placenta forms an impenetrable obstacle against most drugs is now widely regarded as false .The human placenta has a role in drug transfer and metabolism .The increasing experimental data on placental drug transfer has enabled clinicians to make better informed decisions about which drugs significantly cross the placenta and develop dosage regimens that minimise fetal exposure to potentially toxic concentrations. The foetus has now become the object of intended drug treatment.

A. DRUG TRANSFER ACROSS THE HUMAN PLACENTA

It has been shown that nearly all drugs that are administered during pregnancy will enter , to some degree , the circulation of the foetus.

METHODS OF DRUG TRANSFER ACROSS THE HUMAN PLACENTA:-

I . PASSIVE DIFFUTION

Passive diffusion is the predominant form of exchange in the placenta .

II . FACILITATED DIFFUUSION

Only a few drugs have been suggested to be transported across the placental barrier by ***facilitated diffusion .***

III . ACTIVE TRANSPORT

Many investigators have examined the placental transport systems of nutrients such as amino acids , vitamins and glucose , but little is known about the ***active transport*** of drugs across the placental barrier .

B . PLACENTAL METABOLISM OF DRUGS

It seems that for most drugs placental metabolism is relatively minor and is not a significant factor in limiting the extent of their passage across the placenta . In some cases , however , the enzymes activate xenobiotic compounds making them toxic to the foetus.

PHASES OF PLACENTAL DRUG METABOLISM

I . PHASE I REACTIONS

The placenta contains multiple ***CYP isoenzymes*** in the mitochondria and endoplasmic reticulum of trophoblastic cells . It appears that more ***CYP isoforms*** are expressed in the first trimester than at term.

II. PHASE II REACTION

(1) URIDINE DIPHOSPHATE GLUCURONOSYL TRANSFERASES (UGTs)

UGTs are extensively involved in phase II metabolism , where they conjugate glucuronic acid to xenobiotics . This conjugation is generally considered to be a detoxification reaction by making the drug more polar and , thus , more susceptible to excretion**.**

(2) GLUTATHION S-TRANSFERASES (GSTs)

GST activity in the placenta has been related to hormone metabolism rather than detoxification of xenobiotics .

(3) EPOXIDE HYDROLASE

Only one form of ***epoxide hydrolase*** has been found in the human placenta , being detectable from 8–9 weeks of gestation onwards .

(4) SULFOTRANSFERASES

Sulfotransferases are of great importance in the sulfate conjugation of steroids and catecholamines in human tissues, including the placenta , but little is known about their involvement in placental drug metabolism .

2. DRUG SAFETY DURING PREGNANCY

METHODS TO ESTABLISH DRUG SAFETY:-

I . HUMAN EPIDEMIOLOGIC STUDIES

It is evident that epidemiologic studies are very limited in their capacity to establish the safety of drugs in pregnancy . Nevertheless, epidemiologic studies that investigate the safety of drugs in pregnancy are increasingly performed . Most teratogens are not teratogenic throughout the entire organogenic period , let alone the entire first trimester and from animal studies it appears that all teratogens show a **"no-effect dose"**. So ***dose*** and ***precise timing of exposure*** as well as ***duration of exposure*** are important considerations **.**

II. ANIMAL STUDIES

The structural differences in placentas from different species affects their function . In particular, ***the transfer and metabolism of drugs*** varies enormously between species , making data from animal studies difficult to interpret with respect to predicting feto-maternal drug disposition in human pregnancy .The results of animal teratology studies of drugs submitted for registration can be divided into 3 main groups ***("NO EFFECT"GROUP, EMBRYOTOXICITY GROUP, STRUCTURAL BIRTH DEFECTS GROUP) .***

DRUG PRESCRIPTION DURING PREGNANCY

For a drug that is not a" known "human teratogen it is necessary to acknowledge that there is very little direct evidence that it is safe in pregnancy . ***No drug has been shown to be entirely safe in human pregnancy ; indeed , it would be impossible to establish complete safety .*** Clearly use of any of these

drugs in pregnancy carries some degree of risk for the embryo but the level of risk is undefined **.**If one takes a pessimistic viewpoint about the safety of drugs in pregnancy, it may be necessary to withhold medication from women of childbearing age unless they can prove that they are not pregnant or likely to become pregnant . It is unlikely that the majority of practitioners adopt such an extreme position.They might instead insist that although medications should be avoided during pregnancy there is no evidence that most drugs do cause birth defects and if they are needed for some specific condition , the ***risk-benefit*** should lie on the benefit side**.** But , if one takes an optimistic viewpoint,drugs that cause birth defects in humans are rare , comprising less than 1% of the therapeutic drugs currently available.

EXAMPLES OF SAFE DRUGS DURING PREGNANCY

• ***Doxylamine*** should be the first choice, preferably combined with ***pyridoxine*** ; otherwise, ***meclizine*** should be used that for ***(NVP)*** . ***Metoclopramide*** seems safe and efficacious for (NVP) and (GERD), it should probably be first choice among the dopamine antagonists.

•***Antacids*** and ***sucralfate*** are generally considered ***safe*** in all phases of pregnancy**.** But , the unrestricted / Long-term use during pregnancy should be avoided **.** ***H2RB*** may be prescribed when antacids or sucralfate have failed . ***Ranitidine*** is preferable to other H2RB **,**that for **(PU)** and **(GERD) .**

•***Omeprazole*** is a drug of choice for reflux esophagitis in pregnancy .

•***Butylscopolamine*** is the spasmolytic of choice in ***anticholinergics*** during pregnancy.

• After ***stool-bulking agents***, ***lactulose*** is the first-choice laxative in pregnancy . But a consensus meeting on the management of constipation in pregnancy considered ***PEG*** to meet the criteria for ***an ideal laxative in pregnancy*** [effective, not absorbed (non-teratogenic) , well tolerated and low risk**].** When constipation needs to be treated with medication and neither ***bulk*** nor ***osmotic***

laxatives like ***lactulose*** work effectively enough , ***bisacodyl*** is the drug of choice throughout the entire pregnancy**.**

•***Penicillins*** are the antibiotics of choice in pregnancy, ***Cephalosporins*** Can be used safely during pregnancy if needed , ***Erythromycin*** is still the drug of choice among the macrolides .

•***INH*** is the drug of choice for prophylaxis and treatment of tuberculosis in pregnancy, ***Rifampicin*** is a drug of choice for the treatment of tuberculosis during pregnancy, ***Ethambutol*** is a first-line drug for treatment of tuberculosis during pregnancy in combination with ***INH*** and ***rifampicin***.

•***Hepatitis A vaccine*** and ***Hepatitis B vaccine*** can be given to the pregnant woman at high risk of infection **.** It is recommended that women in the second and third trimesters should be routinely offered ***Influenza vaccination*** **.**Since ***rabies*** is an illness with fatal consequences, a pregnant woman must always be simultaneously immunized (actively and passively) following a bite from an animal suspected to be rabid**.*****Tetanus vaccination*** can be made up in the second or third trimester . The mother may also be immunized in the first trimester if this is indicated .

•***PARACETAMOL*** is the analgesic and antipyretic of choice in pregnancy , ***ASPIRIN*** is the analgesic and antipyretic of second choice in pregnancy .

•***Probenecid*** is the drug of choice to achieve elimination of uric acid during pregnancy , Allopurinol is relatively contraindicated during pregnancy, Colchicine is a drug of second choice in cases of gout attacks during pregnancy.But ,in case of ***FMF*** in pregnant women, long-term treatment with ***colchicine*** may be indicated to improve maternal and fetal outcome . After ***colchicine*** use in the first trimester , a detailed fetal ultrasound should be recommended **.**

•***Sulfasalazine*** is the ***DMARD*** of first choice during pregnancy.

•***INTERFERONS*** are acceptable if no other similarly effective and better-proven drugs are available.

•The ***short-acting β2-agonists*** are first-choice drugs in the treatment of pregnant women , ***Inhalation*** is preferred. ***INHALED IPRATROPIUM BROMIDE*** Can be considered in women presenting with acute asthma who do not improve with the first inhaled β-agonist treatment **. *Inhaled corticosteroids*** are the first drugs of choice for the treatment of asthma in pregnant women.The use of ***beclomethasone*** or ***budesonide*** is preferred.***Systemic*** use of the corticosteroids , ***prednisone,***and ***prednisolone***, is indicated in case of acute exacerbations of asthma during pregnancy . ***THEOPHYLLINE*** May be used for cases where the inhaled ***β2-agonists*** and ***corticosteroids*** are insufficient to control the asthma.

•***N-acetylcysteine, ambroxol and bromhexine*** are first choice mucolytics during pregnancy,if (oral) fluid therapy and other nonmedical treatment is not effective.

•For allergic rhinitis, ***intranasal corticoids*** may be used.

• ***α- METHYLDOPA*** is one of the preferred first-line drugs of choice for the treatment of hypertension in pregnancy, ***Labetalol, propranolol*** and ***metoprolol***, are among the first-line drugs of choice for treating hypertension in pregnancy. ***Nifedipine or verapamil,*** are the preferred first-line drugs of choice in calcium antagonists for the treatment of hypertension or cardiac arrhythmias in the second and third trimesters , In the first trimester, calcium antagonists are considered to be second-line therapy. ***MAGNESIUM SULFATE*** is The drug of choice for treatment of seizures in eclampsia .

•***Hydrochlorothiazide*** is the diuretic of choice .***Furosemide*** can be given when treatment of heart or renal failure requires a diuretic.If therapy with aldosterone antagonists is absolutely necessary, ***spironolactone*** should be chosen .

•***LMWH*** may be regarded as the anticoagulant drugs of choice for thromboprophylaxis and for the treatment of ***VTE*** during pregnancy. The

combination of ***LMWH*** and ***low-dose aspirin*** is recommended for the prevention of pregnancy loss in women with phospholipid antibodies and previous pregnancy loss .

•***Protamines*** can be used during pregnancy in cases of ***heparin (or LMWH)*** overdose **.** But in cases of ***LMWH*** overdose , its efficacy as an antidote seems to be less

• ***Nitrates*** may be used in pregnancy for appropriate indications.

•**A type I diabetic woman** should have good glycemic control before becoming pregnant . The drug of choice is ***regular insulin***. If there is excellent glycemic control on ***insulin lispro*** , it is not compulsory to change to ***regular insulin*** if the patient is pregnant**.Pregnant women with type II diabetes or gestational diabetes** should have ***regular insulin*** , if diet alone is insufficient for control . If blood sugar levels are only at a critical threshold and if there is accompanying fetal macrosomia , therapy with ***insulin*** should be initiated **.**

•Correction of maternal thyroid deficiency with ***L-thyroxine(T4)*** **and** ***Liothyronine (T3)*** is not associated with abnormal fetal outcome .

•***Propylthiouracil*** is the thyrostatic drug of choice in pregnancy , especially in the first trimester .

<u>Drugs of choice for the treatment of pregnant women with arrhythmia:-</u>

•CLASS IA: ***quinidine.*** •CLASS IB: ***lidocaine.***

•CLASS IC: ***propafenone*** and/or, in the second or third trimester,***flecainid***

•CLASS II : ***β-blockers*** for long-term use.

•If CLASS III antiarrhythmics are absolutely necessary, ***sotalol*** should be chosen**.** •In CLASS IV: ***VERAPAMIL and DELTIAZEM*** are acceptable.

•The drug of first choice for treatment of fetal (SVT) is ***DIGOXIN*** ; the second choice is ***SOTALOL*** or ***FLECAINIDE* .**

FDA RATING SYSTEM FOR DRUGS DURING PREGNANCY:-

The FDA assigns a safety category for medications by using a 5-letter system : **A, B, C, D** and **X , (SeeTable 1 -19)** .

(Table 19) FDA PREGNANCY CATEGORIES OF SOME DRUGS (DRUGS.COM,2009)

DRUG	CAT.	DRUG	CAT.
Abciximab	C	Bumetanide	C
ACEIs	D	Butylscopolamine	C
Acrivastin	B	Carbamazepine	D
Acyclovir	B	Cabergoline	B
Adalimumab	B	Carbimazole	D
ADENOSINE	C	Carbinoxamine	C
Alimemazine	C	Carvedilol	C
Allergen Immunotherapy	C	Castor oil	X
ALLOPURINOL	C	Cephalosporins	B
Alprazolam	D	Cetirizine	B
Alteplase	C	Chloramphenicol	C
Amantadine	C	Chlorpheniramine	C
AMILORIDE	B	Chlorpropamide	C
Aminoglycosides	D	CHOLESTYRAMINE	C
AMIODARONE	D	Chromium	C
Amitriptyline	C	Cimetidine	B
Amlodipine	C	Clarithromycin	C
ANTICHOLINERGICS	C	Clavulanat	B
ARBs	D	Clemastine	B
ASPIRIN	C or D	Clindamycin	B
Atenolol	D	CLONIDINE	C
Atropine	C	Clopidogrel	B
AZATHIOPRINE	D	Codeine	C
Azelastine	C	COLCHICINE	X
Azithromycin	B	Colistin	C
Aztreonam	B	COPOLYMER 1	B
Bisacodyl	C	Corticosteroids	C
Bismuth salts	C	CROMOGLYCATE	B
Bisoprolol	C	Cyanocobalamin (Vit. BI2)	C
Bisphosphonate	C	Cyclizine	B
BRETYLIUM	C	CYCLOPHOSPHAMIDE	D
Bromocriptine	B	Cycloserine	C
Brompheniramine	C	CYCLOSPORINE	C
Buclizine	B	Cyproheptadine	B

(Table 19) FDA PREGNANCY CATEGORIES OF SOME DRUGS(cont.)

DRUG	CAT.	DRUG	CAT.
Desloratadine	C	Gancyclovir	C
Desmopressin	B	G-CSF	C
Diazepam	D	Glibenclamide (Glyburide)	B
DIAZOXIDE	C	Gliclazide	C
DIGOXIN	C	Glimepiride	C
DIHYDROERGOTAMIN	X	GOLD COMPOUNDS	C
Diltiazem	D	Haloperidol	C
Dimenhydranate	B	Heparin	C
Diphenhydramine	B	Hepatitis A vaccine	C
Diphenoxylate	C	Hepatitis B vaccine	C
Dipyridamole	B	Human insulin	C
DISOPYRAMIDE	C	HYDRALAZINE	C
Docusate	C	Hydroxyzine	C
Domperidone	C	IBUTILIDE	C
Doxylamine	A	Imipenem	C
D-PENICILLAMINE	D	INFLIXIMAB	B
Droperidol	C	Influenza vaccine	C
Entacapon	C	INH	C
EPINEPHRINE	C	Insulin aspart	B
EPLERENON	B	Insulin detemir	C
Erythromycin	B	Insulin glargine	C
Esmolol	C	Insulin glulisin	C
Esomeprazole	B	Insulin lispro	B
Ethacrynic acid	C	INTERFERONS	C
Ethambutol	B	Iodide	D
Ethionamide	C	Ipratropium bromide	B
Ethosuximide	D	Iron (Ferric Salts)	B
Famcyclovir	B	Iron (Ferrous Salts)	A
Famotidine	B	KETOTIFEN	C
FIBRATES	C	Labetalol	C
FLECAINIDE	C	Lactulose&lactitol	B
Flouride	B	Lamivudine	C
Flouroquinolones	C	Lamotrigine	C
Flumazenil	C	Lanreotide	C
Fluoxetine	C	Lansoprazole	B
Folic acid	A	L-dopa+benserazide	C
Formoterol	C	L-dopa+Carbi-dopa	C
Fosfomycin	B	LEFLUNOMIDE	X
Furosemide	C	LEVAMISOLE	C
Gabapentin	D	Levocetirizine	B

(Table 19) FDA PREGNANCY CATEGORIES OF SOME DRUGS(cont.)

DRUG	CAT.	DRUG	CAT.
LIDOCAINE	B	Omeprazole	C
Lincomycin	C	Organic Calcium salts	C
Liothyronine (T3)	A	Oseltamivir(TAMIFLU)	C
Lithium salts	D	Pancreatic enzymes	C
Loperamide	C	Pantoprazole	B
Loratadine	B	PARACETAMOL	B
L-thyroxine(T4)	A	Paroxetine	D
MAGNESIUM SULFATE	A	PAS	C
MANNITOL	C	PEG	C
Meclizine	B	Pegvisomant	B
Meropenem	B	Pencyclovir	B
Metformin	B	Penicillins	B
Methenamine	D	Pentamidine	C
METHOTREXATE	X	PENTOXIFYLLINE	C
Mesalamine	B	Pergolide	B
Metoclopramide	B	Pethidine	C
Metoprolol	C	Pheniramine	C
Metronidazole	B	Phenobarbital	D
MEXILETINE	C	Phenothiazines	C
Midazolam	D	PHENYTOIN	D
MIDODRINE	C	Polymixine B	C
Mineral oil	NONE	PRAZOCIN	C
Misoprostol	X	PROBENECID	NONE
MMF	C	PROCAINAMIDE	C
Montelukast	B	Prochlorperazine	C
Morphine	C	PROPAFENONE	C
Nadolol	C	Propranolol	C
Nalidixic acid	B	Propylthiouracil	D
Naratriptan	C	Protamines	C
NEDOCROMIL	B	Pyrazinamide	C
Nifedipine	C	Pyridoxine	A
Nimodipine	C	QUINIDINE	C
NITRATES	C	Rabeprazole	B
Nitrofurantoin	B	Rabies vaccine	C
NITROPRUSSIDE	C	Ranitidine	B
Nizatidine	B	RESERPINE	D
NOR-EPINEPHRINE	C	Ribavirin	X
NSAIDs	C or D	Riboflavin(VIT. B2)	A
Octreotide	B	Rifabutine	B
Olsalazine	C	Rifampicin	C

(Table 19) FDA PREGNANCY CATEGORIES OF SOME DRUGS(cont.)

DRUG	CAT.	DRUG	CAT.
Rizatriptan	C	TRIAMTERENE	C
Roxithromycin	B	TRIENTINE	C
Salbutamol	C	Trimethoprim	C
Saline laxatives	C	Triprolidine	C
Salmeterol	C	UDCA	B
Selegiline	C	Urokinase	B
Selenium	C	Valacyclovir	B
Senna laxatives	C	Valgancycliovir	B
Simethicone	C	Valproic acid	D
Sotalol	B	Vancomycin	C
Spiramycin	B	Vasopressin	B
SPIRONOLACTONE	C	Verapamil	C
STATINS	X	Vitamin A derivatives	X
Stool-bulking laxatives	NONE	Vitamin C	A
Streptokinase	C	Vitamin D	C
Streptomycin	D	Vitamin K	C
Sucralfate	B	Warfarin	X
Sulbactam	B	Zafirlukast	B
Sulfa drugs	B or D	Zanamivir	C
Sulfasalazine	B	Zidovudine	C
Sumatriptan	C	Zileuton	C
TACROLIMUS	C	Zinc	C
Tazobactam	B	Zolmitriptan	C
Terbutaline	B	α- METHYLDOPA	B
Tetanus toxoid	C		
Tetracyclines	D		
THALIDOMIDE	X		
THEOPHYLLINE	C		
Thiamazole (methimazole)	D		
Thiamine(VIT. B1)	A		
THIAZIDES	B		
Ticlopidine	B		
Tinidazole	C		
Tirofiban	B		
Tolazamide	C		
Tolbutamide	C		
Torasemide	C		
Tramadol	C		

NONE =Have not been assigned to a pregnancy category by the FDA.

CONCLUSION

No drug has been shown to be entirely safe in human pregnancy ; indeed , it would be impossible to establish complete safety . So , If one takes a pessimistic viewpoint about the safety of drugs in pregnancy, it may be necessary to withhold medication from women of childbearing age unless they can prove that they are not pregnant or likely to become pregnant . But , if one takes an optimistic viewpoint , drugs that cause birth defects in humans are rare , comprising less than 1% of the therapeutic drugs currently available. However , as is often stated, ***"the absence of evidence is not the same as evidence of absence".*** Any drug taken during pregnancy can potentially have an adverse effect on the mother or the fetus.