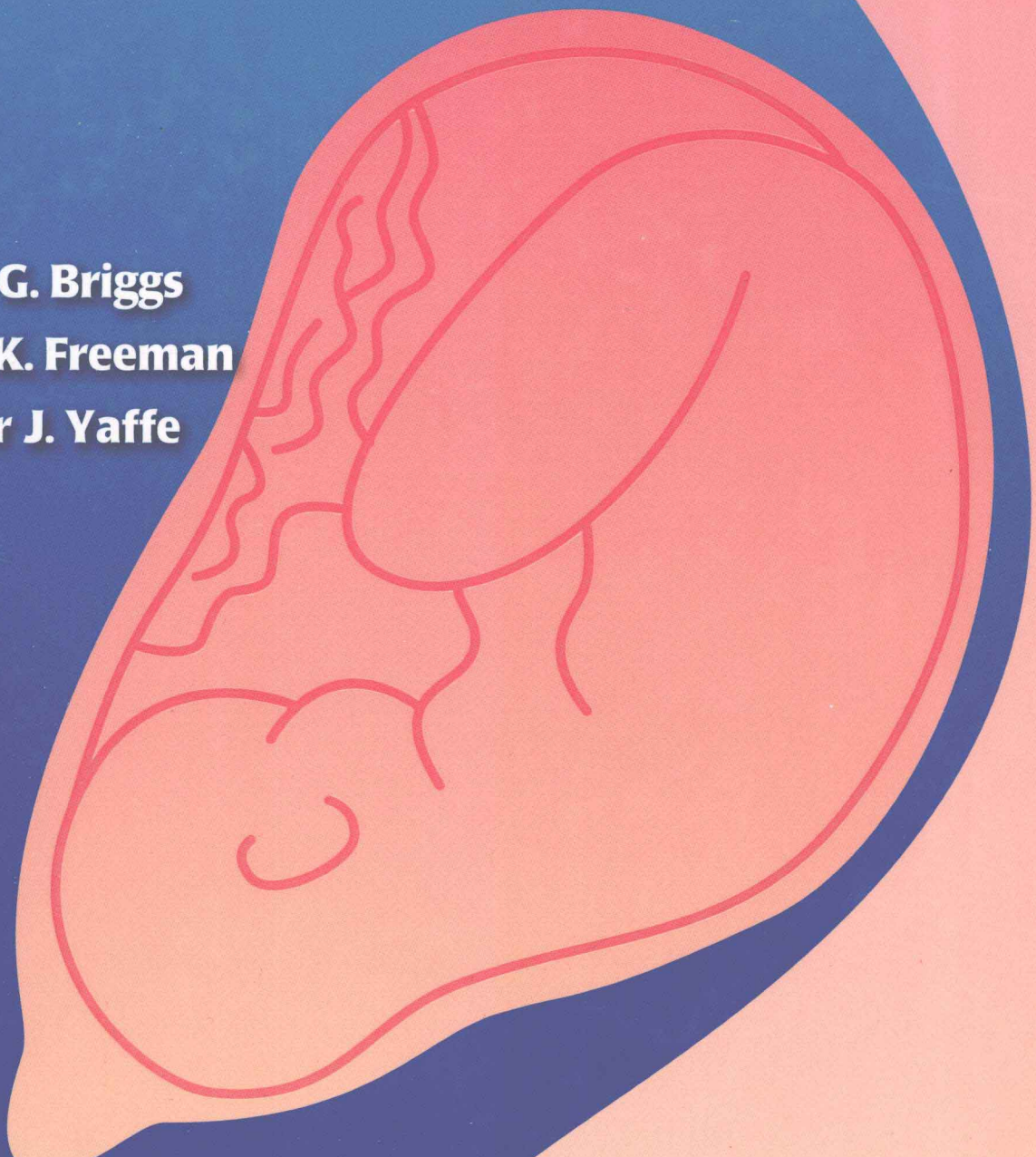
A REFERENCE GUIDE TO FETAL AND NEONATAL RISK

Drugs in Pregnancy and Lactation

Ninth Edition

Gerald G. Briggs
Roger K. Freeman
Sumner J. Yaffe

Includes online access to a mobile application, fully searchable text, and links to the Briggs Update newsletter



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A REFERENCE GUIDE TO FETAL AND NEONATAL RISK

Drugs in Pregnancy and Lactation, Ninth Edition

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In Memory

Susan Abbie (McLennan) Briggs

April 11, 1943–June 28, 2009

She was a generous, wonderful, compassionate woman and mother, who always placed her love and support of family above everything. Her guiding principles were integrity and compassion. She treated all people the same, whether friends or strangers—with kindness and respect—and she greeted everyone with a smile. Her frequent laughter was contagious.

Without her continued support and encouragement, this book would not have been possible.
I was fortunate to share in her life for 46 years.
I miss her a lot.

Foreword

This book is now in its 9th edition and continues to enjoy great success with physicians and other professionals involved in the care of pregnant and lactating patients. There are 105 additional drugs over the 8th edition, and updates have been provided where indicated on many drugs in the book. Many of the reviews are exhaustive but pertinent to the management of pregnant and lactating patients who have already ingested a drug or who are in need of drug therapy where a cost-benefit analysis may be necessary for appropriate counseling. There are seldom absolute answers to questions a woman may have when she ingests a drug when pregnant or nursing because human experience is usually, of necessity, somewhat anecdotal. Even with all the information in this publication, there are risks that are yet unknown that may apply to a small number of people making the dictum of not using drugs in pregnancy without good cause still important. The effect of drugs in animals, the importance of timing and dose, and the effect of environmental factors are all involved in the risks and benefits of drugs in pregnant and/or lactating women and their fetuses/neonates. These factors are considered when data are available, but we must admit that in no individual case is the understanding of risks and benefits absolute.

Because many pregnant and lactating women take substances, both legal and illegal, without the knowledge of their caregivers, the challenge to understand the risks/benefits of any drug and its interactions with these substances is daunting. Today, we are just beginning to understand the specific genetic influences on the action, toxicity, and teratogenicity of drugs in an individual. I expect in the future there will be many identified genetic factors that will influence therapeutic decisions.

It is our hope that the 9th edition will continue to provide the practitioner appropriate assistance with questions regarding drugs in pregnancy and lactation.

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Preface

Three changes in the format of the 9th edition have been made. First, the FDA's risk categories (A, B, C, D, and X) that first appeared in 1979 and have been included in all previous editions of this book have been removed. The reasons for this decision are related to the concerns that have been expressed regarding their use: (i) they were relied on by clinicians because they appeared to provide a simple measure of risk even though they were confusing and overly simplistic, (ii) they led to unnecessary terminations of wanted pregnancies, (iii) they conveyed the incorrect impression that risk increased from A to X and that drugs in the same category had similar risk potential, (iv) they did not discriminate between potential toxicity on the basis of severity, incidence or type of effect or on the basis of dose, duration, frequency, route, and gestational timing, and (v) they focused on planned prescribing and inadequately addressed inadvertent exposures.

In the 7th edition (2005), because we shared the same concerns, we added our own recommendations of pregnancy and breastfeeding risk to each drug. Although we continued to cite the FDA pregnancy categories, we hoped that our recommendations would better define the potential risks. In 2008, the FDA proposed new labeling for pregnancy and breastfeeding risks that eliminated the categories and expanded the material relating to pregnancy and breastfeeding. As this edition went to press, the new labeling requirements have not yet been initiated but, hopefully, will be in the near future. When they are in the place, we believe the combination of the new labeling requirements and our recommendations will assist the clinician in determining the best risk:benefit ratios for exposures during pregnancy and breastfeeding.

The second change from previous editions involves the removal of drugs that are no longer available. The drug names are still included without text but with the notation "Withdrawn from the market. See 8th edition." They also are included in the Index with the notation "See 8th edition." Some drugs that have been recently withdrawn are still included with full text because they may still be of interest. The third change involves the addition to the Index of prescription combination drugs. These agents are listed by trade name with the names of the individual drugs that can be found in the text. We hope these changes will make this edition easier to use.

As in previous editions, some drug reviews have toll-free telephone numbers for the use of health care professionals to enroll patients in observational studies and/or registries. These sources are an important method for gathering prospective data on pregnancy exposures for many drugs, including those considered high-risk. In fact, such sources are often the only human pregnancy experience available for new drugs and pharmacologic drug classes. The data generated by these studies and registries can be valuable for the raising of hypotheses of major teratogenicity or providing some assurance that the agent is not a significant teratogen. Because their importance is so high, healthcare professionals are encouraged to call for information about patient enrollment.

We take great pleasure in the opportunity to thank the many individuals who have helped us. To those who have sent us references, know that your efforts are sincerely appreciated. We also appreciate those who have commented on our work because it identifies areas that may need modification or topics that we need to cover. In addition, the questions we received served to keep us informed of your information needs and often lead to the preparation of new reviews. On the following page, we have listed the LBMMC staff members that have been particular helpful as well as the names of students that have contributed to this edition.

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Acknowledgment

It is a pleasure to acknowledge the assistance of Barbara Malinofsky and Elizabeth Mason-Renteria, Parks Medical Library, Long Beach Memorial Medical Center, who retrieved numerous references for us during the preparation of this edition. Without their assistance, this edition would have been much harder to prepare.

We also are pleased to acknowledge the assistance of our former students in the preparation of some of the reviews contained in this edition. The students came from three schools of pharmacy. During their clerkship training in obstetrics/gynecology, each researched and wrote two drug reviews. It was their first experience in how to assess the reproductive toxicity of drugs, and they did very well.

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Introduction

Sumner J. Yaffe, MD

It is now generally accepted that the developing fetus may be adversely affected by exposure to drugs and environmental chemicals. The stage of development of the intrauterine host is a major determinant of the resultant effect as well as the nature and the concentration of the drug or chemical agent. On a more positive side, fetal therapy (i.e., treatment of fetal disease in utero by administering the drug to the mother or directly to the fetus) has been recognized recently as a rational approach to treat fetal disease.

Forty years ago, the thalidomide catastrophe (limb defects) occurred when this drug was administered to pregnant women as an antianxiety and hypnotic agent during the 1st trimester. Thalidomide had been evaluated for safety in several animal species, had been given a clean bill of health, and had come to be regarded as a good pharmacologic agent (hypnotic/sedative). It is of interest that this drug is being re-evaluated today for use in leprosy and approval for this use has been given by the FDA.

It is important to note that, even though thalidomide produces a distinct cluster of anatomic defects that are virtually pathognomonic for this agent, it required several years of thalidomide use and the birth of many thousands of grossly malformed infants before the cause-and-effect relationship between thalidomide administration in early pregnancy and its harmful effects was recognized. This serves to emphasize the difficulties that exist in incriminating drugs and chemicals that are harmful when administered during pregnancy. Hopefully, we will never have another drug prescribed for use during pregnancy whose teratogenicity is as potent as thalidomide (about 1/3 of women taking this agent during the 1st trimester gave birth to infants with birth defects).

Concern about the safety of foreign compounds administered to pregnant women has been increasingly evident since thalidomide. The direct response to this misadventure led to the promulgation of the drug regulations of 1962 in the United States. According to these regulations, a drug must be demonstrated to be safe and effective for the conditions of use prescribed in its labeling. The regulations concerning this requirement state that a drug should be investigated for the conditions of use specified in the labeling, including dosage levels and patient populations for whom the drug is intended. In addition, appropriate information must be provided in the labeling and be available when the drug is prescribed. The intent of the regulations is not only to ensure adequate labeling information for the safe and effective administration of the drug by the physician, but also to ensure that marketed drugs have an acceptable benefit:risk ratio for their intended uses.

It is clear that any drug or chemical substance administered to the mother is able to cross the placenta to some extent unless it is destroyed or altered during passage or its molecular size and low lipid solubility limit transplacental transfer. Placental transport of maternal substrates to the fetus and of substances from the fetus to the mother is established at about the 5th week of embryo life. Substances of low molecular weight diffuse freely across the placenta, driven primarily by the concentration gradient. It is important to note, therefore, that almost every substance used for therapeutic purposes can and does pass from the mother to the fetus. Of greater importance is whether the rate and extent of transfer are sufficient to result in significant concentrations within the fetus. Today, the concept of a placental barrier must be discarded.

Experiments with animals have provided considerable information concerning the teratogenic effects of drugs. Unfortunately, these experimental findings cannot be extrapolated with certainty from species to species, or even from strain to strain within the same species, much less from animals to humans. Research in this area and the prediction of toxicity in the human are further hampered by a lack of specificity between cause and effect.

Traditionally, teratogenic effects of drugs have been noted as anatomic malformations. It is clear that these are dose and time related and that the fetus is at greater risk during the first 3 months of gestation. However, it is possible for drugs and chemicals to exert their effects upon the fetus at other times during pregnancy. Functional and behavioral changes are much more difficult to identify as to cause and effect. Consequently, they are rarely recognized. A heightened awareness on the part of health care providers and recipients will make this task easier.

The use of dietary supplements as well as complementary or alternative medicine products has been increasing markedly in the Western industrialized world. This use continues unabated during pregnancy and lactation. The efficacy of these compounds is generally unknown, with rare exception, and their safety poorly studied. In particular, little is known about the interaction between the use of a broad range of dietary supplements, alternative medicine

products, and health outcomes in women, developing fetuses and nursing neonates. Such knowledge is essential to the evaluation of both the justification and safety of the use of these products during these critical periods of development. Until this occurs, women should be advised about current lack of knowledge and cautioned as to their use. A notable exception is folic acid supplementation during pregnancy to prevent neural tube defects.

It is crucial that concern also be given to events beyond the narrow limits of congenital anatomic malformations; evidence exist that intellectual, social, and functional development can also be adversely affected by drug administration during pregnancy. There are examples that toxic manifestations of intrauterine exposure to environmental agents may be subtle, unexpected, and delayed. Concern for the delayed effects of drugs, following intrauterine exposure, was first raised following the tragic discovery that female fetuses exposed to diethylstilbestrol (DES) are at an increased risk for adenocarcinoma of the vagina. This type of malignancy is not discovered until after puberty. Many of the drugs prescribed to pregnant women have been evaluated in the following pages as to their propensity to produce congenital anatomic malformations. During the past several decades, awareness that many of these compounds may act after the period of organogenesis, through birth and into lactation, has increased. We now realize that drugs considered safe (i.e., not producing anatomic malformations) can still produce more subtle yet permanent alterations in the physiology and biochemistry of the developing perinate. Furthermore, many of these subtle hitherto unrecognized defects are not present at birth and may be dormant and latent until years later after the time of administration. The teratogen appears to produce a programming or imprinting defect in the developing tissue or organ. This defect need not be expressed until adulthood, because the program may not be required until that time. Consequently, in the absence of anatomical defects readily recognized, there is the danger that these late-onset dysfunctions will either be unrecognized or will be attributed to some other cause.

The purpose of the above paragraph is to raise the concept of a little known but potentially serious health hazard in children and adults. This refers to the ability of perinatally consumed drugs and food additives and nonprescription alternative agents to produce the subtle biochemical defects undetectable or unrecognized in the neonate but expressed years or even decades after birth. How serious a problem is the in utero exposure to drugs and chemicals to the delayed latent defect? The answer may in lie in the use of animals for these fetal origins of adult disease.

The physician is confronted with two imperatives in treating the pregnant woman: alleviate maternal suffering and do no harm to the fetus. Until now, the emphasis has been on the amelioration of suffering, but the time has come to concentrate on not harming the fetus. The simple equation to be applied here is to weigh the therapeutic benefits of the drug to the mother against its risk potential to the developing fetus. Since fetal ova may also be exposed to drugs given to the mother, effects may be evident in future generations.

When one considers that more than a billion drug prescriptions are written each year, that there is unlimited self-administration of over-the-counter drugs, and that approximately 500 new pharmaceutical products are introduced annually, the need for prudence and caution in the administration of pharmaceuticals has reached a critical point. Pregnancy is a symptom-producing event. Pregnancy has the potential of causing women to increase their intake of drugs and chemicals, with the potential being that the fetus will be nurtured in a sea of drugs.

In today's society, the physician cannot stand alone in the therapeutic decision-making process. It has now become the responsibility of each woman of childbearing age to consider her use of drugs carefully. In a pregnant woman, the decision to administer a drug should be made only after a collaborative appraisal between the woman and her physician of the risk:benefit ratio.

BREASTFEEDING AND DRUGS

Between 1930 and the late 1960s, there was a dramatic decline in the percentage of American mothers who breastfed their babies. This was also accompanied by a reduction in the length of breastfeeding for those who did nurse. The incidence of breastfeeding declined from approximately 80% of the children born between 1926 and 1930 to 49% of children born some 25 years later. For children born between 1966 and 1970, 28% were breastfed. Indeed, in 1972 only 20% of newborns were breastfed. As data have become available for the following years, it is clear the decline has been reversed. By 1975, the percentage of first-born babies who were breastfed rose to 37%. At the present time in the United States, a number of surveys indicate that more than 50% of babies discharged from the hospital are breastfed, and the number is increasing. Breastfeeding is difficult to contemplate, as more than 50% of mothers work and return to work soon after delivery. New solutions must be found by employers to encourage breastfeeding and develop the logistics to enable employees to breastfeed on the job.

Breast milk is known to possess nutritional and immunologic properties superior to those found in infant formulas. An American Academy of Pediatrics position paper emphasizes breastfeeding as the best nutritional mode for infants for the first 6 months of life. In addition to those qualities, studies also suggest significant psychologic benefits of breastfeeding for both the mother and the infant.

The upswing in breastfeeding, together with a markedly increased concern about health needs on the part of parents, has led to increased questioning of the physician, pharmacist, and other health professionals about the safety and potential toxicity of drugs and chemicals that may be excreted in breast milk. Answers to these questions are not very apparent. Our knowledge concerning the long- and short-term effects and safety of maternally ingested drugs on the suckling infant is meager. We know more now than Soranus did in 150 AD, when he admonished wet nurses to refrain from the use of drugs and alcohol, lest it have an adverse effect on the nursing infant. We must know more! The knowledge to be acquired should be specific with respect to dose administered to the mother, amount excreted in breast milk, and amount absorbed by the suckling infant. In addition, effects on the infant should be determined (both acute and chronic).

It would be easy to recommend that the medicated mother not nurse, but it is likely that this recommendation would be ignored by the mother and may offend many health providers, as well as their patients, on both psychosocial and physiologic grounds.

It must be emphasized that many of the investigations concerned with milk secretion and synthesis have been carried out in animals. The difficulty in studying human lactation using histologic techniques and the administration of radioactive isotopes is obvious. There are considerable differences in the composition of milk in different species. Some of these differences in composition would obviously bring about changes in drug elimination. Of great importance in this regard are the differences in the pH of human milk (pH usually >7.0) compared with the pH of cow's milk (pH usually <6.8) where drug excretion has been extensively studied.

A number of reviews give tables of the concentration of drugs in breast milk. Often, these tables also give the milk:plasma ratio. Most of the values from which the tables are derived consist of a single measurement of the drug concentration. Important information, such as the maternal dose, the frequency of dose, the time from drug administration to sampling, the frequency of nursing, and the length of lactation, is not given.

The significance of these concentration tables only means that the drug is present in the milk, and they offer no advice to the physician. Because the drug in the nursing infant's blood or urine is not measured, we have little information about the amount that is actually absorbed by the infant from the milk and, therefore, have no way of determining the possible pharmacologic effects on the infant. In fact, a critical examination of the tables that have been published reveals that much of the information was gathered decades ago when analytic methodology was not as sensitive as it is today. Because the discipline of pharmacokinetics was not developed until recently, many of the studies quoted in the tables of the review articles do not precisely look at the time relationship between drug administration and disposition.

Certain things are evident with regard to drugs administered during lactation. It is necessary that physicians become aware of the results of animal studies in this area and of the potential risk of maternal drug ingestion to the suckling infant. Many drugs prescribed to the lactating woman need to be studied more so that their safety during lactation can be assessed. It is clear that if the mother needs a drug that has a moderate-to-high potential to cause infant harm, then she should consider not nursing. The ultimate decision must be individualized according to the specific illness and the therapeutic modality. Nursing should be avoided following the administration of radioactive pharmaceuticals that are usually given to the mother for diagnostic purposes.

CONCLUSIONS

Two basic situations are dealt with throughout this book: (a) risk potential to the fetus of maternal drugs ingested during the course of pregnancy and (b) risk potential to the infant of drugs taken by the mother while nursing.

The obvious solution to fetal and nursing infant risk avoidance is maternal abstinence. However, from a pragmatic standpoint, that would be impossible to implement. Another solution is to disseminate knowledge, in an authoritative manner, to all those involved in the pregnancy and breastfeeding processes: physician, mother, midwife, nurse, father, and pharmacist.

This book helps to fill a communication and information gap. We have carefully evaluated the research literature, animal and human, applied and clinical. Each of the more than 1180 drugs has a risk factor assigned by the manufacturer or ourselves in keeping with the FDA guidelines. We have also assigned our own recommendations for use of these drugs in pregnancy and lactation. We believe that this book will be helpful to all concerned parties in developing the risk:benefit decision.

This is but a beginning. It is our fervent hope that the information gained from the use of this book will cause the concerned parties to be more trenchant in their future decision making, either before prescribing or before ingesting drugs during pregnancy and lactation.

Instructions for Use of the Reference Guide

The Reference Guide is arranged so that the user can quickly locate a monograph. If the American generic name is known, go directly to the monographs, which are listed in alphabetical order. If only the trade or foreign name is known, refer to the Index for the appropriate American generic name. Foreign trade names have been included in the Index. To the best of our knowledge, all trade and foreign generic names are correct as shown, but because these may change, the reader should check other reference sources if there is any question as to the identity of an individual drug. Some prescription combination products are listed in the Index. If not listed, the user should refer to the manufacturer's product information for the specific ingredients, and then use the Reference Guide as for single entities.

Each monograph contains eight parts:

Generic Name (United States)
Pharmacologic Class
Pregnancy Recommendation
Breastfeeding Recommendation
Pregnancy Summary
Fetal Risk Summary
Breast Feeding Summary
References

PREGNANCY SUMMARY

The Pregnancy Summary is intended as a brief overview of the reported data in pregnancy, both animal and human, whereas the Fetal Risk Summary provides the specific details of the data. Both the Pregnancy Summary and the Fetal Risk Summary support the Pregnancy Recommendation.

FETAL RISK SUMMARY

The Fetal Risk Summary is an analysis of the literature concerning use of the drug in pregnancy. The intent is to provide clinicians and others with sufficient data to counsel patients and to arrive at conclusions as to the risk:benefit ratio a particular drug poses for the embryo, fetus, and newborn. The molecular weight of most drugs has been included in the reviews because they help determine if a drug can reach the embryo or fetus but this value, by itself, may not predict the amount crossing the placenta. The major determinant of the drug concentration in the embryo or fetus is the blood concentration of the drug in the mother. Other important factors include the elimination half-life, metabolism, placental blood flow, the placental surface area available for crossing (i.e., correlated to the gestational age), and the lipid solubility, protein binding, and the amount of ionization of the drug at physiologic pH.

Because few absolutes are possible in the area of human teratology, the reader must carefully weigh the evidence, or lack thereof, before utilizing any drug in a pregnant woman. Readers who require more details than are presented should refer to the specific references listed at the end of the monograph. See Definitions for recommendations.

BREASTFEEDING SUMMARY

The Breastfeeding Summary is a brief review of the literature concerning excretion of the drug into human breast milk and the effects, if any, on a nursing infant. Unfortunately, in many cases, there is no published information about use of the drug during lactation. Moreover, when studies do exist, infants often were not allowed to breastfeed. Readers should pay close attention to this distinction (i.e., excretion into milk vs. effects on the nursing infant) when using a

Summary. Those who require more details than are presented should refer to the specific references listed at the end of the monograph. See Definitions for recommendations.

PREGNANCY AND BREASTFEEDING RECOMMENDATIONS

The pregnancy recommendations are intended to assist the reader in determining the level of risk of a specific drug. They only apply to the usual therapeutic dose of the drug in a typical patient. Because the genetic makeup of a specific patient may significantly alter the risk, the recommendations may not apply to the entire population. In addition to the animal reproduction data and known human pregnancy outcomes, the assessment of risk includes, when relevant, other major factors such as route of administration, metabolism to active metabolites, species differences, type of defects, pharmacokinetics, effects of other agents in the drug class, and the embryo-fetal effects of untreated or under treated maternal disease. Moreover, drug exposures represent different levels of risk depending on the stage of pregnancy and, thus, timing of the exposure is critical in determining risk. Because short statements of risk may not always adequately assess the risk throughout the pregnancy, readers are encouraged to review the entire monograph before estimating the risk for a specific patient.

The risks also change during breastfeeding because nearly all reported adverse effects in nursing infants have occurred in infants <6 months of age. The neonate and very young infant are most at risk for toxic effects from drugs present in breast milk. The recommendations for breastfeeding are based on the known toxicity of the drug or similar drugs in adults or children (when known) and the amount of drug excreted into breast milk (if known). Although most drugs taken by the mother are probably present in milk, the milk concentrations are usually unknown. Fortunately, the amounts are usually too low to cause toxicity. However, the therapeutic dose for infants of most drugs is rarely known. Therefore, we used a proposal from the literature (Ito S. N Engl J Med 2000;343:118-28) to classify exposures as clinically insignificant if, in the absence of data suggesting otherwise, the estimated dose ingested by a nursing infant was no more than 10% of the mother's weight-adjusted dose. In some cases, this classification may not be relevant. For example, the potential for neurotoxicity in a nursing infant from long-term maternal use of psychotropic medications continues to be a concern.

DEFINITIONS OF PREGNANCY RECOMMENDATIONS

Compatible

The human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent. Animal reproduction data are not relevant.

No (Limited) Human Data - Probably Compatible

There may or may not be human pregnancy experience, but the characteristics of the drug suggest that it does not represent a significant risk to the embryo-fetus. For example, other drugs in the same class or with similar mechanisms are compatible or the drug does not obtain significant systemic concentrations. Any animal reproduction data are not relevant.

Compatible - Maternal Benefit >> Embryo-Fetal Risk

There may or may not be human pregnancy experience, but the potential maternal benefit far outweighs the known or unknown embryo-fetal risk. Animal reproduction data are not relevant.

Human Data Suggest Low Risk

There is limited human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, including the 1st trimester, suggesting that the drug does not represent a significant risk of developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death) at any time in pregnancy. The limited human pregnancy data outweighs any animal reproduction data.

No (Limited) Human Data - Animal Data Suggest Low Risk

Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). The drug does not cause developmental toxicity (at doses that did not cause maternal toxicity) in all animal species studied at doses ≤10 times the human dose based on body surface area (BSA) or AUC*.

No (Limited) Human Data - Animal Data Suggest Moderate Risk

Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). The drug causes developmental toxicity (at doses that did not cause maternal toxicity) in one animal species at doses ≤10 times the human dose based on body surface area (BSA) or AUC*.

No (Limited) Human Data - Animal Data Suggest Risk

Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). The drug causes developmental toxicity (at doses that did not cause maternal toxicity) in two animal species at doses ≤10 times the human dose based on body surface area (BSA) or AUC*.

No (Limited) Human Data - Animal Data Suggest High Risk

Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). The drug causes developmental toxicity (at doses that did not cause maternal toxicity) in three or more animal species at doses ≤10 times the human dose based on body surface area (BSA) or AUC*.

Contraindicated - 1st Trimester

Human exposures in the 1st trimester, either to the drug itself or to drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). The drug should not be used in the 1st trimester.

Contraindicated - 2nd and 3rd Trimesters

Human exposures in the 2nd and 3rd trimesters, either to the drug itself or to drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavior deficits, or death). The drug should not be used in the 2nd and 3rd trimesters.

Contraindicated

Human exposures at any time in pregnancy, either to the drug itself or to drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death). Animal reproduction data, if available, confirm the risk. The drug should not be used in pregnancy.

No (Limited) Human Data - No Relevant Animal Data

There is no human pregnancy data or relevant data in animals, or the human pregnancy experience, that may or may not include the 1st trimester, is limited. The risk in pregnancy cannot be assessed.

Human Data Suggest Risk in 1st and 3rd Trimesters

Evidence (for the drug or similar drugs) suggests that there may be an embryo-fetal risk for developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death) in the 1st and 3rd trimesters but not in the 2nd trimester. The human pregnancy data outweigh any animal reproduction data.

Human Data Suggest Risk in 2nd and 3rd Trimesters

Evidence (for the drug or similar drugs) suggests that there may be a fetal risk for developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death) in the 2nd and 3rd trimesters but not in the 1st trimester. The human pregnancy data outweigh any animal reproduction data.

Human Data Suggest Risk in 3rd Trimester

Evidence (for the drug or similar drugs) suggests that there may be a fetal risk for developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death) in the 3rd trimester, or close to delivery but not in the 1st or 2nd trimesters. The human pregnancy data outweigh any animal reproduction data.

Human (and Animal) Data Suggest Risk

The human data for the drug or drugs in the same class or with the same mechanism of action, and animal reproduction data if available, suggest there may be a risk for developmental toxicity (growth restriction, structural anomalies, functional/behavioral deficits, or death) throughout pregnancy. Usually, pregnancy exposure should be avoided, but the risk may be acceptable if the maternal condition requires the drug.

**AUC = area under the plasma concentration vs time curve; a measure of the systemic exposure of a drug*

DEFINITIONS OF BREASTFEEDING RECOMMENDATIONS

Compatible
Either the drug is not excreted in clinically significant amounts into human breast milk or its use during lactation does not, or is not expected to, cause toxicity in a nursing infant.

Hold Breast Feeding
The drug may or may not be excreted into human breast milk, but the maternal benefit of therapy far outweighs the benefits of breast milk to an infant. Breastfeeding should be held until maternal therapy is completed and the drug has been eliminated (or reaches a low concentration) from her system.

No (Limited) Human Data - Probably Compatible
Either there is no human data or the human data are limited. The available data suggest that the drug does not represent a significant risk to a nursing infant.

No (Limited) Human Data - Potential Toxicity
Either there is no human data or the human data are limited. The characteristics of the drug suggest that it could represent a clinically significant risk to a nursing infant. Breastfeeding is not recommended.

No (Limited) Human Data - Potential Toxicity (Mother)
Either there is no human data or the human data are limited. The characteristics of the drug suggest that breastfeeding could represent a clinically significant risk to the mother such as further loss of essential vitamins or nutrients. Breastfeeding is not recommended.

Contraindicated
There may or may not be human experience, but the combined data suggest that the drug may cause severe toxicity in a nursing infant, or breastfeeding is contraindicated because of the maternal condition for which the drug is indicated. Women should not breastfeed if they are taking the drug or have the condition.

Comparison of Agents within the Same Pharmacologic Class
The Appendix arranges the drugs by their pharmacologic category. This allows the reader to identify all of the drugs that have been reviewed within a specific category, thus allowing, if desired, a comparison of the drugs. For example, the subsection *Antihypertensives* lists together those agents used for this purpose under the general heading *Cardiovascular Drugs*. To assist the reader in locating an agent in the Appendix, page numbers (in parentheses) referring to the location in the Appendix have been added to the generic names (shown in **bold**) in the Index.

FDA Risk Categories Definitions
Although the FDA risk categories have been excluded from this edition, readers wanting this information can obtain it from the manufacturer's product information.

Contents

A

ABACAVIR

Antiviral

PREGNANCY RECOMMENDATION: Compatible - Maternal Benefit >> Embryo-Fetal Risk

BREASTFEEDING RECOMMENDATION: Contraindicated

PREGNANCY SUMMARY

The animal data suggest moderate risk. Although the human pregnancy experience does not suggest a risk of structural anomalies, other potential developmental toxicities require study. Antiretroviral nucleosides have been shown to have a direct dose-related cytotoxic effect on preimplantation mouse embryos (see Didanosine, Stavudine, Zalcitabine, and Zidovudine). This toxicity has not been studied in humans. Mitochondrial dysfunction in offspring exposed in utero or postnatally to nucleoside reverse transcriptase inhibitors (NRTIs) has been reported (see Lamivudine and Zidovudine), but these findings are controversial and require confirmation. However, if indicated, the drug should not be withheld because of pregnancy.

FETAL RISK SUMMARY

Abacavir is a synthetic carbocyclic nucleoside analogue that is converted by cellular enzymes to the active metabolite, carbovir triphosphate. It is a NRTI used for the treatment of HIV type 1 (HIV-1). Other drugs in this class are didanosine, lamivudine, stavudine, zalcitabine, and zidovudine (1).

In reproduction studies, doses of abacavir up to 8 times the human therapeutic dose (HTD) based on BSA had no effect on the fertility or mating performance of male and female rats. However, embryo toxicity (increased resorptions, decreased body weight) was observed. During organogenesis, doses up to 35 times the human exposure based on AUC (about 16 times the HTD) resulted in fetal growth restriction (reduced body weight and crown–rump length) as well as increased incidences of fetal anasarca and skeletal malformations. Offspring exposed from implantation through weaning had an increased incidence of stillbirth, and survivors had decreased body weights throughout life. In contrast, no developmental toxicity or malformations were observed in rabbits at doses up to 8.5 times the human exposure based on AUC (1).

Abacavir crosses the human placenta. In four women being treated for multiple agents for HIV infection, the mean abacavir cord:maternal blood ratio was 1.03 at a mean of 3.5 hours (range 0.4–9.0 hours) after a dose (dose not specified), and the amniotic fluid concentration in one woman was 1.6 mg/L (2). These results are consistent with the relatively low molecular weight (about 671) and high lipophilic properties of abacavir. In an ex vivo human placental model, the antiviral agent readily crossed to the fetal side with a high clearance index of about 50% that of antipyrine (3). No accumulation of the drug was found on the fetal side.

The Antiretroviral Pregnancy Registry reported, for the period January 1989 through July 2009, prospective data (reported before the outcomes were known) involving 4702 live births that had been exposed during the 1st trimester to one or more antiretroviral agents (4). Congenital defects were noted in 134, a prevalence of 2.8% (95% confidence interval [CI] 2.4–3.4). In the 6100 live births with earliest exposure in the 2nd/3rd trimesters, there were 153 infants with defects (2.5%; 95% CI 2.1–2.9). The prevalence rates for the two periods did not differ significantly. There were 288 infants with birth defects among 10,803 live births with exposure any time during pregnancy (2.7%; 95% CI 2.4–3.0). The prevalence rate did not differ significantly from the rate expected in a nonexposed population. There were 1547 outcomes exposed to abacavir (628 in the 1st trimester and 919 in the 2nd/3rd trimesters) in combination with other antiretroviral agents. There were 45 birth defects (19 in the 1st trimester and 26 in the 2nd/3rd trimesters). In reviewing the birth defects of prospective and retrospective (pregnancies reported after the outcomes were known) registered cases, the Registry

concluded that except for isolated cases of neural tube defects with efavirenz exposure in retrospective reports, there was no other pattern of anomalies (isolated or syndromic) (4). (See Lamivudine for required statement.)

Two reviews, one in 1996 and the other in 1997, concluded that all women receiving antiretroviral therapy should continue to receive therapy during pregnancy and that treatment of the mother with monotherapy should be considered inadequate therapy (5,6). The same conclusion was reached in a 2003 review with the added admonishment that therapy must be continuous to prevent emergence of resistant viral strains (7). In 2009, the updated U.S. Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1–infected patients continued the recommendation that therapy, with the exception of efavirenz, should be continued during pregnancy (8). If indicated, abacavir should not be withheld in pregnancy because the expected benefit to the HIV-positive mother outweighs the unknown risk to the fetus. Updated guidelines for the use of antiretroviral drugs to reduce perinatal HIV-1 transmission also were released in 2010 (9). Women receiving antiretroviral therapy during pregnancy should continue the therapy, but regardless of the regimen, zidovudine administration is recommended during the intrapartum period to prevent vertical transmission of HIV to the newborn (9).

BREASTFEEDING SUMMARY

No reports have been located that describe the use of abacavir during human lactation. The molecular weight (about 671) suggests that the drug will be excreted into breast milk. The effect on a nursing infant is unknown.

Reports on the use of abacavir during human lactation are unlikely because the drug is used in the treatment of HIV-1 infections. HIV-1 is transmitted in milk, and in developed countries, breastfeeding is not recommended (5,6,8,10–12). In developing countries, breastfeeding is undertaken despite the risk because there are no affordable milk substitutes available. Until 1999, no studies had been published that examined the effect of any antiretroviral therapy on HIV-1 transmission in milk. In that year, a study involving zidovudine was published that measured a 38% reduction in vertical transmission of HIV-1 infection despite breastfeeding when compared with controls (see Zidovudine).

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ABATACEPT

Immunologic Agent (Immunomodulator)/Antirheumatic Agent

PREGNANCY RECOMMENDATION: No Human Data - Animal Data Suggest Low Risk

BREASTFEEDING RECOMMENDATION: No Human Data - Potential Toxicity

PREGNANCY SUMMARY

No reports describing the use of abatacept in human pregnancy have been located (1,2). One source recommends discontinuing the drug 10 weeks before pregnancy (2). Developmental toxicity was not observed in three animal species at doses ≤10 times the HD, but the absence of human pregnancy experience prevents a more complete assessment of the embryo and/or fetal risk. The protein does cross the placenta. It is not known if in utero exposure could result in autoimmune diseases in later life (3). Until human pregnancy data are available, the safest course is to avoid use