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## Pharmacogenetics and Other Reasons Why Drugs Can Fail in Pregnancy: Higher Dose or Different Drug?

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### Abstract

Changes in maternal physiology during pregnancy can alter the absorption, distribution, and clearance of many drugs. When presented with a clinical situation where it does not appear that a prescribed drug is working, clinicians must either change drugs or increase the dose of the current drug to achieve the desired clinical effect. A case highlighting antihypertensive medication in pregnancy and the effect of changed drug metabolizing enzymes is presented. Understanding pregnancy's effect on drug-metabolizing enzymes, transporters, and receptors can help clinicians make individualized pharmacotherapeutic decisions for patients. Pharmacogenetics potentially can aid clinicians in treating pregnant women in the future as more data are generated and individualized therapeutic models are constructed.

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Pregnancy presents unique challenges to clinicians prescribing medications for patients with pre-existing or pregnancy-related conditions. The physiological changes throughout pregnancy can alter the absorption, distribution, and clearance of many drugs.(1, 2) Recently the advent of pharmacogenetics and the effect on drugs used in pregnancy have been discussed.(3) Adding pharmacogenetics to potential explanations why drugs fail in pregnancy is an important consideration.

### Case

A patient with chronic hypertension who continued to take 50 mg twice daily oral metoprolol before and during pregnancy presented with elevated blood pressure (>150/100) as she entered her third trimester. Her baseline blood pressures in her first and second trimester were well controlled, averaging 110/70. Workups for preeclampsia and other causes of hypertension exacerbation were negative. The clinical question now revolves around whether to increase her dose of metoprolol or substitute a different drug.

After discussing the safety of different anti-hypertensive drugs in pregnancy and the physiological changes that occur to drug metabolism in pregnancy, her dose of metoprolol was titrated up to 150 mg three times daily. Knowing that concentrations of drugs in pregnant women are often less than in non-pregnant women on the same dose her metoprolol dose was maintained at 150 mg three times daily for the remainder of her pregnancy. The usual daily dose of oral metoprolol is 50–100 mg with a maximum of 450

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mg/day. Her blood pressure normalized and she went on to deliver a term, healthy baby. After delivery, knowing that the drug metabolizing enzymes and physiological changes would gradually return to baseline, she was followed closely in the outpatient clinic and her dose was eventually returned to her pre-pregnancy dose after 2 months postpartum.

## Pharmacogenetics

### CYP2D6

Metoprolol is a drug that is metabolized by the enzyme Cytochrome P450 (CYP) 2D6. This enzyme reaction deactivates the drug and allows its excretion from the body. CYP2D6 is involved in the metabolism of approximately 25% of commonly prescribed drugs.(4) Pregnancy increases the activity of CYP2D6 as it does for many other liver enzymes that metabolize drugs.(5–9) In fact, pregnancy is the only known cause of increased CYP2D6 activity. CYP2D6 activity increases beginning early in the 2<sup>nd</sup> trimester and continues to increase as the pregnancy progresses.(8) Other drugs commonly used in pregnancy also metabolized by CYP2D6 are clonidine; fluoxetine and several selective serotonin reuptake inhibitors; codeine; metoclopramide; ondansetron; promethazine; and propranolol. An updated reference listing drugs metabolized by different CYP enzymes can be found at [medicine.iupui.edu/clinpharm/ddis/table.aspx](http://medicine.iupui.edu/clinpharm/ddis/table.aspx). Table 1 highlights CYP2D6 substrates and inhibitors relevant to obstetrics and gynecology.

In addition to CYP2D6's increased activity in pregnancy, this enzyme is highly polymorphic. Genetic differences in individuals' CYP2D6 encoding genes lead to a high degree of variation in CYP2D6 activity. Many people are poor metabolizers (PMs), expressing very little of the enzyme. These individuals may have a high response to a drug like clonidine, including more side effects. Some people's genes encode for a normally functioning enzyme, leading to extensive metabolizers (EM). Some individuals have multiple copies of the gene product and are ultra-rapid metabolizers (UMs). Up to 7% of U.S. major ethnic populations are UMs, with gene multiplication UMs as high as 45% in Asians.(10, 11) These individuals may metabolize the drug so quickly that they get little effect at all. Conversely, if the drug is a pro-drug like codeine, which is converted to morphine by CYP2D6, a UM will get an enhanced pain relief and possibly more side effects compared to a PM. Thus, when prescribing drug therapy for patients, providers should be aware that an individual may have either a pronounced drug effect or no drug effect if the patient has a polymorphism in a drug metabolizing or other pathway enzyme to explain the observed response. For instance, if the patient in the case was an EM and this was known beforehand, the provider would have expected her CYP2D6 activity to increase further during pregnancy and might have been able to anticipate the need to increase her metoprolol dose.

### Physiologic changes in pregnancy

Drug clearance increases for many drugs in pregnancy, leading to more rapid elimination from the body.(1, 5, 12) This has been clearly demonstrated for metoprolol.(13, 14) Thus, the answer to the posed question in the title is often that as pregnancy progresses, physiologic changes during pregnancy may alter drug metabolizing enzymes and renal physiology, causing many drugs to be metabolized and eliminated faster as the pregnancy progresses and necessitating higher doses for pregnant women. Some examples of drugs that may be commonly under-dosed in pregnancy are levothyroxine, amoxicillin, and oseltamivir.(15–18) Sometimes required drug doses may even be higher than those recommended in non-pregnant individuals.(19) Conversely, some pregnancy physiological changes may cause other drugs to be eliminated more slowly, potentially leading to a lower required dose or increased adverse side effects.

## Other considerations

Clinicians should consider pharmacogenetic influences on drug effects. Knowing a patient's genotype before initiating therapy may lead to alternative drug choices. For instance, knowing that a patient is a CYP2D6 UM may lead a provider to prescribe anti-hypertensive drugs other than metoprolol or pain medications other than codeine that are not metabolized by liver enzymes like CYP2D6.(20)

Knowing the patient's genotype before writing a prescription currently is not practical. Barriers to genotyping include the time it takes to isolate DNA from the biological sample, the time it takes to run the assay and analyze the results, and the cost of performing the tests. Sophisticated dosing models based on genotype and physiological and demographic characteristics have also not been built for most drugs. On the positive side, DNA reliably can be obtained from non-invasive saliva samples. Additionally, the Genetic Information Nondiscrimination Act imposes personal genetic information protections for patients. Thus, when the current barriers to implementation are resolved, utilizing pharmacogenetics for individualized pharmacotherapy may become a reality.

While knowing everyone's genotype before writing a prescription is a current barrier, there are several areas of medical care where pharmacogenetically-informed therapy is commonplace. These include genotyping to guide therapy for drugs like abacavir (HLA-B\*5701), cetuximab (KRAS), imatinib (BCR-ABL), clopidogrel (CYP2C19), and warfarin (CYP2C9, VKORC1).(21–26) As more pharmacokinetic and pharmacogenetic data are gathered in conjunction with robust clinical outcomes (pharmacodynamics), pregnancy pharmacology may have certain areas where genotype data can inform drug choice. When this occurs, there are models in other diseases to help guide implementation of these tests into clinical care.

## Conclusion

While clinicians have always sought to individualize drug therapy for pregnant women based on clinical observations, providers now have more tools and potential explanations for observed differences in drug response. A recent case has been made for more research on medication effects in pregnancy by key leaders at the National Institutes of Health.(27) While there is currently no central clearinghouse of pharmacokinetic studies in pregnancy, the establishment of one would be an initial step in helping to educate providers. Utilizing the findings generated by research on individualizing pharmacotherapy in pregnancy(3) has the potential to help clinicians match drug therapy to meet each patient's unique needs: prescribing the right dose of the right drug at the right time.

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**Table 1**

## Drugs That Are Cytochrome P450 (CYP) 2D6 Substrates and Inhibitors

| <u>Relevant CYP2D6 substrates</u>            |                                   |
|--|-----------------------------------|
| Antihypertensives:                           | Clonidine (Catapres)              |
|  | S-metoprolol (Lopressor, Toprol)  |
|  | Carvedilol (Coreg)                |
|  | Propranolol (Inderol)             |
| Antidepressants:                             | Amitriptyline (Elavil)            |
|  | Fluoxetine (Prozac)               |
|  | Fluvoxamine (Luvox)               |
|  | Imipramine (Tofranil)             |
|  | Paroxetine (Paxil)                |
|  | Venlafaxine (Effexor)             |
| Pain medication:                             | Codeine (Tylenol #3)              |
|  | Hydrocodone (Vicodin, Norco)      |
|  | Oxycodone (Percocet)              |
|  | Tramadol (Ultram)                 |
| Gastrointestinal agents:                     | Chlorpromazine (Compazine)        |
|  | Metoclopramide (Reglan)           |
|  | Ondansetron (Zofran)              |
|  | Promethazine (Phenergan)          |
| Others:                                      | Chlorpheniramine (Chlor-trimeton) |
|  | Flecainide (Tambocor)             |
|  | Lidocaine (Xylocaine)             |
| <u>Relevant CYP2D6 inhibitors</u>            |                                   |
| Strong inhibitors                            | Bupropion (Wellbutrin)            |
|  | Fluoxetine (Prozac)               |
|  | Paroxetine (Paxil)                |
|  | Quinidine (Duraquin, Quinact)     |
| Moderate inhibitors                          | Duloxetine (Cymbalta)             |
|  | Sertraline (Zoloft)               |
|  | Terbinafine (Lamisil)             |
| Weak and other CYP2D6 inhibitors of interest | Amiodarone (Cordarone)            |
|  | Cimetidine (Tagamet)              |
|  | Celecoxib (Celebrex)              |
|  | Citalopram (Celexa)               |
|  | Diphenhydramine (Benedryl)        |
|  | Escitalopram (Lexapro)            |
|  | Hydroxyzine (Vistaril)            |
|  | Methadone (Dolophine)             |

|  |                         |
|--|-------------------------|
|  | Metoclopramide (Reglan) |
|  | Ranitidine (Zantac)     |

Commonly used drugs in obstetrics and gynecology relevant to CYP2D6 metabolism listed in generic (common brand name containing the drug) format.

Data from the Indiana University Division of Clinical Pharmacology. P450 Drug Interaction Table. Available at: [medicine.iupui.edu/clinpharm/ddis/table.aspx](http://medicine.iupui.edu/clinpharm/ddis/table.aspx). Retrieved June 25, 2012.

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