DRUG USE IN PREGNANCY

JENNIFER R. NIEBYL

DRUG USE IN PREGNANCY

JENNIFER R. NIEBYL, M.D.
Associate Professor
Department of Obstetrics and Gynecology,
Johns Hopkins University School of Medicine
Baltimore, Maryland

Lea & Febiger 1982 Philadelphia

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106
U.S.A.

Library of Congress Cataloging in Publication Data

Drug use in pregnancy.

(Current concepts in obstetrics and gynecology)
Bibliography: p.

Includes index.
1. Obstetrical pharmacology. 2. Fetus—Effect of drugs on. I. Niebyl, Jennifer R. II. Series.
[DNLM: 1. Drug therapy—Adverse effects. 2. Drug therapy—In pregnancy. 3. Substance abuse—In pregnancy. WQ 240 D793]
RG528.D78 1981 615'.766 81-11719
ISBN 0-8121-0813-2 AACR2

PRINTED IN THE UNITED STATES OF AMERICA

Print Number: 3 2 1

FOREWORD

Any book or monograph that covers the topic of "Drug Use in Pregnancy" cannot be all-inclusive for everyone. This monograph was prompted by the interest of the Johns Hopkins group that began as a postgraduate course on the use of drugs during pregnancy. Individuals were selected from this postgraduate course and others added to complete the overall format of this monograph on the use of drugs in pregnancy. There are few, if any, monographs devoted exclusively to this particular topic and this information will be a welcome addition to the literature.

Much concern has been generated since the saga of thalidomide with the identification of a seemingly-mild hypnotic that has the potential to cause profound teratogenesis. The thalidomide story has not been that many years ago but the significance that thalidomide was never introduced into the United States' market alerted the obstetrician, as well as the pregnant woman, against the use of drugs in pregnancy. These events, coupled with the great interest in naturalness and concern about artificiality, have made everyone aware of a cause-and-effect relationship between drugs and the fetal outcome.

Everyone will agree that the one drug the pregnant woman needs is iron. This approach of complete purity is impractical and is not in keeping with diseases that beset the woman and her fetus. This monograph is designed to address the subject of specific drugs in pregnancy and is a state of the art message of what we currently know about their effects on the fetus. Certain agents that are included here are oftentimes not considered as drugs by the pregnant patient and such examples would be caffeine, alcohol, smoking, and analgesic medications. The real problem of drugs in pregnancy is the fact that teratogenic effects usually occur in the early part of pregnancy and frequently the patient may not perceive that she's pregnant or, if she does know she's pregnant, she does not identify herself to a physician until late in the first trimester or the second trimester of pregnancy. The time for drug planning in pregnancy is prior to conception.

The climate in which we currently function in the United States addresses a cause-and-effect relationship between events that take place during pregnancy and the end result. As long as there are no identified problems, regardless of what transpires, everything seems to be appropriate. However, if a fetus is born with a defect or a problem

that is less than desirable, then the issue emerges as to whether or not a cause-and-effect relationship can be established and, if so, does a medical-legal problem exist. Many of these issues are addressed in this monograph but the bottom-line issue is always appropriate documentation of events.

It is indeed a privilege and a pleasure for the monograph series by Lea & Febiger to introduce this important text to the practicing physician. This multi-authored monograph, edited and authored by Dr. Jennifer Niebyl, identifies physicians with expertise in each of their areas. We are grateful for this significant scientific contribution to the literature.

Frederick P. Zuspan, M.D.

PREFACE

"Behold, thou shalt conceive, and bear a son; and now drink no wine nor strong drink, neither eat any unclean thing."

Judges 13:7

Caution with regard to dietary intake during pregnancy has been advised since ancient times. However, until recently the fetus has been thought to rest in a privileged site, with little exposure to the environment experienced by the mother. The term "placental barrier" has been in widespread use, but is truly a contradiction as the placenta allows ready crossing of many drugs and dietary substances.

Lipid soluble substances readily cross the placenta, whereas water soluble substances pass less well the greater their molecular weight. The degree to which a drug is bound to plasma protein also influences the amount of drug which is free to cross. Virtually all drugs cross the placenta to some degree, with the exception of large organic ions such as heparin and insulin which pass poorly or not at all.

Since the thalidomide tragedy of 1956, pregnant patients have frequently questioned the safety of drug use during pregnancy. With the data produced from the Collaborative Perinatal Project the first large prospective study of drug use during pregnancy became available. Many authors in this volume have relied heavily on the data published by Heinonen, Slone and Shapiro,[1] as it is our best information to date with regard to possible teratogenic effects of drug use in the first trimester.

Although no evidence for teratogenicity of a drug may be present, if an event occurs with a low frequency, many thousands of cases may be needed to identify a small risk. Thus, although there may be no evidence that a drug is teratogenic, this does not mean that it cannot be a teratogen with low frequency, and so caution is advised with respect to taking any drugs in early pregnancy.

With the description of adverse effects of smoking and alcohol use during pregnancy, awareness developed that risks of drug use extend beyond the first trimester. Although gross morphologic abnormalities

[1]Heinonen OP, Slone D, and Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, Massachusetts, Publishing Sciences Group, Inc., 1977.

are produced at the time of organogenesis, beyond this point the internal organs, the genitalia and brain continue to develop and can be adversely affected by drugs such as diethylstilbestrol, alcohol, and smoking. Also, obstetrical adverse effects such as abruptio placenta, intrauterine growth retardation, and preterm delivery have now been shown to be influenced by smoking. Adverse effects of narcotic use in pregnancy may be most obvious even beyond the delivery when withdrawal symptoms occur in the neonate.

This volume is designed to provide information of use to practitioners about the effects of exposure to drugs during pregnancy. Common drugs such as mild analgesics, antiemetics, and antibiotics are covered as well as less frequently used drugs such as anticoagulants and antineoplastic agents. Attention is also given to specific effects of drugs such as 17α-hydroxyprogesterone caproate (Delalutin), corticosteroids and tocolytic agents in the prevention and management of preterm delivery. Although not all drugs can be covered in a series such as this, these authors were chosen because of their expertise and interest in the particular drugs discussed.

I would like to thank Mrs. Carol Parks who provided excellent secretarial assistance in the typing of several of the manuscripts.

Baltimore, Maryland — Jennifer R. Niebyl, M.D.

CONTRIBUTORS

Richard Berkowitz, M.D.
Associate Professor,
Yale University School of Medicine,
Department of Obstetrics and Gynecology,
New Haven, Connecticut 06510

David A. Blake, Ph.D.
Associate Professor
Departments of Gynecology/Obstetrics and Pharmacology,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

John N. Chappel, M.D., F.R.C.P.(C)
Professor of Psychiatry,
School of Medical Sciences, University of Nevada,
Career Teacher in Alcohol and Drug Abuse,
Reno, Nevada 89557

Loretta P. Finnegan, M.D.
Associate Director of Nurseries,
Associate Professor of Pediatrics, Psychiatry and Human Behavior,
Director of Family Center Program,
Jefferson Medical College,
Philadelphia, Pennsylvania 19107

Edward Goldberg, M.D.
Assistant Professor, Department of Gynecology and Obstetrics,
The Johns Hopkins Hospital,
Baltimore, Maryland 21205

Kamal A. Hamod, M.D., M.P.H.
Assistant Professor, Gynecology and Obstetrics,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

John W.C. Johnson, M.D.
Associate Professor, Obstetrics and Gynecology,
Director, Division Maternal-Fetal Medicine,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Timothy R.B. Johnson, Jr., M.D.
Instructor, Department of Gynecology and Obstetrics,
Fellow, Division of Maternal-Fetal Medicine,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Victor A. Khouzami, M.D.
Instructor, Gynecology and Obstetrics,
Fellow, Maternal-Fetal Medicine,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Mary Jeanne Kreek, M.D.
Senior Research Associate and Physician,
The Rockefeller University,
New York, New York 10021

Paul S. Lietman, M.D.
Wellcome Associate Professor, Clinical Pharmacology
Associate Professor, Medicine, Pediatrics, Pharmacology and
Experimental Therapeutics,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Keith D. Maxwell, M.D.
Instructor, Department of Obstetrics and Gynecology,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Irwin R. Merkatz, M.D.
Professor, Obstetrics and Gynecology
University Hospitals of Cleveland,
Cleveland, Ohio 44106

Mary B. Meyer, ScM
Associate Professor,
The Johns Hopkins University School of Hygiene
and Public Health,
Baltimore, Maryland 21205

Jennifer R. Niebyl, M.D.
Associate Professor, Gynecology and Obstetrics,
The Johns Hopkins Medical Institutions,
Baltimore, Maryland 21205

Robert Romero, M.D.
Instructor, Yale University School of Medicine,
Department of Obstetrics and Gynecology,
New Haven, Connecticut 06510

Stephen P. Spielberg, M.D., Ph.D.
Assistant Professor of Pediatrics,
Assistant Professor of Pharmacology and Experimental Therapeutics,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Jeffrey L. Stern, M.D.
Chief Resident and Fellow,
Department of Gynecology and Obstetrics,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205

Barry Stimmel, M.D.
Associate Dean of Academic Affairs,
Associate Professor of Medicine,
Mount Sinai School of Medicine of the City University of New York,
New York, New York 10029

Joan Stryker, M.D.
Associate Professor of Obstetrics and Gynecology,
Wayne State University School of Medicine,
Administrator of Hutzel Hospital Pregnant Addict
Methadone Program,
Detroit, Michigan 48201

CURRENT CONCEPTS IN
OBSTETRICS AND GYNECOLOGY

Frederick P. Zuspan, M.D., *Editor*

Department of Obstetrics and Gynecology
Professor and Chairman
The Ohio State University College of Medicine
Columbus, Ohio
and
Obstetrician-Gynecologist-in-Chief
University Hospitals
Columbus, Ohio

Series Books

Greenblatt, Robert B.: Induction of Ovulation, 1979, 167 pp. $14.75 (Canada $17.75)
Ledger, William J.: Infection in the Female, 1977, 240 pp. $12.00 (Canada, $14.50)
Lindheimer, Marshall D. and Katz, Adrian J.: Kidney Function and Disease in Pregnancy, 1977, 241 pp. $15.00 (Canada $18.00)
Sabbagha, Rudy E.: Ultrasound in High-Risk Obstetrics, 1979, 108 pp. $11.00 (Canada $13.25)

CONTENTS

CHAPTER

1

REQUIREMENTS AND LIMITATIONS IN REPRODUCTIVE AND TERATOGENIC RISK ASSESSMENT

David A. Blake

Prompted by the thalidomide incident of the early 1960s, regulatory agencies initiated requirements for animal testing of therapeutic drugs that hopefully would detect teratogenic potential prior to their widespread distribution. The experience of two subsequent decades of extensive testing has failed to demonstrate the reliability of animal studies in the prediction of human teratogenic potential. There are so many examples of inconsistency between results of animal teratologic studies and the human experience that a credibility gap has developed. Epidemiologic studies have shown that numerous drugs have insignificant human teratogenic potential,[4] and yet many of these drugs have produced positive results in multiple laboratory animal species.[13] This chapter will outline the current procedures for in vivo teratogenicity testing in animals, discuss probable reasons for their limitations, and provide a preliminary critical evaluation of the degree of predictability.

PROCEDURES

Teratogenicity means the capacity to induce congenital monsters. Historically the focus has been on *major overt morphologic* abnormalities. There is, however, a growing tendency to broaden the

definition of teratogenicity beyond *major dysmorphogenesis* by including minor and latent (covert) structural abnormalities. Furthermore, it is recognized that functional behavioral abnormalities should also be considered, particularly in mature offspring. Unfortunately, the majority of teratologic testing has focused only on the state of anatomic development at the end of pregnancy.

Pregnant animals are treated during the period of embryonic development (organogenesis) (Fig. 1–1) and fetuses are removed from killed mothers a few days prior to parturition. It is argued that mothers will cannibalize abnormal or dead offspring if allowed to deliver spontaneously. The usual periods of treatment (in days of gestation with day zero being the day of conception) are: mice and rats—6 to 15 days; rabbits—6 to 18 days. Treatments are avoided before and after these periods to minimize the chance that the teratogenic potential of a chemical might be obscured by its lethal effect on the conceptus. In addition, there is some evidence that initiating treatment substantially before the critical period of gestation will provide an opportunity for induction of detoxification enzyme activity resulting in reduced fetal exposure to the agent. Potential embryolethality is evaluated by decreased litter size or disparity between ovarian corpora lutea and implantations.

It is common practice to evaluate gross abnormalities initially and then to group living fetuses for examination of visceral anomalies or skeletal anomalies. Results are separately tabulated as: litter size

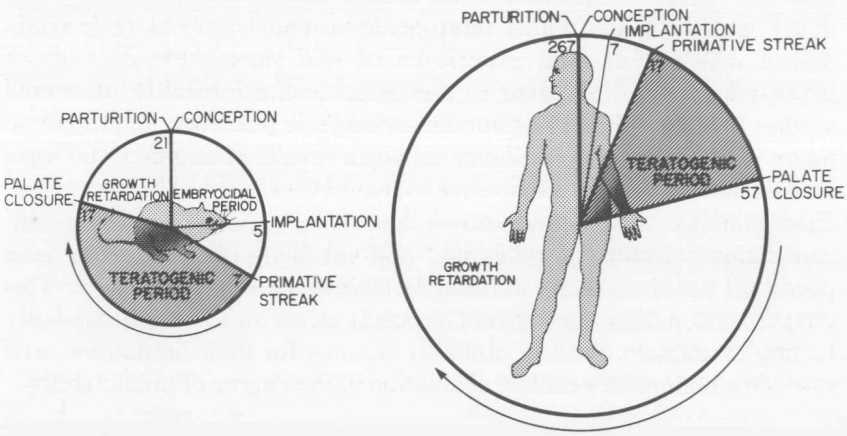

Figure 1–1. *Gestational Clocks. These diagrams indicate the approximate gestational days encompassing the classic teratogenic period for rats and humans. This period coincides with the period of organogenesis and is the time of greatest sensitivity to dysmorphic abnormalities. (It should be noted that the common clinical practice is to date the beginning of pregnancy as the first day of the last menstrual period which adds at least 14 days to those shown above.)*

(number of implantations), lethal effect (number of resorbed embryos and dead fetuses), teratogenic effect (number of malformed live fetuses), and fetal growth retardation (reduced body weight of live fetuses). The practice of separate categorization of offspring hampers statistical analysis for dose-related effects since an embryopathic chemical often causes primarily deaths at high levels resulting in decreased apparent malformation rates. In studies with thalidomide in rabbits, Schumacher et al[12] demonstrated a linear relationship between the log of dose and total "abnormalities" when dead or malformed fetuses were considered to be abnormal. Such a categorization seems reasonable unless fetal death and fetal malformation can be shown to be mutually exclusive events. A linear dose-response curve provides the opportunity for statistical determination of the 50% embryopathic effect level which can be compared to the maternal LD_{50} for evaluation of direct embryotoxicity. Using this approach to evaluate animal teratogenicity data from the literature, Jusko[6] has demonstrated that drugs can be classified into two categories: those that have a dose threshold for teratogenic effect and those that do not. The former group (including aspirin) has 50% embryopathic doses that are close to the maternal lethal doses, whereas the latter group (including thalidomide) has greater direct embryopathic potential. Presumably, there is greater teratogenic risk with a compound that has no apparent threshold to its effect and causes malformations at a dose level considerably below that causing maternal toxicity. Although such dose-effect analyses are common in other branches of toxicology, it is rare to find them in the teratologic literature.

Multigeneration reproductive studies have been advocated by regulatory officials[8] although an advisory panel has questioned their value beyond the second filial generation.[1] It is generally accepted that a complete evaluation of reproductive toxicity should include study of the reproductive performance in the F_1 animals which have been exposed continuously to the test substance from the time of conception and during the periods of embryogenesis, infancy, puberty, and reproductive maturity. This assessment requires observation of the growth and development of the F_2 generation through weaning.

POSSIBLE REASONS FOR DEFICIENCIES

Dosage. As previously discussed, meaningful interpretation of teratologic studies requires consideration of the relationship between the teratologic dose range and the maternal toxic dose range. Since abnormal fetal development is likely to result if the mothers are "sick," it is generally recommended that the highest dose level produce minimal, but measurable, maternal toxicity. Indirect

"pseudoteratogenicity" can also occur if the treatment causes excessive depression of maternal eating or drinking.[5,7]

Pharmacokinetics. The fraction of administered dose ultimately reaching sites of teratogenic action in the conceptus or placenta is governed by multiple kinetic factors including rates of absorption, biotransformation, placental passage, and maternal excretion. Inconsistent teratologic results between experiments, laboratories, species, and strains of animals can often be explained by variations in these factors. Keller and Blake[7] demonstrated a 400% difference in plasma levels of thalidomide in rabbits depending on the oral dosage formulation. The widely investigated strain-dependent susceptibility of mice to cortisone-induced anomalies correlates with slower maternal elimination of the drug in the more susceptible strain.[10] Although transport of chemicals across the placenta late in gestation has received a great deal of experimental attention, there is much less information on maternal-fetal exchange early in gestation when morphologic teratogenesis is induced. Moreover, there is a complete void in our knowledge of the amount of maternally administered drug reaching the early human embryo at known levels of exposure. Thus, it is difficult to devise rational dosing regimens in animal experiments that would be relevant to the human situation.

Until recently, it was thought that the fetus lacked the enzyme activity responsible for biotransformation of drugs and other xenobiotics. Through improved analytic methodology it is now known that fetal liver, particularly in primates, possesses many of the metabolic capabilities of adult liver. Some of these metabolic transformations result in the formation of reactive metabolites that can bind to cellular macromolecules and thereby cause cancer, mutations, and cell death. Emerging evidence suggests that metabolites play a role in the mechanism of embryopathy. Because the enzymatic activity responsible for these reactions is related to genotype and multiple environmental factors, it may also provide an explanation for species and other variations in teratologic results. The anticonvulsant phenytoin (Dilantin) is metabolized to a dihydrodiol metabolite via a reactive arene oxide intermediate. The arene oxide intermediate presumably binds covalently to fetal macromolecules and may be the cause of the well-documented teratogenic effect of the drug in mice.[11] Studies in our laboratory have shown a species correlation between susceptibility to phenytoin-induced teratogenesis and formation of the dihydrodiol metabolite in fetal liver.[2] There is also a strain-dependent embryopathic sensitivity to certain polycyclic aromatic hydrocarbons (PAH's) in mice which is related to the genotype determining inducibility of aryl hydrocarbon hydroxylase (AHH).[9] AHH converts PAH's to reactive toxic metabolites. We have recently found that fetal livers from four strains of mice activate benzo(a)pyrene to mutagenic

metabolites at an efficiency that linearly correlates with their induced levels of AHH.[3] These findings provide a basis for the widely discussed genetic-environmental interactions that presumably subserve multifactorial inheritance of susceptibility to birth defects.

PREDICTABILITY OF TERATOGENIC POTENTIAL

The ultimate utility of any animal toxicologic testing procedure depends on the degree of extrapolatability to human beings. Thalidomide is the only chemical known to have a profound teratogenic effect in humans at non-toxic maternal dose levels and the failure to detect positive results with standard teratologic tests in mice and rats is well known. It was determined retrospectively that thalidomide was teratogenic in rabbits and monkeys but there is no assurance that these species would be better predictors for other human teratogens. Since there are only a few drugs with known human teratogenic potential,[4] it is difficult to evaluate predictability against known positives.

In contrast, there are numerous therapeutic drugs now known to have little or no human teratogenic risk.[4] This information is derived from a review of the data from the Perinatal Collaborative Project, a prospective and concurrent epidemiologic study of more than 50,000 pregnancies. The ascertainment of drug exposure in the first four months of pregnancy and uniformity of categorization of major structural anomalies is unparalleled by any other study to date. For many popular drugs, there were sufficient numbers of exposed cases to permit statistical confidence of the lack of teratogenic effect, at least under prevailing conditions of use. The results obtained for 16 drugs are listed in Table 1–1; values are given for the number of exposed cases (at least 100 for each drug selected) and the relative risk ratio after standardization for race, and survival. A ratio of 1.0 indicates an identical frequency of congenital anomalies between exposed and non-exposed cases. The only drug on this list with a ratio significantly greater than unity is insulin. As maternal diabetes is known to be associated with an increased risk of congenital anomalies, this cannot be construed as cause and effect. Also, shown in the table are the results of animal teratologic tests in various species taken from the reference text of Shepard.[13] A degree of subjective judgment was required to translate Shepard's comments into + or − categories and no consideration is given to the relevance of dose levels employed.

It can be seen that for 8 of 16 drugs (aspirin, salicylamide, sulfisoxazole, phenytoin, phenobarbital, meclizine, prochlorperazine and d-amphetamine) there was disagreement between animal tests and the human experience; the animal test results were positive (for at least