Published in final edited form as:
Semin Perinatol. 2014 December ; 38(8): 534–540. doi:10.1053/j.semperi.2014.08.017.

Is Personalized Medicine Achievable in Obstetrics?

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Abstract

Personalized medicine seeks to identify the right dose of the right drug for the right patient at the right time. Typically, individualization of therapy is based on the pharmacogenomic make-up of the individual and environmental factors that alter drug disposition and response. In addition to these factors, during pregnancy a woman's body undergoes many changes that can impact the therapeutic efficacy of medications. Yet, there is minimal research regarding personalized medicine in obstetrics. Adoption of pharmacogenetic testing into the obstetrical care is dependent on evidence of analytical validity, clinical validity, and clinical utility. Here, we briefly present information regarding the potential utility of personalized medicine for treating the obstetric patient for pain with narcotics, hypertension, and preterm labor and discuss the impediments of bringing personalized medicine to the obstetrical clinic.

Obstetrics is a discipline focused on the care of women during pregnancy, an inherently normal phase of life. Unlike other medical specialties, obstetric care providers oversee a natural process which has been successfully navigated by women for thousands of years, even before modern medicine. Over time, care for the patient with abnormal pregnancy or medical complications of pregnancy has been added to the spectrum of care provided by obstetricians. These conditions are often corrected through procedural interventions on the mother or fetus, or through medical management.

Perhaps as a consequence of the perception of normalcy and concerns for harming the fetus, only a limited number of therapies have been developed to treat the complications of pregnancy. Medications approved by the US Food and Drug Administration (FDA) for use in pregnancy fall into a small number of major categories: tocolytics, antiemetics, labor induction agents, and a few others. In comparison to many other fields of medicine, the rate

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

of approval of new medications for obstetrical indications has been slow. Uncharacteristically, the past four years has seen the FDA approval of 2 medications indicated for use in pregnancy: hydroxyprogesterone caproate (Makena®, Ther-Rx Corporation) and doxylamine + pyridoxine (Diclegis®, Duchesnay USA, Inc.). However, both medications represent a repackaging of previously accepted therapies. Hydroxyprogesterone caproate has been used since the late-20th century as a progestational agent, though it was not until the turn of the century that usage became more widespread[1]. Diclegis® is a variant of Bendectin®, a medication previously approved for treatment of hyperemesis gravidarum in pregnancy. The story of Bendectin® has been previously outlined extensively and represents an important lesson in the dangers inherent in fear about teratogenicity from medication usage in pregnancy[2]. The components of these two medications have been used off-label for years, though safety concerns still lingered among clinicians. The FDA approval of Makena® and Diclegis® formalize the acceptance of use of the medications in pregnancy. The approval of these two agents, with a long history of off-label use in pregnancy, also accentuates the difficulty in developing drugs to treat conditions in pregnancy. Truly innovative development of drug therapy in obstetrics leading to drug approval by the FDA has not occurred in many years.

Beyond medications used for obstetric indications, pregnant women are also exposed to treatments for medical co-morbidities complicating pregnancy. The selection of a medication to treat a given pathology (e.g., lupus, hypertension, seizure disorders) rests on evidence of efficacy in the non-pregnant population, balanced against teratogenicity or correlation with poor obstetric outcomes. Historically, the FDA has maintained a pregnancy drug rating system to summarize the known information on risk of drug usage in pregnancy. This A-B-C-D-X letter rating has been misinterpreted by many clinicians and has led to the withholding of therapy due to the perceived risk of medications within specific classes[3]. As early as 1997, the FDA recommended changes in drug labeling to move towards a descriptive rating system to encourage clinicians to more carefully consider the evidence supporting the use of a drug in pregnancy[4,5].

The variability in patient response to medications that occurs in general, and to an even greater extent in pregnancy, has been a factor in the increased perception of risk during this period. In addition to baseline genetic diversity, the physiologic changes of pregnancy can accentuate inter-individual differences in drug response. These physiologic changes can alter the ADME (absorption, distribution, metabolism, elimination) properties of a drug and its resultant efficacy. For example, 17α-hydroxyprogesterone caproate administered to prevent recurrent preterm delivery may have a decreased effect in women with particular progesterone receptor subtypes[6]. The variability in patient response to 17α-hydroxyprogesterone caproate may be further compounded by inter-individual differences in creatinine clearance, volume of distribution, or other contributing factors during pregnancy. Betamethasone is provided to promote fetal maturity in cases of anticipated preterm delivery; however, the effects are not uniform in all treated fetuses. Recently, genetic variations have been identified that may influence the success of this intervention[7].

The unpredictability of adverse events related to patient variability in obstetrics has led to undesirable consequences. Providers favor older drugs with minimal risks over newer,

untested medications. Litigation resulting from drug-related adverse events has further dampened enthusiasm to provide appropriate therapy to pregnant patients. Paradoxically, few drugs are routinely monitored during pregnancy despite the increased variability. Therapeutic drug monitoring is limited by a lack of available clinical assays for most drugs.

Despite these obstacles, developments in obstetric therapeutics now occur against the background of a growing body of pharmacogenomic data on drugs in general, which can be used to improve the therapeutic range of the available therapies for pregnant women and their children. Persuasive arguments have been advanced in support of using genetic information to guide the choice of drug, the dose involved and the need for monitoring[8,9]. The FDA has included pharmacogenomic information in over 130 drug labels with over 50 genes implicated in drug efficacy or safety[10]. A large portion of pharmacogenomics information in drug labels relates to drug metabolism enzymes and many are in the form of “black box” warnings. It is estimated that one fourth of all outpatients receive one or more drugs with pharmacogenomic information in the label for that drug[11].

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The pregnant woman differs in many aspects from the non-pregnant patient. Not only are there longitudinal physiologic changes that effect drug pharmacokinetics[12,13], but the genetic make-up of the fetus differs from that of the mother. While in some cases fetal genetics may play a role in fetal response to drugs[14], maternal genetics will likely play the larger role in determining disposition and response. In addition, although pharmacogenomics is increasingly recognized as a key determinant of response for drugs, few studies have been conducted in pregnant women. Thus, as with many areas of obstetrics, we must extrapolate knowledge of pharmacogenomics to this orphaned population.

The FDA labeling for several drugs commonly prescribed by obstetricians contains pharmacogenomics information (Table 1). Below, we provide examples of pharmacogenetic information of potential value to pregnant women and their health care providers, including data relevant to the use of narcotics to treat severe pain and the treatment of hypertension and preterm labor.

Narcotics

Peripartum pain is commonly treated by narcotic pain relievers, such as codeine and hydrocodone. These prodrugs require biotransformation through CYP2D6 metabolism to their active moieties, morphine and hydromorphone, respectively. CYP2D6 activity is induced during pregnancy[15]. In addition, more than 80 pharmacogenomic variants have been reported for *CYP2D6* (http://www.cypalleles.ki.se.cypalleles.com), many of which alter the activity of the enzyme (Table 2). Approximately 7% of Caucasians have a variant that leads to a CYP2D6 poor metabolizer (PM) phenotype, which results in reduced enzyme activity. For instance, these individuals have reduced capacity to convert codeine to morphine[16,17] and do not obtain adequate pain relief from codeine. Conversely, about 2–3% of Caucasians possess multiple copies of active *CYP2D6* alleles, leading to an ultrarapid metabolism (UM) phenotype. In these individuals, codeine is rapidly converted to morphine, potentially leading to toxicity[16,17]. While rare, cases of death in UM individuals treated with

clinical doses of codeine have been reported[18–20]. In some of these individuals, the presence of a variant that reduces the activity of UDP-Glucuronosyltransferase-2B7 (UGT2B7), the enzyme responsible for inactivation of morphine, may have also contributed to the toxic concentrations of morphine. After the report of an infant death associated with the CYP2D6 UM genotype of a breastfeeding mother taking codeine for post-Cesarean pain relief[21], the U.S. FDA issued a Public Health Advisory cautioning women on the use of narcotic analgesics during breastfeeding[22]. Additionally, the Clinical Pharmacogenomics Implementation Consortium (CPIC) has issued guidelines on the use of codeine with respect to *CYP2D6* genotype[17]. While hydrocodone and oxycodone undergo similar metabolic activation via CYP2D6, there are not adequate data regarding the consequences of PM or UM phenotype for use of these agents.

Antihypertensives

Commonly used to treat hypertension in pregnancy, metoprolol is metabolized primarily by CYP2D6. A meta-analysis of studies in non-pregnant individuals recently identified a 15-fold difference in apparent oral clearance of metoprolol between ultrarapid and poor metabolizers for CYP2D6[23]. In addition to the pharmacogenetic variation of *CYP2D6*, the enzyme's increased activity in pregnancy[15] may necessitate increased doses of metoprolol compared to those used in non-pregnant women.

Similar to metoprolol, labetalol's half-life is decreased during pregnancy[24]. A recent study found that gestational age and lean body weight were significantly associated with oral clearance[25]. Labetalol is cleared predominantly by glucuronidation through UGT1A1 and UGT2B7[26]. The documented increase in UGT1A1 expression during pregnancy has been attributed to the induction of UGT1A1 by progesterone[26]. A study in healthy Chinese males was unable to confirm an association with UGT1A1 genotype, but did find higher plasma concentrations of labetolol in CYP2C19*2*2 expressers, accounting for 60% of the total variation in plasma exposure[27], indicating that oxidative metabolism may be an important component of labetalol's clearance. To our knowledge, no studies of pharmacogenomics of labetalol in pregnancy have been conducted. Hydralazine, a vasodilator available for the treatment of hypertension since 1952, is one of the few medications available to treat hypertensive emergencies in pregnancy, including severe preeclampsia. Hydralazine is primarily metabolized and cleared from the body by the N-acetyltransferase enzyme[28]. Based on a small study examining the metabolism of caffeine, N-acetyltransferase activity does not appear to significantly change during pregnancy[29]. That said, functional polymorphisms in the genes encoding the two human n-acetyltransferases, *NAT1* and *NAT2*, are common[28]. Over 50% of Caucasians are slow acetylators, leading to increased plasma concentrations of hydralazine, and therefore, increased risk of toxicity.

Treatment of Preterm Labor

While the β2 adrenergic receptor agonists, e.g. ritodrine, terbutaline, and hexoprenaline, have fallen out of favor in the treatment of preterm labor due to increased adverse effects and limited efficacy, it is important to note the potential for interindividual variability in response to the agents. There is evidence that polymorphisms in the β2 adrenergic receptor

(ADRB2) are protective against preterm delivery[30–32]. In addition, Landau et al. found that homozygosity in Arg16 improved the tocolytic response to hexoprenaline[33]. Additional studies are needed to examine the effect of polymorphisms in ADRB2 on response to β2 adrenergic receptor agonists. However, clinicians should be aware of the potential contribution of pharmacogenetics to the interindividual variability in response to these drugs, which may necessitate the increase of dose to improve efficacy or decreasing the dose to prevent adverse drug events.

The calcium channel blocker nifedipine is metabolized by CYP3A enzymes in the liver and gastrointestinal tract. CYP3A activity increases during pregnancy[15,34], resulting in higher clearance of nifedipine[35]. Since CYP3A activity is highly variable within and between individuals, it is not surprising that plasma concentrations of nifedipine are highly variable (30–70%) among pregnant women. Studies of nifedipine in pregnant women have found that *CYP3A5* genotype and concomitant administration of CYP3A inhibitors, such as clarithromycin, erythromycin, and fluoxetine, are associated with altered nifedipine pharmacokinetics[36,37]. In addition to the potential effect of polymorphisms in drug metabolizing enzymes, genetic polymorphisms in components of the L-type calcium channel (*CANC1C*, *CACN1D*) and the large-conductance calcium and voltage-dependent potassium channel ß1 subunit gene (*KCNMB1*) are associated with responsiveness and risk of cardiovascular side effects in patients taking calcium channel blockers for hypertension[38–40]. At present, it is unknown if these variants influence the tocolytic response to nifedipine.

The prostaglandin inhibitor indomethacin is widely used as a tocolytic, and is primarily metabolized through O-demethylation by CYP2C9[41]. The activity of CYP2C9 is increased during pregnancy[12,42,43]. Additionally, CYP2C9 is highly polymorphic with 10–20% of Caucasians and up to 6% of blacks expressing poor metabolism phenotypes arising from CYP2C9*2 or CYP2C9*3 alleles[44]. It is estimated that 50% of indomethacin clearance is due to CYP2C9, and poor metabolism status is predicted to increase exposure by 1.8-fold in non-pregnant individuals[45]. However, to our knowledge, no clinical studies have examined the effect of CYP2C9 genotype in pregnancy or on indomethacin tocolysis.

While its effectiveness as a tocolytic is marginal[46], magnesium sulfate is commonly used for fetal neuroprotection[47–49]. Magnesium sulfate is cleared through renal filtration with homeostatisis maintained by reabsorption through a variety of passive and active transport mechanisms[50]. To our knowledge, the pharmacogenomics of magnesium sulfate have not been examined.

Betamethasone and, less commonly, dexamethasone are administered to women at risk of preterm birth to promote fetal lung maturity. Several studies have examined pharmacogenomics of corticosteroids, although few have focused on this indication. Pharmacogenomic studies in asthma have associated variants in several genes in the corticosteroid pathway with responsiveness to inhaled corticosteroids: corticotropin releasing hormone receptor 1 (*CRHR1*)[51]; T-box 21 (*TBX21*)[52]; neurokinin receptor 2 (*NK2R*)[52]; Stress-induced phosphoprotein 1 (*STIP1*)[53]; dual specificity phosphatase 1 (*DUSP1*)[54]; the Low affinity IgE receptor, *FCER2* (rs28364072)[55]; and the glucocorticoid-

induced transcript 1 gene (*GLCC1*)[56]. In a study of 62 preterm neonates born to mothers who had received betamethasone, the I105V variant in glutathione-S-transferase-P1 (*GST-P1)* was associated with reduced occurrence of respiratory distress syndrome[57]. GST-P1 is the primary GST isoform expressed in the placenta, and this variant leads to reduced enzyme activity, which could result in increased fetal concentrations of betamethasone. Haas et al. conducted a pharmacogenomic study examining SNPs in the betamethasone metabolic pathway in cohort of 109 pregnant women and 117 maternal-neonatal pairs treated with betamethasone for fetal lung maturation[14]. A multivariate analysis controlling for various demographic and clinical factors found a statistically significant association of maternal *CYP3A5* genotype, maternal *N43C1* (rs41423247), fetal *ADCY9* (rs2230739), and fetal *CYP3A7*1E* with neonatal respiratory distress syndrome (RDS). Of these genes, fetal *CYP3A7*1E* genotype was found to have the highest odds ratio of 23.68 (95% CI: 1.33–420.6) for development of RDS[14], potentially due to an increased clearance of betamethasone by CYP3A7. Additional analysis of this same cohort identified SNPs in maternal or fetal importin 13 (*IPO13*) that were associated with outcomes such as surfactant use and bronchopulmonary dysplasia[7].

Clinical Utility of Pharmacogenomic Tests in Obstetrics

Despite the widespread availability of a large number of pharmacogenetic tests[58], the widespread use of pharmacogenomic testing is inherently dependent on the generation of evidence that supports it. Three key elements of evidence are required: analytical validity, clinical validity and clinical utility.

Analytical validity refers to the reproducibility of a given test in the laboratory. In contrast, clinical validity refers to the ability of a test to act as a robust predictor of a clinical parameter, for example, a pharmacokinetic variable that summarizes drug exposure such as the plasma half-life or area under the plasma drug concentration-time curve (AUC). Clinical utility assesses the ability of a test to reliably predict a change in treatment necessitated by the result of the genetic test. The treatment change may include a change in drug, dose, or monitoring[59]. While analytical validity is widely available and accepted for most clinically available pharmacogenetic tests, clinical validity and utility have been less well studied or documented[59].

These criteria should be met in pregnant women prior to applying pharmacogenomics testing to obstetric therapeutics. However, research to document clinical utility will require significant effort and breadth of vision, since clinical utility has not been established in cases specific to pregnant patients. That said, this is also the case for many drugs used both in obstetrics and pediatrics where drugs are often prescribed “off label” because of the lack of trials in the appropriate populations. However, as with other aspects of drug therapy in pregnancy, it may be acceptable to extrapolate pharmacogenetic information from the non-pregnant population. For example, it is reasonable to presume that the pharmacogenetic testing for HLA-B*5701 that is standard of care before the use abacavir in HIV patients to prevent potentially fatal and disfiguring abacavir-related skin hypersensitivity[60] should also be provided to pregnant women with HIV.

Economic considerations are also important. While many pharmacogenetic tests are now available in the United States for less than a few hundred dollars, this is not universally the case. Some institutions and laboratories continue to charge thousands of dollars for tests that cost much less to carry out. The economic value of most pharmacogenetic tests, even in general practice, remains a notably understudied area[61–63]. There is an increasing realization that pharmacogenetic testing may be a means that can be used by large health care systems to improve the quality of care and save costs by reducing the significant human and economic damage brought about by adverse drug reactions[64], and ensuring that appropriate therapies are given to the patients most likely to benefit.

Conclusion

Obstetrical patients have long been an orphaned population with respect to medical advancement. However, a recent directive from the Institute of Medicine's committee on Women and Health Research that promotes the inclusion of pregnant women in clinical studies[65] and the establishment of the NICHD's Obstetric and Fetal Pharmacology Research Unit Network symbolize a recognition that the nearly four million women who are pregnant annually in the United States[66] are not immune to diseases necessitating drug therapy. While obstetrics may trail behind other medical specialties in the development of personalized medicine, in some cases knowledge obtained from other therapeutic areas can be extrapolated to the pregnant population. Additionally, the principles of analytic, clinical, and perhaps economic validity of pharmacogenomic testing developed in other populations can guide the implementation of personalized medicine to obstetrical patients. Development of models that bring together an individual's pharmacogenetic make-up and the physiologic changes associated with pregnancy may eventually guide individualization of drug selection and dosage during pregnancy to optimize drug benefit in the obstetric patient.

Acknowledgments

This work was supported by the Obstetric-Fetal Pharmacology Research Units Network grant number 1U10HD063094-0, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health. SKQ is also supported by 1 K23 HD071134-01A1, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

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Table 1

Pharmacogenomic information in the FDA label of drugs commonly administered to pregnant women.

Drug Name	Gene	Pharmacogenomic Information in FDA Label
Tramadol	CYP2D6	Concentrations in PM's were 20% higher than in EM's
Codeine	CYP2D6	Respiratory depression and death have occurred in UM children and in breast-fed infants whose mothers are UM's
Hydralazine	NAT1-2	Mean absolute bioavailability varies from 10–26% with higher percentages in PM's; EM's have lower exposure
Metoprolol	CYP2D6	EM's who concomitantly take CYP2D6 inhibitors and PM's have increased concentrations, decreasing metoprolol's cardioselectivity
Glyburide	G6PD	Hemolytic anemia linked to G6PD deficiency
Esomeprazole & Omeprazole	CYP2C19	Induction of CYP3A4 by St. John's wort led to 37.9% decrease in omeprazole AUC in PM's and a 43.9% decrease of AUC in EM's
Lansoprazole	CYP2C19	Concomitant administration with tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are IM's or PM's. Coadministration to EM's taking clopidogrel reduced the AUC of clopidogrel's active metabolite by 14%.
Pantoprazole	CYP2C19	PM's have elimination half-life of 3.5 to 10 hours; in EM's, 71% of the dose is excreted in urine and 18% through biliary excretion
Metoclopramide	CYB5R1-4 G6PD	Patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended.
Nitrofurantoin	G6PD	Hemolytic anemia linked to G6PD deficiency
Citalopram	CYP2C19	Cmax and AUC increased by 68% and 107% in PM's. Highest recommended dose in PM's is 20 mg/d due to risk of QT prolongation
Fluoxetine	CYP2D6	PM's have higher concentrations of S-fluoxetine, and lower concentrations of S-norfluoxetine, at steady state. There is no effect of CYP2D6 metabolism status on pharmacodynamics of fluoxetine.
Paroxetine	CYP2D6	In EM's, concomitant administration of paroxetine increased the AUC and Cmax of atomoxetine.

CYP2D6: cytochrome P450 2D6; NAT1-2: N-acetyltransferase 1 and 2; G6PD: glucose-6-phosphate dehydrogenase; CYP2C19: cytochrome P450 2C19; CYB5R1-4: cytochrome b5 reductase 1–4; PM: poor metabolizer; EM: extensive metabolizer; UM: ultra-rapid metabolizer; AUC: area under the plasma concentration-time curve; Cmax: maximum plasma concentration

Table 2

Common CYP2D6 alleles, functional effect, and frequency in African Americans and Caucasians[a]

Allele	Activity	Allele Frequency, Mean(Range)%[b]	
		African Americans	Caucasians
*1	Normal	40 (30–83)	54 (28–83)
*2	Normal	14 (4–29)	27 (10–40)
*3	Non-functional	0.3 (0–0.6)	1 (0–3)
*4	Non-functional	6.2 (4–8)	18 (10–33)
*5	Non-functional	6 (2–9)	3 (0–7)
*6	Non-functional	0.2 (0–1)	1 (0–3)
*9	Reduced	0.5 (0–1)	2 (0–5)
*10	Reduced	4 (3–8)	3 (0.4–15)
*17	Reduced	18 (13–26)	0.3 (0–1.1)
*36	Non-functional	0.6 (0–1)	0
*41	Reduced	9 (2–15)	9 (4–14)
*1×N	Increased	0.4 (0–1.2)	0.8 (0–4)
*2×N	Increased	1.6 (0.1–2)	1.3 (0–6)
*4×N	Non-functional	2 (0.3–4)	0.3 (0–1)

[a] Adapted from Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update.[17]

[b] http://www.pharmgkb.org/download.action?filename=CYP2D6_allele_frequency_table_R2.xlsx, updated August 2013.