Clinical Pharmacology in Pregnancy

Fundamentals and Rational Pharmacotherapy

Helmut P. Kuemmerle, M.D., F.R.S.M.

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Helmut P. Kuemmerle, M.D., F.R.S.M.
Specialist in Obstetrics and Gynecology, Clinical Pharmacology and Chemotherapy
Visiting Professor; Tokyo Medical College, Tokyo
Visiting Professor: Clinical Pharmacology, Hanyang University College of Medicine, Seoul

Co-editor:

Klaus Brendel, Ph.D.
Department of Pharmacology and Toxicology
University of Arizona Health Sciences Center
Tucson, Arizona

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Preface

Clinical pharmacology is the theory of the rational formation of judgments in pharmacotherapy. In other words, it is concerned with experimental and applied clinical testing of therapeutic effects on human subjects.

Pregnancy is a particular phase of life that requires special attention in every respect, especially from the clinico-pharmacologic point of view. The maternal-placental-fetal unit, the triad, has to be understood as a biologic, pharmacokinetic, and pharmacodynamic unit. Consequently the concern of the mother cannot be dealt with alone, but rather both mother and embryo/fetus have to be included in all prophylactic and therapeutic considerations.

The principal target of drugs administered in pregnancy is the mother; the fetus is essentially an unwanted recipient. This feature will be sustained throughout pregnancy up into the early neonatal life, as the possibility for the drug transfer via breast milk in the nursing mother remains. The risk/benefit ratio has to be considered in every respect in pregnancy because fetal effects primarily of a toxic or negative nature have become a major problem in pregnancy-associated therapeutics.

The concern of this book is to consider the current status and the actual role of clinical pharmacology in pregnancy for the rational use and for the evaluation of drug prophylaxis and drug therapy in pregnancy. It should be considered as a basic constituent for today's drug development, drug prophylaxis, drug therapy, and drug safety in pregnancy.

All aspects and principles that are important for the rational use of drugs in pregnancy are discussed and interpreted from the fundamental up to the practical use of the various drug classes. This book will be a reliable guide and a valuable source of information for all involved in prescribing and using drugs in pregnancy. It is a clinically oriented and well documented text providing all physicians with an indispensable guide to contemporary drug therapy in pregnancy available and known today.

Clinical Pharmacology in Pregnancy brings together the knowledge, experience, and understanding of the fundamentals and principles of drugs and pharmacotherapy of 29 eminent international contributors.

We are very grateful to our publisher, especially Dr. Günther Hauff, Mr. Achim Menge, Mrs. Jill Rudansky, and Mr. James Costello for their good cooperation as well as for their patience.

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H. P. Kuemmerle
K. Brendel

Contributing Authors

Ingrid Amon, M.D.
Professor of Clinical Pharmacology
Institute of Clinical Pharmacology
University of Greifswald
Greifswald, German Democratic Republic

William Banner, Jr., M.D., Ph.D.
Professor of Pediatrics
Department of Pediatrics
University of Arizona Health Sciences Center
Tucson, Arizona

Klaus Brendel, Ph.D.
Professor of Pharmacology and Toxicology
Department of Pharmacology
University of Arizona Health Sciences Center
Tucson, Arizona

Erwin Deutsch Dr.jur.
Professor of Law
Forschungsstelle für Arzt-und Arzneimittelrecht des Juristischen Seminars der Universität
Federal Republic of Germany

Raymond C. Duhamel, Ph.D.
Department of Pharmacology
University of Arizona Health Sciences Center
Tucson, Arizona

D. F. Hawkins, M.D., Ph.D.
Professor of Gynecology and Obstetrics
Hammersmith Hospital
Institute of Obstetrics and Gynecology
London, United Kingdom

S. Hayashi, M.D.
Department of Obstetrics and Gynecology
Kyoto University School of Medicine
Tatsuno City, Japan

Keith Hillier, Ph.D.
University of Southampton
Southampton, United Kingdom

G. Hitzenberger, M.D.
Professor of Clinical Pharmacology
Department of Clinical Pharmacology
First Medical University Clinic
Vienna, Austria

Hansgeorg Hüller, M.D.
Professor of Clinical Pharmacology
Institute of Clinical Pharmacology, Charite
Humboldt University
Berlin, German Democratic Republic

S. Katagiri, M.D.
Department of Obstetrics and Gynecology
Hirosaki University School of Medicine
Hirosaki, Japan

K. Kido, M.D.
Department of Obstetrics and Gynecology
Kyoto University School of Medicine
Tatsuno City, Japan

Hans Kopera, M.D.
Professor of Clinical Pharmacology
Department of Experimental and Clinical Pharmacology
University of Graz
Graz, Austria

Helmut P. Knemmerle, M.D., F.R.S.M.
Prof. (vis.) of Clinical Pharmacology, Tokyo Medical College
Prof. (vis.) of Clinical Pharmacology, Hanyang University College of Medicine, Seoul
Specialist in Obstetrics and Gynecology, Clinical Pharmacology and Chemotherapy
Bad Heilbrunn, Federal Republic of Germany

G. Laudahn, M.D.
Professor of Internal Medicine
Clinical Research Department
Schering AG
Berlin, Germany

Seiji Matsuda, M.D.
Professor of Gynecology and Obstetrics
Kohto Hospital
Juntendo University
Tokyo, Japan

Teresita Mazzei, M.D.
Professor of Pharmacology
Cattedra di Chemioterapia
Univerita degli studi di Firenze
Firenze, Italy

Domenico Pecorari, M.D.
Professor of Gynecology and Obstetrics
Department of Obstetrics and Gynecology
University of Trieste Ospedale Maggiore
Trieste, Italy

Roger M. Pinder, Ph.D.
CNS Research
Organon International BV
Oss, The Netherlands

D. Reinhardt, M.D.
Professor of Pediatrics
University Children-Hospital A
Duesseldorf, Federal Republic of Germany

O. Richter
Professor of Biometrics and Mathematics
Institut für Landwirtschaftliche Betriebslehre
Abteilung für Angewandte Statistik und Mathematik d. Universität Bonn
Bonn, Federal Republic of Germany

W. A. Ritschel, Ph.D.
Professor of Pharmacokinetics
University of Cincinnati Medical Center
Cincinnati, Ohio

Roberto Serra, M.D.
Professor of Phthisiology
Invited Professor
University of Louvain
Belgium

Shinryo Shinagawa, M.D.
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Hirosaki University School of Medicine
Hirosaki, Japan

Hiroaki Soma, M.D.
Professor of Gynecology and Obstetrics
Department of Obstetrics and Gynecology
Tokyo Medical College Hospital
Tokyo, Japan

Heini Stamm, M.D.
Professor of Gynecology and Obstetrics
Clinic of Obstetrics and Gynecology
Kantons-Hospital
Baden, Switzerland

H. Tuchmann-Duplessis
Professor of Embryology
Laboratory of Embryology
Rene Descartes University
Paris, France

Leo Wisliçki, M.D.
Professor of Gynecology and Obstetrics
The Hebrew University
Hadassah Medical School
Jerusalem, Israel

Noritsume Yamada, M.D.
Professor of Gynecology and Obstetrics
Department of Obstetrics and Gynecology
Kyoto University School of Medicine
Tatsuno City, Japan

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I
Fundamentals of Drug Therapy in Pregnancy

1

Introduction

H. P. Kuemmerle

Introductory Remarks on the Problem Complex

For pharmacotherapy (and thus also for clinical drug trials) pregnancy is a special phase of life that, in general and in particular, differs from all others on medical, ethical, and, above all, legal grounds. However brutally, the well-known drug scandals (Thalidomide, Menocil) have made the public acutely aware of the complex problem. Still, it is once again evident how briefly public attention focuses on such events. The term *drug safety* was initially taken very seriously, but in recent times it has become of symbolic importance only. The problem has not yet been completely grasped in all its sociopolitical ramifications and in the light of its inevitable and serious consequences. To best protect and preserve each individual from questionable treatment, harm, and exposure to arbitrary decisions, the concept of drug safety must be included among genuine sociopolitical necessities.

In this context, the human being must be seen not only as a biologic but also as a social unit, although the various factors cannot always be isolated. Within the physician's realm of responsibility there are few opportunities to counter harmful influences that arise exogenously, except by means of chemical substances—i.e., drugs. In the vast majority of cases this is the only way to affect such influences. This is particularly true for all pharmacotherapeutic measures and all clinical drug trials during the childbearing years.

In the early stages the physician cannot be sure whether a woman of childbearing age is pregnant or not. Precisely because of this, the strictest standards must be observed during this life phase. If medication is required, it must be given only under conditions of the greatest precision and expertise, and always with critical distance. However, it would certainly be a mistake to assume an attitude of therapeutic nihilism because of these strictures. A good rule of thumb ought to be "as few drugs as possible," and those few drugs should be tried and tested ones, never new substances, nor combinations whose characteristic effects are little or not at all known.

The maternal-placental-fetal triad must be understood as a biologic, pharmacokinetic, and pharmacodynamic unit. Consequently, one may not deal with the concerns of the mother alone, but rather mother *and child* have to be included simultaneously in all therapeutic considerations.

As regards the clinicopharmacologic or clinicotherapeutic aspects of a drug, the embryo or fetus has a uniquely specific sensitivity that is not at all comparable with that of the adult. Since adult dosage must be administered to the mother, serious and often irreversible side effects and damage may become manifest in the embryo or fetus, or in the newborn. Thus, any risk of possible injury to the embryo or fetus must be judged too great.

Of course, one exception can be considered permissible: namely, new drugs that are specifically developed for therapeutic use in gravidas and have a predictable chance of success. This exception, however, is only permissible if under two conditions: (a) All legal provisions and the guidelines laid down by professional medical organizations and internationally recognized organizations (e.g., the Declaration of Helsinki, WHO); must be adhered to, and (b) preclinical data that are complete according to the current state of knowledge must be available. If there is the slightest suspicion of possible harm, the trials should be immediately terminated and not resumed until findings from new, nonobjectionable animal experiments approved by an unbiased committee of experts are available.

All those involved in clinical investigations,

whether clinical pharmacologists or specialists, whether engaged in clinical medicine, general medicine, or industry, when participating in special investigations in women of childbearing age and during pregnancy, must let their actions and thinking be guided by the keenest sense of responsibility and duty to conscientiousness. They must foreswear all avant-garde, careerist, and egoistic motivations.

In the maternal-placental-fetal unit the interests of the embryo or fetus and mother can be diametrically opposed, i.e., drug concentrations that are harmless for the mother can clearly influence or damage the embryo or fetus, and vice versa. There is still no completely reliable way known, on the basis of animal experiments, to preclude teratogenic effects, much less to exclude them. Retrospective investigations on humans are the only way to ensure relative innocuousness.

A plethora of questions arises from these considerations. The decisive question nowadays is no longer whether a drug can or cannot be transferred dia- or paraplacentally, but rather: How rapidly does this passage take place? What concentrations are reached in the embryo or fetus? Is the concentration changed or is the drug even totally destroyed during its passage into the placental membrane? The most important question to each physician is: What changes can the drug cause in the embryo or fetus?

The time of initiation and the duration of drug therapy are directly related to the injury triggered. Also of importance are the pharmacokinetic and pharmacodynamic qualities of the substance itself. Special attention must be paid to the fact that the placental membrane behaves selectively toward compounds that are closely related structurally and that have similar pharmacologic and toxic effects on the fetus. The stage of development of the fetal detoxifying and catabolic mechanisms crucially affects the drug's duration of action. Since our present knowledge of the effects of different drugs on the fetus is severely limited, we must refrain wherever possible from administering any drug during pregnancy, especially if there is some vague reason to suspect gravidity.

The therapeutic or prophylactic benefits of a medication must always be carefully weighed against possible damage to the fetus. Pharmacokinetics and pharmacodynamics are directly related to diaplacental passage, since the placenta seems permeable to most drugs. One might assume that only the drug's concentration in the maternal blood and how long that concentration will be maintained will affect the concentrations of the drug reached in the fetal circulation. *But* one should always remember that (a) a concentration that produces a specific effect in the mother will not always be the same in the fetal circulation, and (b) the sensitivity of the embryo or fetus can vary throughout pregnancy. Indeed, concentrations and duration of retention in the fetal blood vary over a broad range.

Drugs can be divided into three groups:

1. Drugs that do not pass through the placenta, and thus can do no direct damage.
2. Drugs with diaplacental passage in the sense of a shallow compartment with which damage is possible.
3. Drugs with both diaplacental passage and fetal accumulation, with which damage is slightly possible.

A general knowledge of the distribution ratio, i.e., the relationship between serum and tissue concentration at any given time (time-dependent), is needed as a parameter to determine the passage of a substance from the mother to the embryo or fetus. Most often, however, a time shift in the concentration curves of both is observed; thus, knowledge of the distribution ratio but rarely permits firm conclusions about the actual and effectual intrauterine concentrations of the drug.

The pharmacologic consequences of drugs administered during the first and second halves of pregnancy can be recognized in changes or developmental disturbances in the fetus or newborn. At the present time they at least allow us to draw certain conclusions about exogenous noxa, e.g., drugs. We now have a reasonably certain understanding of many specific effects on certain organ rudiments, as well as the pronounced phase specificity of drugs in the sequential steps of organ genesis. However, this information is valid only for morphologic research; about the functional stages, i.e., the biochemical mechanisms, we know almost nothing. The indirect effects exerted on the fetus by influences on the maternal function have also been seldom investigated and little is known about them. We can justifiably assume, however, that an insufficient detoxifying function of the maternal liver or kidneys is not without effect on the fetus.