Therapeutic Drug Monitoring
24:15–22 © 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Clinical Relevance of Therapeutic Drug Monitoring During Pregnancy

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Epidemiologic surveys have determined that between one third and two thirds of all pregnant women will take at least one medication during pregnancy (1–5). These data demonstrate that drug use during pregnancy is of public concern. Pharmacotherapy during pregnancy usually focuses on the teratogenic safety of the unborn baby. Moreover, although most drug therapy in pregnancy is directed to maternal requirements it is often carried out without considering the important modifications of drug handling by the pregnant woman. Therapeutic drug monitoring during pregnancy aims to better individualize dosing regimens taking into account relevant pregnancy-induced changes in drug disposition. Therefore, to obtain the clinically relevant data from TDM during pregnancy it is imperative to understand the physiologic changes that occur during pregnancy and their influence on drug disposition. The complex physiologic unit of mother, placenta and fetus undergoes considerable dynamic physiologic changes (6–7). These lead to variations in the processes of absorption, distribution and elimination of drugs. Moreover, as previous studies have determined, most drugs easily cross the placenta (8–9), making the fetus an unwanted or even non-benefiting drug recipient. In general, maternal and fetal drug responses during pregnancy are influenced by two main factors: The changes in absorption, distribution and elimination of the drug in the mother which are dictated from pregnancy-induced physiologic changes, and the placental-fetal unit which affects the amount of drug that crosses the placenta, the fraction of drug being metabolized by the placenta and the distribution and elimination of a drug by the fetus. These factors together with characteristics of the specific drug should be taken in consideration when predicting the time course of drug concentration in the fetal-maternal unit.

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PHARMACOKINETICS OF THE MATERNAL-FETAL UNIT

Although several pharmacokinetic models have been proposed to describe drug disposition in the maternal-placental-fetal unit (10), generally two principal changes characterize pregnancy with respect to drug kinetics: the maternal physiologic changes and the effects of the placental-fetal compartment.

ALTERATIONS IN DRUG KINETICS DUE TO MATERNAL CHANGES

Drug Absorption

Gastrointestinal Absorption

The relaxing effect of progesterone on smooth muscle is believed to be responsible for the reduction in intestinal motility resulting in 30% to 50% increase of gastric and intestinal emptying time (6,11). This may affect T_{max} and therefore may be clinically important when one needs to achieve a rapid onset of drug effect. There is a reduction in gastric acid secretions (40% less than in non-pregnant woman) together with an increase in mucus secretions, both of which lead to an increase in gastric pH and therefore in buffer capacity (12). Clinically this would affect the ionization of weak acids and bases and hence their absorption. Nausea and vomiting which occur frequently during the first trimester may be another reason for decreased GI absorption leading to low plasma drug concentrations.

Patients should be advised to take their medication at times when nausea is minimal, usually during the evening.

Pulmonary Absorption

As cardiac output and tidal volumes are increased in pregnancy, hyperventilation and increased pulmonary blood flow occur (13,14). These alterations favor alveolar uptake and therefore should be considered when administering drugs by inhalation. The rate of induction with inhalational anesthetic agents is not necessarily faster because it depends on both pulmonary equilibrium and tissue distribution kinetics. However, dose requirements for volatile anesthetic drugs are likely to be reduced during pregnancy as was demonstrated for halothane, isoflurane and methoxyflurane (15).

Drug Distribution

The volume of distribution of drugs is usually altered during pregnancy as a result of plasma volume expansion by 50% (16). The increased cardiac output is distributed to different organs: renal blood flow increases by 50% at the end of the first trimester (14–17). The uterine blood flow reaches its peak at term (600–700 mL/min) with 80% perfusing the placenta and 20% the myometrium (18). The total mean increase in total body water is of 8 L, distributed 60% to the placenta, fetus and amniotic fluid and 40% to maternal tissues (6,17). As a result of this volume expansion a decrease in peak serum concentration (C_{max}) of many drugs has been documented . It is expected, therefore, that drugs with relatively small V_d (which are distributed mainly to water compartments) will demonstrate the greatest decrease in peak serum concentrations. Drug dosage requirements would be expected to be greater to achieve the same therapeutic effect if these effects were not offset by other pharmacokinetic changes of pregnancy which are discussed later.

Protein Binding

As pregnancy advances, plasma volume expands in a greater rate than the increase in albumin production, creating physiologic dilutional hypoalbuminemia (6,7,19). Moreover, steroid and placental hormones occupy protein binding sites thus decreasing protein binding of drugs. The overall effect is of a decrease in binding capacity for albumin and therefore an increase in the unbound ("free") drug fraction (19). Because the unbound is the pharmacologically active drug fraction, pregnant women would be expected to have an increased drug effect. However, enhanced hepatic and renal elimination of different drugs together with decreased amount of drug ingested per kg body weight result in lower serum concentrations. Taken together, the above mentioned changes do not alter the steady-state concentration of free drug, unless the unbound fraction exceeds the body's capacity to eliminate the drug, as would occur in some renal or liver disease. In contrast to albumin serum α-1-acid glycoprotein concentrations were found to remain the same as those in nonpregnancy. However, as there is significant decrease in this glycoprotein within the fetus the free fractions of basic drugs in the developing child are higher (20).

Despite the theoretical risk for toxicity of basic drugs in the fetus there is no evidence for any clinical significance. Yet, clinicians who do not have access to measurement of unbound drug, may erroneously interpret lower concentrations of total drug as indicative of lower free drug.

Drug Elimination

Hepatic Drug Elimination

The increased secretion of estrogen and progesterone in normal pregnancy affect hepatic drug metabolism in different ways: a higher rate of hepatic metabolism of certain drugs such as phenytoin is possibly a result of stimulated hepatic microsomal enzyme activity induced by progesterone. On the other hand, hepatic elimination of other drugs such as theophylline and caffeine is reduced secondary to competitive inhibition of microsomal oxidases by progesterone and estradiol (21,22). Finally, the cholestatic effect of estrogen may interfere with the clearance of drugs such as rifampin (23) which are excreted into the biliary system. The above mentioned changes of pregnancy on hepatic physiology may alter drug metabolism but their extent can hardly be quantified.

Renal Drug Elimination

The relationship between creatinine clearance and elimination of drugs excreted mainly by the kidney has been demonstrated for many agents (24). As renal plasma flow increases by 25% to 50% (17) and glomerular filtration rate by 50% (25), drugs which are excreted primarily unchanged in the urine such as digoxin and lithium, demonstrate enhanced elimination and lower steady state serum concentrations. However, these changes are either clinically insufficient or counteracted by other pharmacokinetic processes (i.e., decreased protein binding) to require an alteration in the dose of the above mentioned drugs.

Drug Compliance

In the absence of evidence-based studies many pharmaceutical manufacturers warn the public to minimize or even avoid drugs use during pregnancy. Together with the unrealistically high perception of the teratogenic risk related to drugs (26) and sometimes misinformation regarding unfounded teratogenic potential of safe medications it is not surprising that pregnant women tend to comply less than optimally with drug therapy. The investigation of low drug serum concentrations during pregnancy must therefore, rule out decrease in compliance in addition to the above mentioned pharmacokinetic changes.

PLACENTAL-FETAL COMPARTMENT EFFECT

Several pharmacokinetic models have been proposed in an attempt to characterize drug behavior in the placental-fetal unit (10). Depending on the drug and the available experimental data, the body is represented as a one or more compartmental system. When an administered drug readily equilibrates to achieve a fetal-maternal drug concentration of about unity-a single compartment model may be applied. On the other hand, when the fetal tissue is more slowly accessible, thus representing a deep compartment, a two compartmental model may be more appropriate. In this case the fetal-maternal concentration ratio will be lower during drug administration than during the post distribution phase. Salicylates and diazepam are examples for such a model, as they achieve higher concentrations in the fetal than in the maternal plasma (27–29). Such considerations may be important in assessing fetal exposure to different agents on the basis of maternal plasma concentrations. In addition, different physiologic factors such as differences in plasma protein binding or in acid-base equilibrium of the maternal versus the fetus also contribute to the understanding of fetal-maternal drug concentration ratios.

Effect of Protein Binding

The fetal and newborn plasma proteins appear to bind various drugs (e.g., ampicillin, benzylpenicillin) with less affinity compared with maternal plasma proteins (30). For other drugs (e.g., salicylates) a more extensive binding to fetal than maternal proteins has been documented (27). Maternal plasma albumin gradually decreases during pregnancy whereas fetal albumin progressively increases. This dynamic process results in different fetal-maternal albumin concentration ratios at different gestational ages. The fetal albumin concentration reaches its peak at term when it equals or even exceeds maternal albumin concentration (31). This may be clinically important because the free (unbound) drug fraction is an important determinant of drug movement across the placenta. Because the unbound ("free") drug is the fraction capable of crossing the placental barrier, least protein bound drugs such as digoxin or ampicillin, reach higher concentrations in the fetus and in the amniotic fluid. On the other hand drugs with high protein binding such as dicloxacillin achieve higher maternal than fetal concentrations.

Acid-Base Equilibrium Effect

Non-ionized, high lipid soluble molecules penetrate biologic membranes more quickly when compared with less lipid soluble, ionized molecules. Therefore the maternal and fetal PH are important determinants of placental transfer especially for weakly acidic or basic drugs whose pKa is close to the plasma PH. The fetal plasma PH is usually slightly more acidic than the maternal. Consequently, weak bases will be mainly non-ionized and therefore able to easily penetrate the placental barrier. However after crossing the placenta and making contact with the relatively acidic fetal blood, these molecules will become more ionized. This results in an apparent fall in fetal concentrations of the drug and leads to a concentration gradient and therefore a net movement from the maternal to the fetal system (32). This phenomenon is commonly referred to as "ion trapping." The magnitude of this phenomenon was demonstrated in a study in which sodium salicylate 20 mg/kg body weight was administered intravenously to 115 pregnant women at the begining of labor. Serial blood samples from the mothers and umbilical cord of the newborns were obtained. There was a slow transfer of salicylate from the mothers to the fetus and an increase in neonatal to maternal serum concentration ratio to an average of 1.5 after 4 hours (120 mg/L in newborns, 80 mg/L in the mothers) (33). Thus, at least at term, plasma concentration of salicylate in the fetus are higher, an important consideration when assessing the magnitude of fetal exposure to salicylate on the basis of the mother's drug concentration.

Feto-Placental Drug Elimination

There is some evidence that both the human placenta and the fetus are capable of metabolizing drugs (34–36). A11 enzymatic processes including phase 1 (oxidation, dehydrogenation, reduction, hydrolysis etc.) and phase 2 (glucuronidation, methylation, acetylation) have been

documented in the fetal liver as early as 7 to 8 weeks of pregnancy (34). However, as most enzymatic processes are immature at that stage their degree of activity is very low and therefore their contribution to the overall drug elimination capacity is marginal. On the other hand, the reduced elimination capacity may cause more pronounced and prolonged drug effects in the fetus. The fact that approximately half of the fetal circulation (umbilical vein) reaches directly the heart and brain, bypassing the liver may also contribute to this effect. Elimination of drug from the fetus is primarily by its diffusion of the drug back to the maternal compartment. However, as most metabolites are more polar compared with their parent compounds, they are less likely to cross the placental barriers. This may result in metabolite accumulation in various fetal tissues. As pregnancy progresses, higher amounts of different drugs are excreted into the amniotic fluid, reflecting maturation of the fetal kidney.

PREGNANCY-INDUCED PHARMACOKINETIC CHANGES OF SPECIFIC DRUGS

Anticonvulsants

Epilepsy is a common neurologic disorder, with a prevalence of 1%. In most women with epilepsy, seizures are well controlled during pregnancy, but if frequency changes, it is usually for the worse (37).

The potential problem in the management of these patients arise from altered pharmacokinetics associated with pregnancy. In general, peak plasma levels of anticonvulsant drugs fall during pregnancy as a result of 50% expansion in plasma volume, whereas steady-state concentrations fall secondary to decrease in protein binding and increase in metabolic rate together with a decrease in the amount of drug ingested per kg body weight as pregnancy advances.

As most anticonvulsant drugs are acidic or neutral, they are highly bound to serum albumin During pregnancy, albumin levels fall, with a corresponding fall in the bound drug. The decrease in plasma protein binding leads to more free drug available for biotransformation. Thus, the unbound levels (free drug) remain relatively constant, but total plasma levels (unbound plus protein bound) fall. It should be remembered that the constant, or even higher free drug concentration may secure antiepileptic effect, as it is the free drug that reaches the brain. For practical reason, most laboratories measure total plasma concentration (bound plus unbound), rather than the unbound concentration, which is the pharmacologically active component. Phenytoin and valproic acid are both highly protein bound (approximately 90%) to plasma albumin. Monitoring total plasma levels of these drugs can therefore be misleading. Only therapeutic drug monitoring that will measure both protein bound and unbound drug concentrations can be appropriately interpreted. The increase in glomerular filtration rate (25) and renal plasma flow may enhance the clearance of renally excreted drugs such as primidone, gabapentin and vigabatrin.

Carbamazepine is regarded by many to be the drug of choice for most forms of epilepsy during pregnancy because of its relatively low teratogenic risk (38,39). Phenytoin has been associated with the fetal hydantoin syndrome, and particularly its neurotoxic potential (40–43). Both valproic acid and carbamazepine have been shown to cause neural tube defects, and in women using them full workup should be performed to rule out this malformation (44,45). Phenobarbital is much less commonly prescribed in recent years because of its tendency to produce sedation and impair cognitive function.

Altered pharmacokinetics of commonly used antiepileptic drugs during pregnancy

Carbamazepine: Carbamazepine has a relatively slow absorption, with 70 to 80% protein binding to albumin. The main eliminating route is by hepatic metabolism, and there may be a decrease in serum levels during the first months of therapy as a consequence of autoinduction of metabolism. It is important for the clinician to recognize that dose intervals and sample time are critical in interpreting serum concentrations. Large peak-trough fluctuations can be minimized by using a controlled release formulation (46). As levels tend to be lower in pregnancy, and bioavailability may be lower than with conventional carbamazepine, higher dosage may be required when using controlled release medication (47). The concentration of the primary metabolite—carbamazepine 10,11 epoxide, was reported to increase during pregnancy possibly as a result of increased carbamazepine metabolism and impaired conversion of carbamazepine-10,11-epoxide to carbamazepine-10, 11 trans-diol during pregnancy. This increase may be of importance as it thought to have comparable pharmacologic activity as the parent drug (48).

Phenytoin: Phenytoin follows non linear pharmacokinetics and has a narrow therapeutic window (49). It is mainly cleared by saturable hepatic metabolism. As a result of very high protein binding (90–97%), the decrease in serum albumin during pregnancy, and hence, enhanced hepatic metabolism, changes of bound and unbound drug are particularly important with phenytoin (50,51). Worsening seizure control or a fall in total phenytoin greater than 25% should encourage physicians to

increase the dose, although the fall in total levels by itself may not necessarily be accompanied by loss of seizure control, as discussed above regarding the free plasma level (52).

Valproic Acid: Valproic acid is rapidly absorbed and highly protein bound to plasma albumin (88%–92%) (49). The interpretation of its pharmacokinetics is limited by large fluctuations in the concentration-time profile, wide therapeutic index, and concentration-dependent protein binding (53,54). Analysis of unbound valproic acid is not routine, and similarly there is no established therapeutic range. Dose adjustments during pregnancy should be made best by clinical observation in combination with changes in concentration measurements.

Commonly Used Antibiotics During Pregnancy

β-*Lactams*

β-lactam antibiotics (Table 1) are the oldest class of antibiotics used in the treatment of infections during pregnancy. Penicillin G (benzylpenicillin) is still the most common antibiotic used during pregnancy. Other β-lactam agents are structurally related to penicillin, and are likely to be used more commonly than new compounds because of their proven safety profile. The therapeutic effect of β-lactam antibiotics depends primarily on maintaining adequate plasma concentrations during the entire treatment period. Their activity correlates well with pharmacokinetic characteristics (C_{max}, Area Under the Curve, etc.) and time during which plasma concentration exceeds the minimal inhibitory concentration (MIC) for susceptible bacteria (55). Dosage regimen for β-lactam antibiotics should be calculated according to the pharmacokinetic profile of the drug and its MIC values (56). Most bacterial infections are confined to the extravascular compartment. β-lactam enter the extracellular fluid by passive diffusion (57), and thus the tissue concentrations of hydrophilic β-Lactams will be low, despite excellent penetration properties into this compartment. Because of that, underestimation of β-lactam antibiotic concentration can occur, when measuring tissue concentrations at the infection site (58,59).

TABLE 1. *Pregnancy-induced pharmacokinetic changes for selected drugs*

Drug	Elimination half-life	V_d	Clearance	Protein binding
Amikacin	↓			
Ampicillin	↓	↑	↑	↓
Cephalosporins	↓	↓		
Labetolol	↓			
Meperidine	↑	↓	↓	
Methicillin	↑			
Nifedipine	↓		↑	
Piperacillin		↑	↑	

↑, increase; ↓, decrease.
V_d, volume of distribution.

There is good evidence that direct correlation exists between β-lactam plasma concentrations and response to infections at extravascular site, thus plasma concentration is a predictor for response. β-lactam are acidic agents, their binding to albumin ranges from 2.5% to 97% for different drugs (55).

The total area under the curve values in extravascular sites and plasma are related to the concentration of the non protein bound fraction in the plasma. The degree of protein binding in the plasma affects the penetration of drugs into tissues (60). It is usually of great importance only when the degree of binding exceeds 80% (61). Plasma protein binding can be dependent on plasma concentration, in which higher levels reduce the extent of protein binding (62).

It is important to remember that β-lactam are water soluble and transfer the placenta by passive diffusion along the concentration gradient. As this is a slow process, it takes several hours for fetal and maternal concentrations to reach an equilibrium. In the fetal compartment, water soluble drugs circulate in the fetus and are excreted into the amniotic fluid, recycling again in the fetus by gastrointestinal absorption. Thus, water soluble drugs are eliminated from the amniotic fluid slowly, and this fluid can be regarded as reservoir for hydrophilic drugs (63). For more lipophilic drugs, metabolism is an important means of elimination. Both the fetal liver and placenta can metabolize to some degree lipophilic drugs (64,65). The common denominator to most studies conducted in pregnancy is the substantially lower serum concentrations which in many cases should lead to consider higher doses than before or after pregnancy.

AMPICILLIN

Ampicillin has been studied extensively during pregnancy, and altered pharmacokinetics has been found when compared with non pregnant women (66) leading to plasma concentrations 50% lower in pregnant women than non pregnant (55). In one study 22 women undergoing cesarian section were given a single dose of ampicillin, and pharmacokinetics were compared with that performed 6 weeks post partum, with the same patients serving as their own controls. Pregnancy significantly increased the elimination rate constant, decreased the area under the concentration time curve, and increased the total body clearance (67). Another study has shown

that maternal serum levels decline relatively rapidly after intravenous infusion of ampicillin and demonstrated in fetal serum 30 minutes after maternal infusion, reaching equilibrium with maternal serum in 1 hour. The concentration of ampicillin in amniotic fluid continues to rise up to 8 hours, then slowly declines over the next 19 hours. The elimination half life was reported to be 30 minutes during cesarian section (68), 40 and 58 minutes during delivery (69,70), 40 minutes and 1.6 hours during the third trimester (70,71).

Penicillin V

Phenoxymethylpenicillin (Penicillin V) is the most commonly used antibiotic during pregnancy. Altered pharmacokinetics has been demonstrated in a study comparing 12 pregnant women during the second and third trimesters with 6 non pregnant controls. This study showed significantly faster elimination rates of the drug from the plasma of pregnant women compared with non-pregnant. Area under the curve was lower in pregnant women (441 u/mL·min) compared with non pregnant (887 u/mL·min) as was C_{max} (3.7 u/mL in pregnant versus 5.6 u/mL in nonpregnant women) (72).

Ureidopenicillins

Azlocillin and piperacillin have been demonstrated to cross the human placenta (73,74). In a study of 8 women undergoing caesarian section and 6 non pregnant women undergoing gynecologic operations, mean C_{max} values after administration of 49 piperacillin were significantly lower in the pregnant women than in the non pregnant controls (87.5 mg/L versus 172.2 mg/L). Total clearance was faster in pregnant women compared with non pregnant controls (1538 mL/min vs. 540 mL/min) and volume of distribution was significantly greater (67.6 L *vs* 41.2 L)(74). In another study piperacillin 3g every 4 hours and mezlocillin 4g every 6 hours were evaluated in 6 post partum patients. Serum half life and clearance rates were 82.4 minutes and 202 ± 105 mL/min, respectively, for mezlocillin, and 32.9 minutes and 456 ± 88 mL/min, respectively, for piperacillin (75).

Imipenem

Imipenem is a broad spectrum β-Lactam used in combination with cilastatin, a competitive inhibitor of dehydropeptidase to minimize the renal metabolism of the drug (76). In a study of 14 pregnant women in early and late pregnancy, and 6 non pregnant women, after a single dose was administered, mean peak plasma concentrations were 14.7±4.9, 14.925.2 and 43228.3 μg/mL in early pregnancy late pregnancy and non pregnant women, respectively. Volume of distribution was significantly larger during early and late pregnancy than in non pregnant women, and clearance from plasma significantly faster than in non pregnant women (77).

Lithium

Lower serum concentrations of lithium have been reported during pregnancy. Because this anti-depressant agent is eliminated almost entirely by the kidney, the increase in GFR during pregnancy is consistent with the observed decrease in serum concentrations. Because of its narrow therapeutic range, a drop in lithium serum concentrations may result in sub-optimal therapy. Some lithium is reabsorbed in the proximal renal tubule competitively by the sodium transporter. Pregnant woman with low circulating effective volume secondary either to dehydration (hyperemesis gravidarum, vomiting) or restricted sodium intake (toxemia), may experience higher lithium levels as a result of enhanced renal absorption. Finally, during puerperium, with the decrease in GFR to pre-pregnancy values serum concentrations are expected to rise, potentially leading to toxic levels.

Acknowledgments: Gideon Koren is a Senior Scientist of the Canadian Institutes for Health Research (CIHR). This work was supported by a grant from CIHR and by the Duchesney and Canadian Foundation for Women's Health Chair in Better Pharmacotherapy During Pregnancy and Lactation.

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