Drug Prescription in Pregnancy & Lactation

Dr Radhika S
Associate Professor
Dept of Clinical Pharmacology & Therapeutics
Nizam's Institute of Medical Sciences

Thalidomide was licensed in July 1956 for prescription-free over-the-

Frances Oldham Kelsey

Diethylstilbestrol (DES) is an estrogen that was first manufactured in 1938.

U.S. physicians prescribed DES to pregnant women to prevent miscarriages and avoid other pregnancy problems

As a result, an estimated 5-10 million pregnant women and the children born of these pregnancies were exposed to DES.

In 1953, published research showed that DES did not prevent miscarriages or premature births.

However, DES continued to be prescribed until 1971. In that year, FDA issued a Drug Bulletin advising physicians to stop prescribing DES to pregnant women

Increased risk of Clear cell adenocarcinoma (CCA), a rare kind of vaginal and cervical cancer in the female offspring of women exposed to which drug in pregnancy?

Introduction

Health Care Providers (HCPs) and Pregnant women need access to most useful and latest information about their prescription medicines because:

✓ Most women take at least one medication during pregnancy.

✓ The use of atleast four medications during pregnancy has more than doubled over the last 30 years.

✓ Many pregnant women have chronic conditions—like asthma, diabetes—that require them to continue taking medications

✓ New health problems may begin or old ones may get worse during pregnancy, requiring treatment.

✓ A woman's body changes throughout her pregnancy, which may affect the medication dose she needs.

Best source for getting reliable information regarding medications???

LABEL INFORMATION / PATIENT PACKAGE INSERT

What makes Label more reliable?

- Based on a comprehensive scientific evaluation of the product's benefits and risks under the conditions of use prescribed, recommended, or suggested in the labeling

- Reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively

Difference between

Label information And Other Information

- Prescription drug labeling ‘‘is intended to provide physicians with a clear and concise statement of the data and information necessary for the safe and effective use of the drug”.

- Labeling statements are supported by scientific evidence and are not false or misleading in any particular’’

Physician Labeling Rule, 2006

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION
- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS
- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS
- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE
- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 [text]
- 14.2 [text]

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling

A. 8.1 Pregnancy

1. Pregnancy Exposure Registry
2. Risk Summary
3. Clinical Considerations
4. Data

B. 8.2 Lactation

1. Risk Summary
2. Clinical Considerations
3. Data

C. 8.3 Females and Males of Reproductive Potential

The Pregnancy and Lactation Labeling Rule (PLLR or final rule) requires changes to prescription drug labeling in the Physician Labeling Rule (PLR)

To assist HCPs in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children.

The PLLR removes pregnancy letter categories – A, B, C, D and X.

The PLLR also requires the label to be updated when information becomes outdated.

FDA removes pregnancy category mention in the label information

Pregnancy categories were confusing and did not accurately and consistently communicate differences in degrees of fetal risk.

Pregnancy categories were heavily relied upon by clinicians, in that prescribing decisions were being made based on the pregnancy category, rather than an understanding of the underlying information that informed the assignment of the pregnancy category.

A narrative structure for pregnancy labeling, rather than a category system, is best

Pregnancy and Lactation Labeling Rule (PLLR)

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of reproductive potential

8.1 Pregnancy

- Information regarding pregnancy exposure registry, if one exists (including contact details)

- Risk Summary must include risk statements based on data from all relevant sources that describe, for the drug, the risk of adverse developmental outcomes.

- Information on disease-associated maternal and/or embryo/fetal risk, dose adjustments, maternal/fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery.

- The labeling must also describe the data that are the basis for. the risk statements and clinical information included

8.2 Lactation

- A summary of the risks of using a drug during lactation
- This summary must include, the available, relevant information on the presence of the drug in human milk, effects of the drug on the breast-fed child, and effects of the drug on milk production.
- Include a risk and benefit statement unless it breast feeding is contraindicated during drug therapy.

8.3 Females and Males of reproductive potential

- Include relevant information
- when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or
- when there are human or animal data that suggest drug-associated fertility effects.

FDA RISK CLASSIFICATION SYSTEM (NOW OBSOLETE)

Category A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
Category B: No evidence of risk in humans. Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
Category C: Risk cannot be ruled out. Adequate, well- controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk.
Category D: Positive evidence of risk. Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
Category X: Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk that clearly outweighs any possible benefit to the patient.

A survey of FDA pregnancy risk category assignment of drugs in the 2001 and 2002 Physicians' Desk References

FDA pregnancy risk categories of drugs in the United States, N (%)

FDA risk category	2001 PDR $N = 2{,}249$ drugs	2002 PDR $N = 2{,}150$ drugs
A	5 (0.2)	7 (0.3)
B	291 (12.9)	296 (13.8)
C	821 (36.5)	802 (37.3)
D	99 (4.4)	81 (3.8)
X	117 (5.2)	124 (5.8)
None listed	916 (40.7)	840 (39.1)

D.A. Marcus, P.A. Bain, Effective Migraine Treatment in Pregnant and Lactating Women: A Practical Guide, DOI 10.1007/978-1-60327-439-5_2

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies in rats, rabbits, and mice no evidence of teratogenicity or fetal harm when naproxen was administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1500 mg/day, respectively [*see Data*]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS during labor or delivery. In animal studies, NSAIDS, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Hydroxychloroquine	Current evidence indicates no increased rate of congenital malformations Hydroxychloroquine can be continued throughout pregnancy	100

Pregnancy

Teratogenic Effects: Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated. Embryonic deaths and malformations of anophthalmia and microphthalmia in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers: Caution should be exercised when administering PLAQUENIL to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

PLAQUENIL®
HYDROXYCHLOROQUINE SULFATE TABLETS, USP

Pregnancy:

Teratogenic Effects : *Pregnancy Category B.* Reproduction studies have been performed in rats and rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to sulfasalazine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In a group of 186 women treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable to that for 245 untreated IBD pregnancies as well as to pregnancies in the general population.[1] A study of 1,455 pregnancies associated with exposure to sulfonamides indicated that this group of drugs, including sulfasalazine, did not appear to be associated with fetal malformation.[2] A review of the medical literature covering 1,155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.[3]

No clinical studies have been performed to evaluate the effect of sulfasalazine on the growth development and functional maturation of children whose mothers received the drug during pregnancy.

Nonteratogenic Effects: Sulfasalazine and sulfapyridine pass the placental barrier. Although sulfapyridine has been shown to have a poor bilirubin-displacing capacity, the potential for kernicterus in newborns should be kept in mind.

Metho

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (See **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See **BOXED WARNINGS**.)

Pre

Ter

Psc

See

Nu

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

See

	Pregnancy		
Drug	Statement on compatibility of drug with pregnancy based on evidence	Percentage of agreement with statement	Expert opinion on use of drug in clinical practice (%)*
Infliximab	Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy	100	
Adalimumab	Current evidence indicates no increased rate of congenital malformations; adalimumab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy	100	
Golimumab	Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy	100	
Etanercept	Current evidence indicates no increased rate of congenital malformations; etanercept can be continued up to gestational week 30–32; if indicated, it can be used throughout pregnancy	100	
Certolizumab	Current evidence indicates no increased rate of congenital malformations; certolizumab can be continued throughout pregnancy	100	
Rituximab	Current evidence indicates no increased rate of congenital malformations; in exceptional cases it can be used early in gestation; with use at later stages of pregnancy clinicians should be aware of the risk of B cell depletion and other cytopenias in the neonate	100	

Table 2 Characteristics of studies and outcome of pregnancy exposure related to medications used to treat rheumatic diseases, SLR-period 2008–2015*

Drug	Type of publication in numbers	References on cohorts and case controls	Total pregnancies† (prospective/ retrospective)	Number of miscarriages of eligible pregnancies‡ (%)	Number of congenital malformations of live births§ (%)	Comments on miscarriages (MC) and/or congenital malformations (CM) compared with control groups and/or background data§	Strength of evidence according to GRADE	Oxford
Non-selective COX inhibitors (classical NSAIDs)	3 cohorts 3 case controls	11–16	17 992 (7684/10 308)	530/5609 (9.4)	457/ 12 354 (3.7)	No difference MC or CM	++++	2a
Glucocorticoids (any route/ formulation)	2 cohorts 5 case controls *17 case reports/series* *(1 abstract)*	16 [illegible]–23	3500¶ (94/3406)	70/331 (21.1)	34/3180 (1.1)	MC slightly increased confounded by disease indication, no difference CM compared with control groups	+++	2b
Antimalarials	2 cohorts 4 case controls	16 24–28	492 (170/322)	20/170 (11.8)	23/492 (4.7)	No difference MC or CM	++++	2a
Sulfasalazine	2 cohorts 2 case controls	16 29–31	525 (227/298)	12/186 (6.5)	16/339 (4.7)	No difference MC or CM	+++	2a
Leflunomide	2 cohorts (1 abstract) 1 case control *4 case reports/series*	16 32 33	129 (80/49)	12/122 (9.8)	5/129 (3.9)	No difference MC or CM	+++	2b
Azathioprine	4 cohorts (1 abstract) 7 case controls *7 case reports/series* *(1 abstract)*	16 31 34–42	1327 (434/893)	40/559 (7.2)	65/1327 (4.9)	No significant difference MC or CM compared with disease-matched controls	++++	2a
Methotrexate	2 cohorts 2 case controls *8 case reports/series*	16 27 43 44	372 (332/40)	140/329 (42.6)	15/143 (10.5)	Increased rate MC Increased rate CM with specific pattern	++++	2b
Cyclophosphamide	2 cohorts	45 46	226	No separate	22/86	High rate CM No studies with	+++	2b

THERE IS NO DATA FROM RCTs

ISSUES - DRUG DEVELOPMENT - PREGNANT AND LACTATING WOMEN

Generally, the safety and efficacy of a drug are established for a particular dosage regimen or range of dosage regimens in late phase (Phase 3) clinical trials involving relatively typical representatives from the target patient population.

Pregnant women are actively excluded from these trials, and, if pregnancy does occur, the usual procedure is to discontinue treatment and drop the patient from the study

Consequently, at the time of a drug's initial marketing, except for products developed to treat conditions specific to pregnancy (e.g., oxytocics, cervical ripening agents), there are seldom human data on the appropriate dosage and frequency of administration during pregnancy

Even after years of marketing, data in product labels regarding PK and dose adjustments during pregnancy rarely provide more information for appropriate prescribing in pregnancy than was available at the time of initial marketing.

Majority of published PK studies of anti-infective drug products during pregnancy were conducted at the time of abortion or delivery (usually via cesarean section) and done to determine the transplacental passage of drug

In the absence of data, the usual adult dose is typically prescribed for pregnant women.

Because of the physiologic changes inherent in pregnancy, the result can be substantial under dosing, or, in some cases, excessive dosing.

Ethical issues are important when considering studying drugs in pregnant women.

The physiologic changes have the potential to alter the PK and/or PD of drugs.

Changes in total body weight and body fat composition.

Delayed gastric emptying and prolonged gastrointestinal transit time.

Increase in extra cellular fluid and total body water.

Increased cardiac output, increased stroke volume, and elevated maternal heart rate.

Decreased albumin concentration with reduced protein binding.

Increased blood flow to the various organs (e.g., kidneys, uterus).

Increased glomerular filtration rate.
Changed hepatic enzyme activity

Pregnant women may be involved in PK studies

Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and

The risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

Studies in pregnant women are not recommended if the drug is not used in pregnant women or the drug has known or highly suspect fetal risk.

Animal Studies

1.3 Female Reproduction and Developmental Toxicity Studies

These studies need to be carried out for all drugs proposed to be studied or used in women of child bearing age.

1.3.1 Female Fertility Study (Segment I):

The drug should be administered to both males and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period.

Dams should be allowed. to litter and their medication should be continued till the weaning of pups.

Progress of gestation! parturition periods, length of gestation, parturition, post-partum health and gross pathology (and histopathology of affected organs) of dams should be recorded and pups should be observed for growth parameters, survival and autopsied .

1.3.2 Teratogenicity Study (Segment II):

The drug should be administered throughout the period of organogenesis.

The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level.

All foetuses should be subjected to gross examination, one half of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities.

1.3.3 Perinatal Study (Segment Ill):

This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.

The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams will then be sacrificed and examined.

One male and one female from each litter of Fl generation (total 15 males and 15 females in each group) should be selected at weaning treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation.

Mating performance and fertility of F I generation should thus be evaluated to obtain the F2 generation whose growth parameters should be monitored till weaning.

AS THERE IS NO DATA FROM RCTs

NIH-led task force to address research needs of pregnant women and nursing mothers

Experts seek to identify ethical issues, improve research studies

Wednesday, June 7, 2017

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), established by the 21st Century Cures Act, will advise the Secretary of Health and Human Services on research aimed at optimizing therapies for pregnant women and nursing mothers. Led by NIH's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the task force will conduct its first meeting on August 21-22, 2017, at NIH in Bethesda, MD.

"When clinical studies omit pregnant women and nursing mothers, health care providers are left without evidence-based research to inform care decisions," said Catherine Y. Spong, M.D., NICHD Deputy Director. "Without this research, treatment of pregnant or nursing moms who experience common medical conditions may be not be effective or even potentially cause harm. Therapies for pregnant and lactating women ideally should have the best available evidence, given the implications for the developing fetus and newborn. The task force will address these issues and propose solutions."

TAKE HOME MESSAGE

As the currently available data is from observational studies, Rheumatologists/Physicians and Obstetricians should make a careful risk-benefit assessment before taking decision on initiation / continuation of any medication in pregnant and lactating women

Once, the pregnant women are exposed to any medication during pregnancy considering it as a precious pregnancy, careful monitoring of mother, fetus and baby needs to done and in case any plausible abnormality is observed, cultivate reporting attitude.

THANK YOU