



The American College of Obstetricians and Gynecologists

Women's Health Care Physicians

COMMITTEE OPINION

Number 488 • May 2011

Reaffirmed 2015

Committee on Genetics

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Pharmacogenetics

ABSTRACT: Pharmacogenetics is the study of genetic variations in drug response that are determined by specific genes. It is hoped that the use of pharmacogenetics in clinical practice may improve drug safety and decrease the rate of adverse drug reactions. Given the potential applications of pharmacogenetics to women's health care, obstetricians and gynecologists should be aware of this rapidly developing field. Currently, however, there are limited clinical indications for the use of pharmacogenetics in routine obstetric and gynecologic practice.

Pharmacogenetics is the study of genetic variations in drug response that are determined by specific genes. Pharmacogenomics refers to the interactions of multiple genetic differences, as well as environmental influence, and the effect on drug responses. Adverse drug reactions are one of the leading causes of death in the United States. A 1998 study of hospitalized patients reported that in 1994, adverse drug reactions accounted for more than 2.2 million serious cases and more than 100,000 deaths (1). It is hoped that the use of pharmacogenetics may improve drug safety and decrease the rate of such untoward events. Currently, there are limited clinical indications for the use of pharmacogenetics in routine obstetric and gynecologic practice. However, given its potential applications to women's health care, obstetricians and gynecologists should be aware of this rapidly developing field.

Genetic Variation in Drug Response

Individual variation caused by single nucleotide polymorphisms in genes that encode drug-metabolizing enzymes, transporters, ion channels, and drug receptors has been associated with variation in response to pharmacologic agents. Mechanisms of such variation include extended pharmacologic effect, adverse drug reactions, increased effective dose, and exacerbated drug-drug interactions. Current research in pharmacogenetics focuses on identifying genes that may be targeted in drug development and on genetic variation that affects the level of response to a drug.

Cytochrome P450 Enzyme System

Many early investigations in this field have focused on cytochrome P450, a superfamily of liver enzymes that

catalyzes phase 1 drug metabolism (2). The genes that code for these enzymes are highly polymorphic, and enzyme activity may vary markedly depending on individual genotype (3). Individuals with decreased enzymatic activity (ie, poor metabolizers) would be expected to have a greater likelihood of an adverse reaction to a drug, whereas individuals with high enzymatic activity (ie, ultrametabolizers) would be predicted to have an inadequate therapeutic response to standard dosages.

Although there has been great hope that the determination of an individual's drug metabolism profile could provide a tailored therapeutic approach to treatment with faster attainment of therapeutic levels and fewer side effects, few effective algorithms have been published. This lack of success is most likely related to the multifactorial nature of drug responses. In addition to single nucleotide polymorphisms, other factors that affect drug response include disease pathophysiology, gene-gene interaction, environmental influences, drug-drug interaction, drug allergies, patient adherence, habitus, and body mass index (3).

Warfarin

Warfarin has been the most extensively studied drug in the field of pharmacogenetics. All warfarin derivatives inhibit vitamin K epoxide reductase complex, and variants in the gene for this enzyme (*vitamin K epoxide reductase complex 1*) are known to affect response. A recent review highlights the key issues in the pharmacogenetics of oral anticoagulant therapy, including the effects of genetic variants on dosage and complications (4). Patients carrying the cytochrome P450 alleles cytochrome P2C9*2

or cytochrome P2C9*3 require a lower mean daily warfarin dose than patients homozygous for the cytochrome P2C9*1 allele. These patients show an increased risk of overanticoagulation and major bleeding in the initial phase of warfarin therapy. Likewise, polymorphisms in the *vitamin K epoxide reductase complex 1* gene (especially the 1173 C/T allele) have been associated with lower dose requirements for warfarin.

Much of the variability in warfarin response appears to result from the combination of *vitamin K epoxide reductase complex 1* and cytochrome P2C9 genotypes, but the usefulness of genotype-specific dosages of warfarin is still unclear; several prospective studies have not demonstrated improved outcomes. A recent American College of Medical Genetics policy statement concluded that there is no direct evidence to advise for or against routine genotyping before warfarin therapy (5). A similar conclusion was reached in a review that concluded that nomograms based on clinical characteristics and response to a standardized warfarin dose had similar, if not better, accuracy when compared with pharmacogenetic-based algorithms (6).

Pharmacogenetic Testing in Clinical Practice

Currently, the U.S. Food and Drug Administration recommends pharmacogenetic testing in a few specific instances (see <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>) (7). Testing is currently required before administering maraviroc (for human immunodeficiency virus [HIV] treatment), cetuximab (for colorectal cancer treatment), trastuzumab (for breast cancer treatment), and dasatinib (for acute lymphoblastic leukemia treatment). In such specific situations, pharmacogenetic testing is done to determine if an individual is likely to benefit from the specific therapeutic agent, rather than to tailor the dosage.

The use of pharmacogenetics in obstetrics and gynecology practice holds much promise. As in other fields of medicine, however, there continues to be a lack of evidence for routine use in current practice. Prospective clinical trials are needed to develop the appropriate algorithms to introduce pharmacogenomic testing into routine clinical practice in ways that are demonstrated to improve health outcomes.

Recommendation

At this time there are no standard clinical indications for the use of pharmacogenetic testing in the routine practice of obstetrics and gynecology, and there is limited use in other clinical situations.

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ISSN 1074-861X

Pharmacogenetics. Committee Opinion No. 488. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2011;117:1240–1.