Principles of Pharmacokinetics in the Pregnant Woman and Fetus

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KEYWORDS

- Pharmacokinetics
- Perinatal pharmacology
- Fetal pharmacology
- Developmental pharmacology
- Maternal/fetal drug transfer

KEY POINTS

- Pharmacokinetics of the maternal/placenta/fetal unit change dramatically during pregnancy.
- Drug metabolism as well as drug transporters can alter the amount of drug reaching the fetus.
- Differences in maternal and fetal pharmacokinetics change the fetal/maternal drug concentrations at birth.
- Many aspects of maternal and fetal drug therapy need additional study.

INTRODUCTION

In 1962, prenatal exposure to thalidomide was identified as the cause of a severe congenital multiple malformation syndrome.\textsuperscript{1–4} This was the first time that exposure to a maternal medication had been shown to directly injure the fetus. Since that time, every effort has been made to avoid exposure of the fetus to medications, especially in the first trimester during the critical period of organogenesis. Despite these efforts, there are occasions when fetal exposure to medications may be necessary in order to maintain maternal health, creating a challenging risk-benefit continuum. For example, the anticonvulsant phenytoin is a known teratogen responsible for a cluster of structural anomalies collectively known as the fetal hydantoin syndrome.\textsuperscript{5,6} Fetal pharmacology studies subsequently confirmed that phenytoin is able to cross the placenta to reach the fetus during the period of organogenesis, suggesting a direct

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effect on fetal development. And yet most prenatal exposures do not result in fetal injury. The sporadic occurrence of structural malformations associated with prenatal phenytoin exposure suggested for the first time that congenital malformation syndromes are more complex than simple in utero exposure. It is now clear that genetic factors are involved; specifically, in this instance, the inheritance of a genetic variant of epoxide hydrolase, the enzyme responsible for phenytoin metabolism, which causes the activity of the enzyme to be reduced to less than 30% of normal. Not only can prenatal exposure to phenytoin (and other medications) result in structural malformations, but also in neurodevelopmental delay that may only become apparent later in life.

Advances in perinatal diagnostics and fetal ultrasound during the 1980s allowed for the prenatal identification of conditions previously only recognized after birth. This included not only structural malformations, but also functional disorders such as supraventricular tachycardia and androgenization of a female fetus because of congenital adrenal hyperplasia. Some of these disorders can be prevented and/or treated by achieving an adequate concentration of a given drug within the fetus. As such, deliberate exposure of the fetus to medications can also have a therapeutic objective.

Our understanding of perinatal physiology has increased significantly starting in the 1990s and perinatologists have become more accepting of clinical interventions. There are now numerous examples of the use of maternal drug administration to treat both fetal-related and pregnancy-related disorders, some of which are listed below.

i. Supraventricular tachycardia and other fetal dysrhythmias can be recognized and precisely diagnosed using fetal cardiac ultrasound and can be treated with a variety of anti-arrhythmic medications, usually administered to the mother but sometimes administered directly to the fetus via intra-amniotic injection.

ii. Women pregnant with a female fetus after having delivered a child with androgenizing congenital adrenal hyperplasia can be treated with maternal corticosteroids to suppress the fetal adrenal glands, thereby reducing the production of endogenous fetal androgens and preventing masculinization of the external genitalia. In this way, fetal treatment can either prevent the congenital syndrome altogether or at least minimize the need for extensive postnatal surgical procedures.

iii. Recent studies suggest that some cases of recurrent spontaneous preterm birth (SPTB) can be prevented with progesterone supplementation during pregnancy.

iv. Judicious use of maternal halogenated corticosteroids can be used to reduce morbidities associated with prematurity, such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC).

v. Bacterial infections, such as early-onset neonatal group B streptococcal infection, and vertical transmission of HIV have both been dramatically reduced through intrapartum administration of antimicrobial medications.

Taken together, these clinical situations created a role for drug therapy to directly benefit the fetus and a need to better understand the pharmacokinetic changes in both the mother and the fetus during pregnancy. Over the past few decades, the field of perinatal pharmacology has evolved into a clinically important discipline. It has increased our understanding of the dynamic changes in physiology that occur during pregnancy and their effect on drug transport, metabolism, and degradation in the mother, placenta, and fetus. Although the underlying physiologic changes that accompany pregnancy remain much the same as that outlined by Mirkin in 1973, much has been learned about the patterns of pharmacokinetics that occur at the maternal-fetal interface, which has helped to better understand maternal-fetal drug transfer and inform fetal drug therapy.
The goal of fetal drug therapy is to deliver an effective and nontoxic unbound drug concentration to the site of action within the fetoplacental unit. To achieve this, the clinician must understand the numerous pharmacokinetic changes that accompany the different stages of pregnancy and that may affect the drug concentration reaching the proposed site of action. Fig. 1 lists the various steps involved in the therapeutic process by which medications are administered to the mother, transported across the placenta, and act on the fetus. Interference or dysregulation of any one of these steps may adversely affect drug delivery and fetal therapy. Changes in maternal body composition, physiology, and the activity of cytochrome P450 (CYP) enzymes that affect pharmacokinetics in pregnancy are summarized in Tables 1 and 2 and in Fig. 2 and are discussed in detail below.

CHANGES IN THE MOTHER THAT AFFECT PHARMACOKINETICS

Drug Absorption

Enteral drug absorption is reduced in pregnancy because both gastric emptying and gastrointestinal motility are slowed owing to high levels of circulating progesterone.21 Both a reduction in intrinsic contractility and pressure from the enlarging uterus contribute to the slowing of gastrointestinal transit time.

Drug Distribution

Intravascular volume begins to expand early in pregnancy and continues to do so to term, by which time plasma volume has increased by 50%.22 This expansion of the volume of distribution of polar drugs and those with a large molecular weight that remain primarily within the circulation reduces circulating drug concentrations. This dilutional effect is partially offset by a decrease in circulating protein concentration, which increases the bioavailability of unbound (biologically active) drug. At the same time, the placenta becomes more permeable and results in a greater proportion of the drug being delivered to the fetus. The net effect is an increased delivery of the drug to the proposed site of action, which may be advantageous in situations where the drug is needed to achieve therapeutic concentrations in the fetus.
time, uterine perfusion increases from 2% of cardiac output per minute before pregnancy to 17% during pregnancy, thereby presenting more drug to the placenta and fetus.23

**Drug Metabolism**

Pregnancy-related changes in the activity of maternal phase I microsomal CYP enzymes are complex and variable, with some increasing and others decreasing during pregnancy (see Fig. 2).22 CYP enzymes are essential for the metabolism of many medications, primarily in the liver. Although this class has more than 50 enzymes, 6 of them metabolize 90% of drugs, with the 2 most significant enzymes being CYP3A4 and CYP2D6. Uridyl glucuronosyltransferase 1A1, a phase II enzyme responsible for bilirubin conjugation, increases by midgestation and then remains stable.22 Further complicating our ability to accurately predict changes in drug metabolism during pregnancy is that hepatic blood flow remains relatively constant whereas total cardiac output increases by 33% at term. The net effect is a reduction of the percent of cardiac output perfusing the liver, thus reducing the hepatic first-pass effect in pregnancy. This is not simply of theoretic concern. Table 3 shows some of the medications that are metabolized or conjugated by each of these enzymatic pathways, all of which have altered metabolism in pregnancy. It is important to note that CYP3A4, which metabolizes more drugs than any other CYP enzyme,

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**Table 1**

<table>
<thead>
<tr>
<th>Trimester of Pregnancy</th>
<th>First (%)</th>
<th>Second (%)</th>
<th>Third (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body weight</td>
<td>+6</td>
<td>+16</td>
<td>+23</td>
</tr>
<tr>
<td>Total fat mass</td>
<td>+11</td>
<td>+16</td>
<td>+32</td>
</tr>
<tr>
<td>Total body water</td>
<td>+11</td>
<td>+27</td>
<td>+41</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>+7</td>
<td>+42</td>
<td>+50</td>
</tr>
<tr>
<td>Red blood cell volume</td>
<td>+4</td>
<td>+20</td>
<td>+28</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>−3</td>
<td>−8</td>
<td>−14</td>
</tr>
<tr>
<td>α-1 acid glycoprotein</td>
<td>−1</td>
<td>−22</td>
<td>−19</td>
</tr>
</tbody>
</table>

Data are represented as % change compared with nonpregnant women.


**Table 2**

<table>
<thead>
<tr>
<th>Trimester of Pregnancy</th>
<th>First (%)</th>
<th>Second (%)</th>
<th>Third (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>+18</td>
<td>+28</td>
<td>+33</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>+19</td>
<td>+37</td>
<td>+40</td>
</tr>
<tr>
<td>Effective renal plasma flow</td>
<td>+38</td>
<td>+48</td>
<td>+31</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>+28</td>
<td>+58</td>
<td>+26</td>
</tr>
<tr>
<td>Uterine blood flow</td>
<td>+923</td>
<td>+1567</td>
<td>+2721</td>
</tr>
</tbody>
</table>

Data are represented as % change compared with nonpregnant women.

demonstrates a doubling in its level of activity by the end of pregnancy. Further complicating the situation, CYP3A4 is inhibited by macrolide antibiotics, imidazole antifungals, and many of the antiretroviral medications used to treat HIV. The reduction in activity of CYP2C19 in the latter half of pregnancy (see Fig. 2) may influence the efficacy of anticonvulsant medications as well as proton pump inhibitors and the antiplatelet medication, clopidogrel.

**Drug Elimination**

With an increase in cardiac output, renal plasma flow, and creatinine clearance (Table 2), the clearance of drugs that are renally excreted will usually increase in pregnancy. For this reason, many practitioners may compensate for this increased clearance by increasing the dose or shortening the dosing intervals of medications during pregnancy; however, the reduced protein binding in pregnancy may exaggerate the effects of medications at concentrations usually considered subtherapeutic. Data from studies on digoxin in pregnancy and the puerperium clearly illustrate the effect of renal function on drug clearance. In 1 study, digoxin, which is cleared primarily by renal excretion, was measured in 5 women with rheumatic heart disease at the end of an uncomplicated pregnancy and again 1 month postpartum. Maternal digoxin concentrations increased from $0.6 \pm 0.1$ ng/mL at delivery to $1.1 \pm 0.2$ ng/mL 1 month later, indicating a decrease of almost 50% in drug clearance after delivery.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Representative drugs metabolized by cytochrome P450 enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzyme</strong></td>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>CYP1A1/2</td>
<td>Caffeine, aflatoxin B1, acetaminophen</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine, hydrocodone, flecainide, propranolol, carvedilol, fluoxetine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Phenytoin, warfarin, tolbutamide</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole, pantoprazole, phenobarbital, diazepam, propranolol, clopidogrel, citalopram, bupropion</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Fentanyl, midazolam, cyclosporin, tacrolimus, carbamazepine, progesterone</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Bilirubin, irinotecan</td>
</tr>
</tbody>
</table>

Abbreviation: UGT1A1, uridyl glucuronosyltransferase 1A1.
Placental function is far more complex than a simple filter providing oxygen to the fetus and removing carbon dioxide and other waste products. The basic structural unit of the placenta is the chorionic villus suspended in the intervillous space and bathed in maternal blood. Simple diffusion across membranes accounts for much of the transfer of drugs from the maternal circulation to the placenta and on to the fetus. This usually occurs from higher to lower concentrations (usually from mother to fetus) of nonionized drugs that are not protein bound.

The anatomy and function of the placenta changes throughout gestation, and this affects the ability of drugs to diffuse across to the fetus. Soon after the blastocyst implants into the uterine wall, the outer cells of the trophoblast layer immediately adjacent to the uterine epithelium fuse into multinucleated cells, the syncytiotrophoblast, which is in direct contact with the maternal blood. Lacunae develop within the syncytiotrophoblast that enlarge to become the intervillous spaces. Maternal spiral arteries connect to the intervillous space to establish the uteroplacental blood flow. Fetal vessels extend into the intervillous space in chorionic villi, which initially are several cells thick. During pregnancy, both chorionic layers thin out from a thickness of 50 to 100 μM at 8 to 10 weeks of pregnancy to 4 to 5 μM at term. The immature structure of the early placenta helps to shield the fetus from potentially harmful xenobiotics during the period of organogenesis. The fetoplacental circulation is reversed from that in newborns and adults with fetal arteries carrying deoxygenated blood from the fetus into the umbilical arteries, which flow into the chorionic arteries and capillaries within the placenta. There, gas exchange occurs before the oxygenated blood returns to the fetus through chorionic capillaries that flow into the umbilical vein.

It is important to note that only nonionized, nonprotein bound drugs diffuse passively into the fetal blood. The extent of ionization is determined by the chemical nature of the drug, its ionization constant (pKₐ or pKₐ), and the pH of its environment according to the Henderson-Hasselbach equation as refined by Stewart. The fetal circulation is more acidic than the maternal circulation. This pH difference increases ionization of organic bases in the fetal circulation, which in turn increases their concentration on the fetal side of the placenta.

Several transporter proteins in the syncytiotrophoblast play a prominent role in the ability of drugs to move across the placenta and into and out of the fetal circulation. Specific transporters may be bidirectional in their activity or unidirectional either toward or away from the fetus. These play a critical role in protecting the fetus from drug-related injury. Indeed, genetic polymorphisms in placental transporter genes, especially those that reduce the efflux transporter p-glycoprotein, may increase the risk of drug-induced adverse effects. Other methods of drug transport, such as pinocytosis and phagocytosis, play more minor roles in maternal/fetal drug exchange across the placenta.

Drug Distribution

By term, the placenta has grown to 500 g with a diameter of 15 to 20 cm and a thickness of 2 to 3 cm. It can hold a volume of almost a liter of blood, mostly in the intervillous space, into which drugs may distribute as they diffuse out of the maternal circulation toward the fetus.
Drug Metabolism

The placenta contains several CYP enzymes that are active early in fetal development. These include CYP 1A1, 1A2, 1B1, 2C, 2D6, 2E1, 2F1, 3A4, 5, 7, and 4B1.31 By term, CYP2D6 and 1A2 are no longer detectable in the placenta. Several of these enzymes are essential in the maintenance of pregnancy by metabolizing endogenous compounds, such as steroids, that may otherwise activate parturition.18 Activity of most of these CYPs are highest early in gestation and decrease toward term.32

CHANGES IN THE FETUS THAT AFFECT PHARMACOKINETICS

Drug Absorption

Absorption of drugs by the fetus is usually through the blood returning from the placenta through the umbilical vein. Transcutaneous and oral absorption by the fetus are possible, but have received limited study. With the buildup of the vernix caseosa, a lipid barrier forms on the surface of the skin preventing penetration by many polar compounds and water. Recent studies have shown that vernix is composed of 80% water, 10% proteins, and 10% lipids.33 Vernix components have been shown to be actively involved in host defense, exhibiting antifungal and antimicrobial activity.34 The lipid component of vernix are comprised of an estimated 54 different lipid mediators (21 oxylipins, 23 sphingolipids, and 10 endocannabinoids) all with functions yet to be fully explained.

Drug Distribution

Drug distribution within the fetus is influenced primarily by its body composition. Early in gestation, the fetus is 94% water with 0.5% fat.35 By full term, its water content has decreased to 76% and fat content has increased to 12% to 16%. Clearly, the distribution to tissues of polar as well as lipophilic compounds will vary significantly based solely on body composition related to the stage of gestation.

Drug Metabolism

Fetal drug metabolizing enzyme activity varies markedly during pregnancy. Older studies reported high level of activity of several enzymes early in pregnancy, including

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**Fig. 3.** Drug transport within the syncytiotrophoblast. The major transporter proteins within the syncytiotrophoblast responsible for the movement of drugs into and out of the fetal circulation are shown. BCRP, breast cancer resistance protein; CYP's, cytochrome P450's; MRP, multidrug resistance-associated protein; NET, norepinephrine transporter; OAT4, organic acid transporter 4; OATP2B1, organic anion-associated polypeptide 2B1; OATP4A1, organic anion-associated polypeptide 4A1; OCT3, organic cation transporter 3; OCTN1 and 2, organic acid/carnitine transporters; P-gp, P-glycoprotein; SERT, serotonin transporter; UGTs, uridine diphosphate glucuronosyl-transferases. (Adapted from Rubinchik-Stern M, Eyal S. Drug interactions at the human placenta: what is the evidence? Front Pharmacol 2012. https://doi.org/10.3389/fphar.2012.00126.)
CYP1A1/1A2, CYP1B1, CYP2C8/2C9/2C18/2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, and CYP3A7. Although these enzymes can help protect the fetus from potential toxins, many are also involved in the metabolism of endogenous compounds essential for fetal development. As in older children and adults, the liver contains most of the enzymes involved in drug metabolism. In a recent review, Hines described 3 general patterns of developmental changes in fetal drug metabolizing enzymes. One group of enzymes demonstrate their highest activity early in gestation and either stay the same or decrease later in pregnancy. These include CYP3A7, flavin monooxygenase 1, and sulfotransferases 1A3/4 and 1E1. The second group of enzymes express their activity at a relatively constant level from fetal development into adulthood, and include CYP3A5, sulfotransferase 1A1, and CYP2C19 (although the latter does show a moderate increase during the first year of life). The third and largest group of enzymes begin with little or no activity in the fetus and later increase to adult activity. These include CYP1A2, CYP2C9, CYP2D6, CYP2E1, CYP3A4, flavin monooxygenase 3, and sulfotransferase 2A1. The time course for the increase in activity is highly variable, ranging from 2 to 3 weeks to many years, an interval that is, particularly relevant to pediatric therapeutics.

The placental barrier

There seems to be both an anatomic and physiologic barrier to fetal drug exposure early in gestation. There is clear anatomic separation of the maternal and fetal circulations during the early stages of placental development, and there is variable activity of critical CYP’s and macromolecule transporters within the fetoplacental unit during this same time period. This is well illustrated by the developmental differences in fetal gentamicin concentrations during continuous infusions in midpregnancy compared with full term (Fig. 4). In both of these studies, gentamicin was infused continuously to the pregnant woman and each time point represents 1 pair of simultaneous maternal and umbilical plasma concentrations of gentamicin. The time course and extent of the passage of gentamicin from the mother to the fetus during continued maternal drug infusion to maintain a constant maternal concentration is shown.

![Fig. 4](https://clinicalkey.com/resources/graphs/1075759)

Fig. 4. Difference in maternal/fetal gentamicin concentrations early and late in gestation. Continuous maternal infusion of gentamicin at 18 to 23 weeks’ gestation (solid line and X) compared with maternal gentamicin infusion at full term (solid circles and dashed line). (Data from Kauffman RE, Azarnoff DL, Morris JA. Placental transfer and fetal urinary excretion of gentamicin - comparison between an animal model and the human fetus. In: Morselli PL, Garattini S, Sereni F, editors. Basic and therapeutic aspects of perinatal pharmacology. New York: Raven Press; 1975. p. 75–82; and Daubenfeld O, Modde H, Hirsch HA. Transfer of gentamicin to the foetus and the amniotic fluid during a steady state in the mother. Arch Gynakol 1974;217(3):333–40.)
Despite infusion for almost 6 hours, the fetal concentration at 18 to 23 weeks of gestation remains less than 40% of the maternal concentration. In contrast, at term, fetal concentrations reach 100% of maternal concentrations within 5 hours.

INTERPRETATION OF MATERNAL/UMBILICAL DRUG CONCENTRATIONS AT BIRTH

Many studies have used the ratio of drug concentrations in maternal and umbilical blood samples to determine how much drug is being transferred to the fetus. However, this can be misleading. Because of differences in the pattern of clearance from the maternal circulation, passage across the placenta, and clearance within the fetus, this ratio can vary widely depending on the time interval at which the last dose was administered to the mother.20 This can be illustrated by plotting pairs of maternal/fetal drug concentrations from several mothers and newborns according to the time after the last maternal dose. Using data from studies of the maternal and umbilical cord blood concentrations of the antibiotic cephaloridine drawn at the time of birth, Fig. 5 shows how the umbilical/maternal ratio can vary widely from 0.35 to 1.92 depending on how long it takes for delivery after the last maternal dose. It also illustrates the marked difference in the pattern of change in drug concentrations between the fetus and mother. These variations in maternal and fetal kinetic patterns mean that single sets of maternal and umbilical blood drug concentrations cannot be relied on to accurately reflect the extent of maternal to fetal drug transfer.

Specific Examples of Fetal Drug Therapy

Antenatal corticosteroids to reduce neonatal lung disease in premature newborns

Pioneering work led by Professor Graham (Mont) Liggins from New Zealand illustrates the importance of pharmacokinetics within the fetoplacental unit. While using direct fetal infusions of corticotropin, dexamethasone, or cortisol to induce preterm delivery in sheep, Liggins39,40 noted improved aeration of the lungs at a stage in gestation when newborn lambs almost always developed RDS with progressive atelectasis. This improvement in RDS was confirmed in sheep and rabbits and, combined with...
the observations by Naeye and colleagues\textsuperscript{41} of smaller adrenal glands in newborns dying from RDS, suggested that a corticosteroid deficiency or depletion may be causally related to the development of RDS. As an obstetrician familiar with the clinical sequelae of RDS, Liggins began a clinical trial of antenatal glucocorticoid treatment of mothers in preterm labor at 24 to 36 weeks’ gestation. Maternal treatment used a compound formulation of a halogenated corticosteroid derived from prednisolone known as betamethasone, a stereoisomer of dexamethasone with the same structure and molecular weight but a different spatial orientation of the 16-methyl group. This formulation of betamethasone (Celestone) was a combination of 6 mg of the immediate release phosphate salt and 6 mg of the poorly soluble, slowly released acetate salt. The intramuscular (i.m.) injection was repeated once 24 hours later if the mother had not delivered. The success of this transplacental therapy can be explained by the pharmacokinetics of betamethasone and dexamethasone and how they cross the human placenta. The placenta protects the fetus from increased maternal cortisol concentrations through the activity of 11β-hydroxysteroid dehydrogenase type 2, which inactivates cortisol to cortisone.\textsuperscript{42} In contrast, the synthetic halogenated structural isomers, betamethasone and dexamethasone, are minimally inactivated by 11β-hydroxysteroid dehydrogenase type 2 and pass through the placenta largely unchanged.

The original study\textsuperscript{16} was blinded and controlled, with the control group receiving 6 mg cortisol, a minimal dosage. Of 117 betamethasone and 96 control mothers enrolled, 94 betamethasone and 78 control subjects continued pregnancy for at least 24 hours, which was considered the minimal time for induction of an effect on surfactant release/synthesis, and which also allowed for 2 doses of steroids to be administered. In the betamethasone-treated group, the frequency of RDS progressively decreased with increasing time to delivery up to 7 days, from 24.0% for delivery at less than 24 hours to 10% for delivery at 24 to 48 hours and 3.6% at 2 to 7 days. Although RDS was reduced significantly overall from 24.0% to 4.3%, the significant reduction was confined to infants delivering at 26 to 32 weeks’ gestation (69.6% to 11.8%). In the most premature newborns, no IVH was seen in the betamethasone-treated group, but was seen in 4 of the controls.\textsuperscript{16} Although not statistically significant, this reduction in IVH with betamethasone treatment was later confirmed in larger studies.\textsuperscript{43,44} Despite 2 NIH Consensus Conferences that supported treatment with betamethasone to reduce RDS,\textsuperscript{45,46} prenatal corticosteroid treatment was slow to gain acceptance. This might have related to the then-recent memory of long-term problems associated with attempts to prolong pregnancy using diethylstilbestrol leading to cancer in the children and young adults exposed in utero.\textsuperscript{47,48} Such intervention has now become “standard of care” for impending preterm birth less than 34 weeks. A recent Cochrane review carried out a meta-analysis of 30 studies confirming that antenatal steroids reduced perinatal death by 28%, neonatal death by 31%, RDS by 34%, moderate/severe RDS by 41%, IVH by 12%, as well as NEC, need for mechanical ventilation, and early-onset systemic infections within the first 48 hours after birth.\textsuperscript{44}

Given these beneficial effects, what more do we need to know about antenatal treatment with corticosteroids? Here are some unanswered questions: What is the optimal dose? Is the current dosage of 2 doses of 12 mg of betamethasone acetate and phosphate administered 24 hours apart the optimal treatment? The initial study by Liggins and Howie\textsuperscript{16} did not include a dose-ranging study or variation of the interval between doses. Although 12 mg doses administered 24 hours apart is effective, some authors recommend completing the betamethasone treatment in a shorter time interval, such as 12 hours.\textsuperscript{49} With the 24 hour treatment course with betamethasone, Liggins and Howie\textsuperscript{16} noted adrenal suppression in the mothers for around 72 hours and other...
studies have shown a suppression of neonatal cortisol secretion for several days after birth.\textsuperscript{50} A lower betamethasone dosage might be equally effective as the Liggins’ protocol, but produce less suppression of the hypothalamic-pituitary-adrenal axis. Studies by Jobe and colleagues\textsuperscript{51} have shown that a single dose of the slowly released betamethasone acetate is more effective than 2 doses of the rapidly released betamethasone phosphate. In another study in sheep, an even lower dose of betamethasone acetate improved lung function.\textsuperscript{52} Similar studies in humans may provide similar benefits of antenatal corticosteroids with less hypothalamic-pituitary-adrenal suppression.

Such questions are not uncommon when discussing drug treatment. If the initial dosage tested is effective and relatively safe, additional studies may be difficult to conduct to attempt to reduce the dose or change the dosing interval. This is especially the case in obstetrics and pediatrics, whereby drug studies are time-consuming and expensive with few sites prepared to carry them out. It is nonetheless important to understand the extent of the initial studies of a drug and whether alternate doses, dose intervals, and formulations have been adequately explored and tested.

If 1 course (2 doses totaling 24 mg) of antenatal corticosteroids is good, can repeated courses sustain or even amplify the improvement? The effectiveness of betamethasone decreases in most studies by 7 days after the initiation of treatment, so some obstetricians began to repeat the 24 mg dosage on a weekly basis. If the pregnancy continued, repeated administration was continued for several weeks up to 11 times. In 1999, a retrospective review published by Banks and colleagues\textsuperscript{53} suggested that repeated courses of antenatal corticosteroids increased perinatal mortality, reduced fetal growth, and prolonged adrenal suppression. This was followed in 2000 by an NIH Consensus Conference recommending that only a single course of antenatal corticosteroids be administered unless repeated courses were part of an investigative protocol.\textsuperscript{46} Like all retrospective studies, the study by Banks and colleagues\textsuperscript{53} was susceptible to confounding effects that might not be known and could not be controlled for. Several prospective randomized studies of repeated courses of antenatal corticosteroids followed. A meta-analysis in 2017 of 30 studies, including 9 with repeated courses of antenatal corticosteroids, concluded that both single and repeated doses of antenatal corticosteroids reduced perinatal death, neonatal death, RDS, moderate/severe RDS, IVH, NEC, need for mechanical ventilation, and infections within 48 hours of birth.\textsuperscript{44} No serious adverse events were reported.

Although it is clear that fetuses can respond favorably to antenatal corticosteroids, the stages of lung development when that response occurs was not initially clear. Liggins and Howie found a reduction in RDS in fetuses who received antenatal corticosteroids and delivered at 26 to 32 weeks of gestation.\textsuperscript{16} The benefit for the most immature preterm newborns (<26 weeks) was initially uncertain. However, more recent studies have shown reductions in RDS and mortality also at gestations of less than 25 weeks.\textsuperscript{54,55} The upper limit of gestational age at which fetuses could respond to antenatal corticosteroids has expanded as well and now includes late preterm fetuses (gestational age 34–37 weeks), a group who are known to have increased respiratory morbidities compared with full term newborns. In 1 prospective randomized trial, antenatal corticosteroid treatment of late preterm deliveries reduced surfactant use, transient tachypnea, and bronchopulmonary dysplasia without increasing neonatal sepsis.\textsuperscript{56} The reduction was modest (14.4\% versus 11.6\%) and hypoglycemia was increased in the betamethasone-treated group. Other recent studies support antenatal corticosteroid treatment before elective cesarean section at term to reduce respiratory morbidity.\textsuperscript{57}
Multiple studies have followed the initial 1972 report from Liggins and Howie, and all support single course treatment of mothers in preterm labor to improve neonatal outcomes. The importance of controlled trials in perinatal medicine to improve pregnancy outcomes has had other far reaching and often unanticipated consequences, including a major contribution to the development of the Cochrane systematic reviews.58–60 Questions still remain regarding antenatal corticosteroid treatment that deserve continued study to determine the minimal effective dosage, optimal interval between doses, whether adverse effects of repeated maternal treatment harm a specific population or are safe, and whether there are upper and lower limits of gestational age at which benefits no longer occur. Long-term follow-up studies of people exposed in utero to antenatal corticosteroids to investigate growth, cardiovascular health, and neurologic outcomes should continue as this population ages.

**Progesterone to prevent preterm birth, the intersection of pharmacogenomics and pharmacokinetics**

The decrease in recurrent SPTB with progesterone supplementation has significantly reduced morbidity associated with prematurity and raised several possible explanations. After several small studies, a large prospective, randomized trial suggested that 17-hydroxyprogesterone caproate (17OHPC) reduced the recurrence of SPTB in singleton pregnancies at high risk of this event by virtue of a prior SPTB over a broad range of gestations, and resulted in a reduction in NEC, IVH, and need for supplemental oxygen.15 The possible explanation for this effect involves pharmacokinetics and pharmacogenomics.61

One study of the pharmacokinetics of 17OHPC in singleton pregnancies was extended after delivery with continued sampling up to 28 days postpartum.61 Women were treated weekly with 17OHPC 250 mg i.m. formulated in oil starting in the early second trimester. At birth, the umbilical to maternal plasma concentrations averaged 0.2, and the umbilical concentrations did not change with the time after the last maternal dose. The concentrations of 17OHPC varied inversely with body mass index, which may indicate a need for weight-based dosage adjustment. Clearance was faster in African American women; unfortunately, the CYP3A4 genotype, which is responsible for metabolism of 17OHPC was not determined in this cohort. Interestingly, the disposition half-life of 17OHPC was 18 ± 6 days, which led to progressive accumulation of drug with weekly injections.61

In another study, supplementation of women with twin pregnancies with 17OHPC allowed evaluation of both the pharmacokinetics and potential mechanism of action.62 Concentrations of 17OHPC were inversely correlated with gestation at delivery, with lower concentrations at more advanced gestations, the opposite of what would be expected. Circulating C-reactive protein concentrations were increased in pregnancies with the highest concentrations of 17OHPC, but it did not reach statistical significance. The authors of this study speculated that the rise in C-reactive protein was related to the underlying mechanisms of parturition rather than to treatment with 17OHPC. This study along with many subsequent publications showed no lengthening of gestation with 17OHPC supplementation in the setting of multiple gestations (twins or triplets) or for women with a shortened cervical length.63

Roughly two-thirds of high-risk women with singleton pregnancies who receive 17OHPC supplementation do not respond and will go on to have a recurrent SPTB.64 Although a pharmacokinetic explanation is possible, Manuck and colleagues65 used DNA from the original study by Meis and colleagues15 to look more closely at progesterone receptors A and B. Because of variation in allele frequency by race, the samples were stratified by self-reported race into African American and
White/Hispanic. Several gene response interactions were observed which differed by race/ethnicity. Some haplotypes identified women with an underlying risk of SPTB, others identified women with a favorable response to 17OHP, whereas other genotypes were associated with an increased risk of SPTB in women who received 17OHP supplementation. Thus, successful prevention of SPTB with 17OHP treatment is not simple pharmacokinetics, but a complex interplay between pharmacogenetics and pharmacokinetics.

In women without a history of SPTB but who are found in the midtrimester to have a short cervix on transvaginal ultrasound, supplementation with vaginal progesterone is currently recommended by the American College of Obstetricians and Gynecologists. This is not a US Food and Drug Administration recommended intervention. Although some evidence exists to suggest that vaginal progesterone may be superior to intramuscular 17OHP, the American College of Obstetricians and Gynecologists has not yet endorsed the primary use of vaginal progesterone for prevention of recurrent SPTB. The pharmacokinetics of vaginal progesterone for SPTB prevention has not been adequately studied.

SUMMARY

Pregnancy profoundly alters a woman’s physiology. When combined with the progressive impact of the developing fetus and placenta, these changes result in multiple alterations in drug absorption, distribution, metabolism, and elimination. As outlined earlier in this article, these changes emphasize the pharmacologic complexity of pregnancy. They also emphasize the dangers of extrapolating pharmacologic expectations from nonpregnant populations to pregnant women and their fetuses. Although concerns about fetal safety have historically limited pharmacokinetic studies during pregnancy, it is important to recognize that many medications are clinically indicated for various maternal or fetal conditions. Recommendations for the use of medications in pregnancy should be based on the prevailing evidence, including short-term and long-term outcome data.

REFERENCES


