DRUG THERAPY IN OBSTETRICS AND GYNECOLOGY

William F. Rayburn
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Drug Therapy in Obstetrics and Gynecology

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Preface

Numerous drugs are prescribed to treat a variety of obstetric and gynecologic disorders in ambulatory and hospital settings. Furthermore, many drugs used in the treatment of other disorders may affect the course of a woman's pregnancy, the health of her fetus or neonate, or her reproductive function. Information about drug therapy is increasing as further clinical knowledge expands in the subspecialties of maternal-fetal medicine, reproductive endocrinology, and gynecologic oncology. With these considerations and despite heavy workloads, clinicians are asked to provide quality health care and be aware of implications from the use of currently prescribed drugs. Consequently, an effort to find in-depth information about drug therapy may be time-consuming and often frustrating.

Several texts are already available which discuss therapy of specific disorders in obstetrics and gynecology. Instead, this book provides information about specific drugs used in daily clinical practice. Current drug therapy is reviewed in a concise and comprehensive manner in each of the three major sections: obstetrics, gynecology, and drugs for general use. Each chapter introduces the nature of certain disorders or patient concerns and then describes the characteristics and indications for the use of each drug. The chapters were planned, written, and revised by the combined efforts of individuals within the following disciplines: obstetrics and gynecology, pharmacology, pharmacy, neonatology, anesthesiology, and psychiatry. Along with a review of the current literature, many useful tables and figures are included for quick reference. Over-the-counter drugs are discussed, and comparative cost considerations are also featured when appropriate.

We hope that this text is instructive to clinicians, house officers, and students for improving patient care through the safe, accurate, and rational use of drugs in the specialties of obstetrics and gynecology.

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Contents

PART ONE: OBSTETRICS

1. Principles of Perinatal Pharmacology

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Pharmacology is the science which deals with the study of drugs and the complex interaction of pathways for the absorption, distribution, metabolism, and excretion of drugs (Fig. 1-1). The absorption of a drug across a membrane (gastrointestinal, placenta, or into breast milk) is related to the following factors: the chemical properties of the drug (molecular weight, spatial configurations, degree of protein binding, ionic dissociation or pKa, lipid solubility); tissue pH; drug concentration; and exposure time. Nonionized, low molecular weight, lipid-soluble compounds are usually well absorbed. The most common mechanism of drug transport across a membrane is passive or simple diffusion from a high to a low concentration. Facilitated diffusion which requires a carrier, and active transport, which requires energy transport across a concentration gradient, are less common transport mechanisms for drugs.

The distribution of absorbed drugs in the bloodstream and tissues is dependent on drug-binding to proteins, local blood perfusion, capillary permeability of the unbound or "free" drug, pH of the target tissue, and membrane permeability. A drug crosses cell membranes selectively by many transport mechanisms and binds to intracellular receptors. The duration of a drug effect is related to the route of administration, dissolution rate, dose, time required to reach equilibrium, half-life of the drug, and degree of drug-receptor binding.

The metabolism of a drug is a complex event occurring primarily in the liver, and is carried out by microsomal enzymes. Representative drug metabolism reactions include oxidation, reduction, dealkylation, and synthesis. These processes transform drugs into either active or inactive compounds. Most reactions form more polar, and therefore more water-soluble, compounds which can be eliminated by the kidney.

The excretion of metabolized drugs by the kidneys is related to the volume of distribution of the drug, glomerular filtration rate, renal tubular reabsorption, urine pH, and tubular secretion. Lipid-soluble, nonionized compounds are more likely to be reabsorbed than compounds which are significantly ionized at the pH of the urine. Excretion from the intestines (in bile), lungs, and sweat glands is less common but significant for certain drugs.

Drug-drug interactions are encountered frequently and can interfere with absorption, plasma and tissue protein-binding, access to cell receptors, and renal excretion. Certain drugs may also induce (phenobarbital) or inhibit (disulfiram) enzymes responsible for the metabolism of other drugs or endogenous substances.[1]

The identification and quantitation of drugs and their metabolites have been accomplished primarily by the newest techniques in radioimmunoassay (RIA), combined gas chromatography and mass spectrometer (GC-MS) computer systems, and high-pressure liquid chromatography (HPLC). Animal and human experiments utilizing these and other instru-

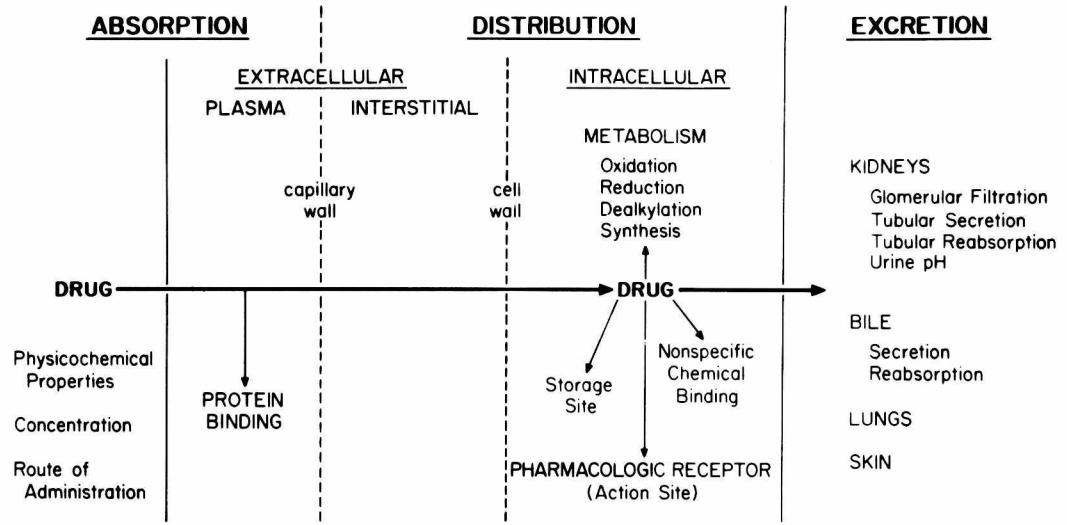

Figure 1-1. Pathways of drug metabolism.

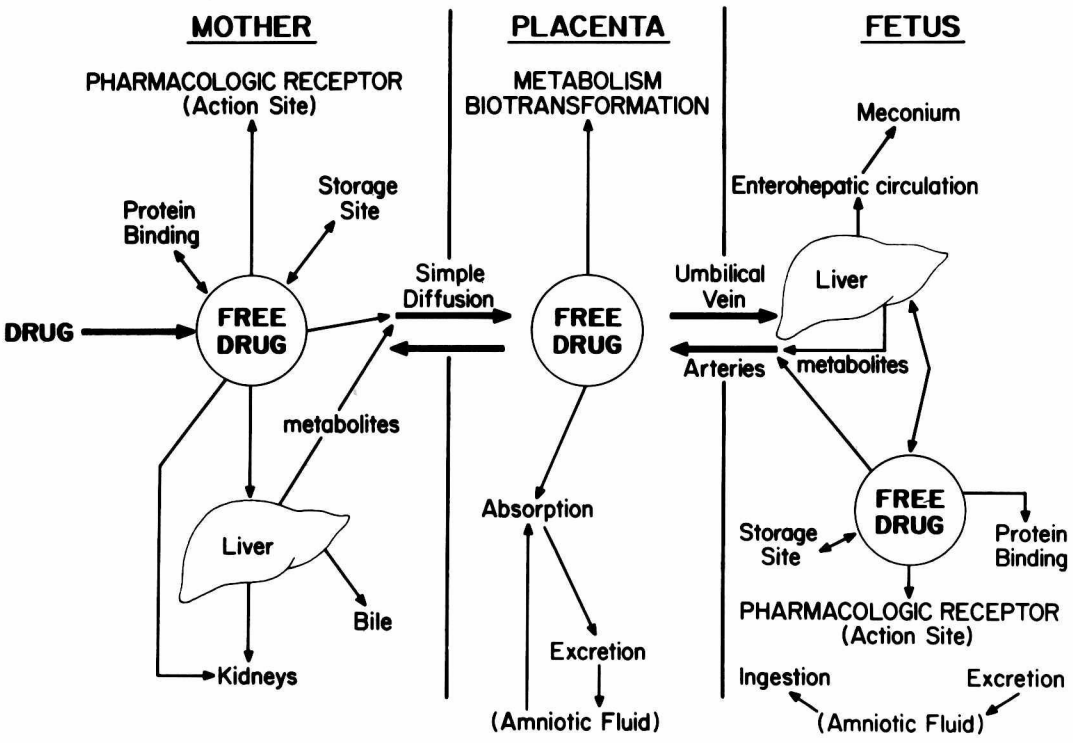

Figure 1-2. Drug pathways within the maternal, placental, and fetal units.

mental methods of analysis have revealed the potential deleterious effects and fate of drugs on the developing fetus. From these studies, new information has been gathered concerning the distribution and pharmacokinetic properties of drugs and metabolites in the maternal-fetal unit.

The study of perinatal pharmacology represents a complex interrelationship among maternal changes, placental factors, fetal development, and neonatal adaptation. These pathways are shown in Figure 1-2 and discussed in the sections that follow.

MATERNAL CHANGES

The absorption of drugs in the gastrointestinal tract during pregnancy has not been well studied but is thought to be similar to nonpregnant patients.[2] Decreased gastric tone and motility are related to progesterone effects. Hydrochloric acid secretion in the stomach is decreased during the first and second trimesters, but increased during the third trimester and postpartum periods. Whether this influences the preferential absorption of certain drugs is unclear. Pregnancy has little effect on gastrointestinal secretion, digestion, or absorption.

The distribution of a drug taken during pregnancy is influenced by many factors. Before or during conception the luminal secretions and drug concentrations in the semen, fallopian tubes, and uterus are influenced by certain drugs.[3] The extracellular volume (including intravascular volume), intracellular volume, and uterine blood flow increase gradually during pregnancy. Despite an increased production during pregnancy, serum albumin has a relatively lower concentration because of plasma volume expansion. The albumin-binding capacity to drugs is also decreased, and more unbound or "free" drug is therefore available for placental transfer.

The metabolism of drugs in the liver during pregnancy is influenced by increasing amounts of circulating steroid hormones. Enzyme induction or inhibition by the hepatic microsomes can arise by stimulation from certain drugs. Hepatic blood flow is not increased during pregnancy, and minimal centrilobular bile stasis occurs in the liver as pregnancy progresses.[4] The excretion of drugs by the kidneys can be more rapid because of increased renal perfusion and glomerular filtration. Renal blood flow increases by 25 to 50 percent during pregnancy (550 to 800 cc/minute) because of the increased cardiac output, while glomerular filtration is also increased by 50 percent.[4]

ROLE OF THE PLACENTA

The placental transfer of drugs and other substrates is complex and no method of study is ideal. Several models have been used to better understand placental transfer. Pregnant animals have been injected with drugs in varying concentrations and subsequently sacrificed at certain intervals to determine the concentration of drugs or metabolites in fetal tissues. Drug concentrations in umbilical cord or neonatal sera have also been measured and shown to correlate with maternal serum levels. Human placentas have been cultured and exposed to drugs to determine their metabolic capabilities. It has been determined that the transfer of drugs across the placenta is primarily by simple diffusion and is dependent on the chemical properties and concentration gradients of the free drug.[5] Most drugs have a molecular weight of 250 to 500. An unbound and unionized drug of molecular weight less than 1000 is usually lipid-soluble and will rapidly penetrate the trophoblast, connective, and endothelial tissues which separate the fetal and maternal circulations.[3] Drug transfer is greater during late gestation, and explanations[6] for this increased transfer are listed in Table 1-1. Any drug in sufficient concentration will eventually cross the placenta, especially when maternal therapeutic blood levels of a drug have been maintained for an extended period of time. Pathologic processes causing an inflammatory reaction, hypoxia, vascular degeneration, or partial separation of the placental

TABLE 1-1 REASONS FOR INCREASED PLACENTAL DRUG TRANSFER IN LATE PREGNANCY

1. Increased free drug available for transport
2. Increased utero-placental blood flow (500 ml/min)
3. Increased placental surface area.
4. Decreased thickness of the semipermeable lipid membranes (2 μm at term) between the placental capillaries
5. Greater physical disruption of placental membranes
6. More acidic fetal circulation to "trap" basic drugs

implantation can affect utero-placental blood flow and drug transfer. Uterine contractions, cord compression, and supine positioning of the mother can lead to transient utero-placental hypoperfusion.

Examples of drugs which readily cross the placenta within minutes after maternal administration include ampicillin, penicillin G, cephalothin, kanamycin, tetracycline, sulfonamides, streptomycin, diazepam, phenytoin, barbiturates, ethanol, meperidine, salicylate, lidocaine, mepivacaine, bupivacaine (with or without epinephrine), and propranolol.[3]

The placental metabolism of drugs is not well understood and is likely to be less active than metabolism within the fetal liver.[6] However, biochemical transformations may require enzymatic reactions at both sites. Certain substances may cross the placenta only after transformation by any of the four possible metabolic reactions (oxidation, reduction, dealkylation, and synthesis). The synthetic capabilities of the placenta (including conjugation or oxidative metabolism) has not been well demonstrated. Certain drugs can also induce or inhibit placental enzymes necessary for the metabolic conversion of endogenous substances or for energy-requiring transport mechanisms.[6] Furthermore, drugs may act on the fetus and placenta to reduce placental blood flow or interfere with the active transport or other nutritive functions of the placenta.[7]

DRUG EFFECTS ON THE FETUS

Drugs that cross the placental barrier usually reach fetal levels which often correspond to 50 to 100 percent of maternal serum concentrations.[3] Exceptions are diazepam and the local anesthetics that reach drug levels in the fetus at equilibria which are greater than those in the mother. The total exposure of a drug in the fetus is more important than the rate of transplacental transport. Chronic drug exposure, rather than single-dose therapy, may influence fetal cell growth during the early (hyperplasia stages) or later (hypertrophy stages) periods of development.[7,8] Drugs may act as teratogenic agents in many ways: abortions, malformations, altered fetal growth, functional deficits, carcinogenesis, or mutagenesis (see Chap. 2).

Drugs transported in the umbilical vein travel to the fetal liver (portal vein) or are shunted through the liver to the right side of the heart (ductus venosus). Factors determining the flow direction through the ductus venosus or portal vein are not well understood. Cardiac output is proportionally greater in the fetus than in the adult, and blood is preferentially circulated to the essential organs (brain, heart, placenta) through less resistant pathways. Blood-brain permeability is greater in the fetus than in the adult. Mitochondria, the main intracellular sites for metabolism, increase in number in the fetal brain and heart and show increasing enzyme content with fetal age.[9] More than half of the cardiac output is directly returned to the placenta through the umbilical arteries. This is greater when fetal acidosis is present. The maternal-fetal concentration gradient is therefore decreased, and further transfer of drugs or metabolites is retarded.[10]

Despite preferential circulation to the heart and brain, drug distribution in the fetus eventually becomes diffuse. Total body water increases with fetal maturity but decreases

proportionally with total body mass (95 percent at mid-gestation to 75 percent at term). The total concentration of plasma protein and the protein-binding properties are lower in the fetus than in the mother. More free drug is therefore available for tissue penetration or competitive protein-binding with other drugs or endogenous compounds. Conclusions about drug deposition within the fetus obtained from maternal or fetal serum levels alone may not accurately reflect fetal pharmacokinetics or drug distribution patterns.

Concentrations of drugs in the fetus vary but decrease when sampling from the umbilical vein, umbilical artery, and fetal tissue (fetal scalp), respectively. The rate of tissue permeability of a drug is unknown but probably increases with gestation.[11] Autonomic receptors (α and β) in the ileum, carotid artery, and aortic arch sinuses are present in fetal animal studies in the early second trimester and respond to catecholamine stimulation.[11,12] Response curves from drugs are considered similar throughout gestation, but the strength of receptor response increases remarkably with fetal development.[10,11] Some drugs may also have a higher affinity for specific target tissues. Examples of organs which are affected by specific drugs include the heart (digoxin, phenytoin); skeleton (tetracycline, warfarin); red blood cells (sulfonamides); central nervous system (diazepam, ethanol, narcotics); platelets (aspirin); adrenal gland (sex steroids, phenytoin); mullerian duct and vagina (diethylstilbestrol); and auditory nerve (gentamycin).[3]

Many fetal organs are capable of substantial metabolic activity, but drug metabolism occurs principally in the fetal liver. Human fetal liver microsomes have significant cytochrome P_{450} levels and NADPH–cytochrome c reductase which can be measured as early as the 14th week of gestation.[11] Oxidation and reduction reactions have been described as early as the 16th week.[13] The activity and concentration of certain hepatic microsomal enzymes and the rate of oxidative and conjugative reactions are probably less than in the adult.[13] Therefore, direct pharmacodynamic effects from drugs may be more pronounced and more prolonged in the fetus than in the mother. Certain drugs, such as phenobarbital or ethanol, which readily cross the placenta, may induce specific fetal liver enzymes.[3] Following chronic exposure, enzyme induction increases the smooth endoplasmic reticulum, and the hepatic drug metabolism capabilities of the fetus are activated. Prolonged phenobarbital, narcotic, or ethanol exposure has been shown to stimulate glucuronyl transferase to conjugate circulating bilirubin over several days and thereby diminish the amount of unconjugated hyperbilirubinemia in the neonate.[14] Furthermore, by stimulating hepatic enzymes, phenobarbital may enhance the metabolism and elimination of phenytoin.[15] An absence or excessive presence of one or more enzymes may go unrecognized if the embryo or fetus does not survive.

The excretion of most drugs is slower in the fetus than in the adult, since many systems are not fully developed. The primary routes of elimination involve the placenta and fetal urine. The placental transfer of drugs from the fetus to the mother is the primary route of drug elimination in early pregnancy and is dependent on simple diffusion, free drug chemical properties, and concentration gradients. Drug elimination in the latter half of pregnancy is determined by the immature fetal kidneys contributing to the amniotic fluid. In the absence of gastrointestinal atresia, great amounts of amniotic fluid can be swallowed by the fetus and can be recirculated into the enterohepatic circulation. The measurement of some drug and metabolite concentrations is possible by amniotic fluid sampling and by meconium analysis.

Drug therapy for various fetal complications is another area presently under investigation. Examples of prior treatment of fetal complications are listed in Table 1-2. Drug administration can occur by the passive, transplacental route or by direct intra-amniotic instillation or intramuscular injection. The direct route has clear invasive risks, but would quickly aid the fetus if drug-transplacental transfer is slow. These risks and benefits for

TABLE 1-2 DRUG THERAPY FOR VARIOUS FETAL CONDITIONS

Fetal Conditions	Therapeutic Agents
Heart failure, tachycardia	Digoxin
Hypothyroidism	Thyroxine
Syphilis exposure	Penicillin
Adrenal hyperplasia	Hydrocortisone
Respiratory distress syndrome	Glucocorticoids

fetal therapy remain uncertain and require further investigation.

NEONATAL PHARMACOLOGY

Drugs absorbed transplacentally from the mother before or during labor may remain in the neonate for a prolonged period. Drug effects on the fetus may be assessed immediately at birth by Apgar scores, drug concentration measurements of the umbilical blood, and a search for gross anomalies. Neurobehavioral examination of the neonate is also useful in the determination of more subtle and transient drug effects.[16] These include body tone, rooting reflex, Moro response, and response to pinprick stimulation.

Nearly all active or inactive drugs circulating within the mother can also be transferred into the breast milk or colostrum (see Chap. 15). Those drugs passing into the breastfed infant may be further metabolized in the gastrointestinal tract. Absorption processes in the untested gastrointestinal tract of the neonate are similar to the adult, and lipid-soluble drugs are well absorbed. The absorption of drugs administered intramuscularly or subcutaneously is dependent on an adequate local circulation.

Distribution of drugs in the newborn is similar to the adult. Circulatory alterations after the umbilical cord is clamped involve more blood flow to the lungs and extremities and less to the liver and brain. Total body water and extracellular volume are proportionally higher in the infant, while adipose tissue is less than in the adult. Total serum protein is less in the infant than in the adult, and competition between drugs and endogenous substrates (sulfonamides and bilirubin) for binding sites in albumin may displace more free drugs and bilirubin into the circulation.[17,18]

Metabolism in the premature and term infant occurs primarily within the liver. The four basic metabolic reactions (oxidation, reduction, dealkylation, and synthesis) for conversion or detoxification of foreign compounds are present but less active. Drugs such as salicylates, ethanol, and diazepam are therefore biotransformed much less rapidly than in the older child or adult and would contribute to any delays in neonatal adaptation.[16] Asphyxia, inadequate nutrition, hypoglycemia, insufficient body temperature control, inborn errors of metabolism, specific diseases, and toxic effects from drugs (local anesthetics, autonomic nervous system drugs, narcotic addiction, chronic barbiturate use) or endogenous and exogenous substrates can further retard metabolic processes.[3,18] Conversely, drugs may induce enzyme activity and accelerate the metabolism of certain drugs or other essential biochemicals. The measurement of serum bilirubin levels in the neonate can provide a better understanding of the metabolism of certain drugs (sulfonamides, diazepam, methyldopa, nitrofurantoins) since many metabolic processes are shared by other endogenous and exogenous compounds.[17]

Excretion of drugs is also delayed in the infant. Elimination processes are principally