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Pharmacogenomics J. Author manuscript; available in PMC 2016 November 10.

Published in final edited form as:

Pharmacogenomics J. 2016 August ; 16(4): 303–304. doi:10.1038/tpj.2016.33.

Prenatal Pharmacogenomics: A promising area for research

Elizabeth H. Dorfman, PhD[1], **Edith Y. Cheng, MD**[2,3], **Mary F. Hebert, PharmD FCCP**[4], **Kenneth E. Thummel, PhD**[5], and **Wylie Burke, MD PhD**[6]

[1]University of Washington, Institute for Public Health Genetics, Seattle WA

[2]Department of Obstetrics and Gynecology, Seattle WA

[3]Department of Internal Medicine Division of Medical Genetics, Seattle WA

[4]Department of Pharmacy, Seattle WA

[5]Department of Pharmaceutics, Seattle WA

[6]Department of Bioethics and Humanities, Seattle WA

Abstract

Clinical applications of prenatal genetic screening currently focus on detection of aneuploidy and other genetic diseases in the developing fetus. Growing evidence suggests that the fetal genome may also be informative about fetal exposures, through contributions to placental transport as well as placental and fetal metabolism. Possible clinical applications of prenatal pharmacogenomic screening include prospective optimization of medication selection and dosage, as well as retrospective assessment of whether a fetus was previously exposed to significant risk. Newly available non-invasive methods of prenatal genetic screening mean that relevant fetal genotypes could be made available to obstetricians for use in management of a current pregnancy. This promising area for research merits more attention than it has thus far received.

The demonstration of noninvasive prenatal sequencing of a fetal genome using cell-free fetal DNA(1) stimulated extensive discussion of the implications of this technological advancement, including the recent publication of a joint position statement from the European Society of Human Genetics and the American Society of Human Genetics with recommendations for responsible innovation in non-invasive prenatal screening (NIPS).(2) Noninvasive fetal genotyping and sequencing could enable expansion of prenatal genetic screening far beyond common aneuploidies, to potentially include diagnosis of Mendelian diseases and identification of carrier status and disease susceptibility markers. Much of this information has uncertain clinical utility, even for adults, and would include the identification of many gene variants of unknown clinical significance. It therefore raises

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CORRESPONDING AUTHOR/REPRINTS: Wylie Burke MD PhD, Department of Bioethics and Humanities, University of Washington, Box 357120, 1107 NE 45th St, Ste 305, Seattle, WA 98195-7120, Phone 206-221-5482, Fax 206-685-7515, wburke@u.washington.edu.

CONFLICT OF INTEREST

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ethical concerns. Left out of this discussion is the value fetal genomic data could offer to obstetric management of a current pregnancy, principally though pharmacogenomic and toxicogenomic effects, and the attendant research priorities and clinical screening opportunities.

A defining example of the fetotoxicity of some maternally administered medications is thalidomide. For this and a small number of other medications, including warfarin, isotretinoin and methotrexate, robust evidence exists to contraindicate their use in pregnancy. However, for over 90% of drugs there is significant uncertainty regarding both safety and efficacy for obstetric use.(4) This evidence deficit is a long-standing and serious problem that has the potential to harm both women and infants through the continued use of ineffective or harmful medications as well as underutilization of drugs that are both safe and effective. A better understanding of fetal drug exposures is needed determine whether adverse fetal outcomes are attributable to medication exposure, the maternal condition being treated, or other factors. Prenatal pharmacogenomics offers a path forward in this understudied area.

There is a growing body of evidence(5-7) to support the contribution of fetal genotype to inter-individual differences in placental drug transport as well as placental and fetal drug metabolism, all of which may influence the fetal safety profiles of maternally-administered medications and other chemical exposures. Nearly all drugs and xenobiotics pass through the placenta into fetal circulation to some extent, with neutral, lipophilic molecules of small molecular weight crossing most readily through passive diffusion. Fetal-origin efflux transport proteins in the apical (maternal-facing) brush border membrane of the placenta's syncytiotrophoblast are believed to play a major role in limiting fetal exposures, and several transporter genes that are ubiquitously expressed throughout the body, including P-glycoprotein (*MDR1, ABCB1*) and breast cancer resistance protein (BCRP, encoded by the gene *ABCG2*), have their highest expression levels in this tissue.(8)

Few studies have directly assessed the relationship between fetal genotype and fetal exposure to medications and other xenobiotics in humans, but variants in genes for membrane transporters are of increasing clinical interest. The International Transporter Consortium recently identified two common polymorphisms, including one in *ABCG2*, with sufficient evidence of impact to medication disposition or response to warrant their incorporation into the drug development process.(9) Polymorphisms that reduce the efflux capacity of placental membrane transporters may result in higher fetal drug exposure levels and increased concerns for fetal safety for medications used to treat a condition affecting a pregnant woman. Clinical applications could include both prospective testing to identify pregnancies likely to have significantly altered placental transfer, allowing for changes in dosing and medication selection to optimize safety and efficacy, as well as retrospective testing to identify whether fetuses may have been previously exposed to significant risk. Less common but also relevant are situations where treatment of the fetus or the placenta is the goal, such as transplacental administration of antiarrhythmic drugs to treat fetal tachycardia.(10) Characterization of variation in placental transfer may enable dosing adjustments to maintain desired therapeutic drug concentrations at the target site in these instances as well.

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Inherited variability in drug metabolism has been the subject of the majority of pharmacogenetic research to date, as this pharmacokinetic parameter can significantly affect a drug's safety and efficacy profile, as well as the dosing required to achieve the same steady-state drug concentration across individuals. The human placenta and developing fetus each have some xenobiotic metabolizing capacity, although both are minor overall relative to that of the mother, and unlikely to significantly contribute to the total pharmacokinetics of a maternally administered medication. Placental, embryonic and fetal metabolism are, however, speculated to play a role in intrauterine toxicity, particularly through the local formation of teratogenic, mutagenic and carcinogenic metabolites by cytochrome P-450 (CYP)-mediated oxidative metabolism.(11)

In contrast to most species in animal studies, the human embryo and fetus express multiple CYP isoforms in both hepatic and extra-hepatic tissues, which are thought to be involved in normal fetal development. CYP3A7 is the major CYP constituent in the fetal liver, where it participates in synthesis of estrogens and may play a significant role in fetal metabolism of exogenous compounds. Over 100 missense and nonsense variants have been observed in this gene, as well as extensive variability in gene expression and protein catalytic activity in the fetal liver,(12) and multiple CYP3A7 exogenous substrates have been identified, including several that are metabolically activated by the enzyme.

While xenobiotic metabolizing enzymes (XMEs) comprise only a small fraction of total CYP content in the placenta, several medications and other xenobiotic compounds including polycyclic aromatic hydrocarbons have been shown to undergo metabolism in this tissue. Of particular interest is CYP1A1, or aryl hydrocarbon hydroxylase (AHH), which has low constitutive activity but is highly inducible by maternal cigarette smoking. Polymorphisms in *CYP1A1* can augment AHH inducibility and increase the risk of lung cancer in smokers.(13) Placental AHH inducibility has been positively associated with the risk of low birth weight among the offspring of women who smoked during pregnancy,(14) but the overall role of fetal *CYP1A1* in smoking-associated intrauterine toxicity remains uncertain and is likely complex, with the enzyme involved in both toxicity-inducing and protective detoxification processes.

The involvement of the fetal genome in exposure-related adverse pregnancy and neonatal outcomes has strong biological plausibility and a growing evidentiary basis, but additional research is needed to demonstrate specific instances of clinical validity and utility. Pharmacological research in obstetric populations can be logistically complex; investigators must enroll participants and have them complete study procedures within limited gestational windows for eligibility, and negotiate transfer of care in high-risk pregnancies as well as the unpredictability of the timing and location of delivery. These challenges are not insurmountable, but they merit greater acknowledgement in study budgets and timelines. Interventional trials in pregnant women can also be ethically complex, although significant knowledge can be gained through minimal-risk observational studies of pregnant women who are already taking a medication. As one example, simultaneously drawing maternal and fetal umbilical cord blood at delivery enables assessment of relative and absolute fetal exposure at term and whether these parameters or clinical outcomes are influenced by fetal genotype for transporters and XMEs of interest.

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The prioritization of this research is justified by the substantial knowledge deficits that exist in maternal-fetal medicine. There is also growing interest in the intra-uterine environment and the possible fetal origins of adolescent- and adult-onset disease. Research focused on the effects of polymorphisms in placental transporters, as well as variants in XMEs expressed in the fetus and placenta, may contribute not only to a better understanding of exposure-associated adverse fetal outcomes, but also to long-term health. While caution is warranted as we consider an expanded scope of prenatal genetic screening, cell-free fetal DNA-abased methods of genomic analysis may offer an opportunity to assess and avoid harmful fetal exposures. Responsible innovation involves both minimizing the harms and maximizing the benefits of new technologies, and NIPS for pharmacogenomic and toxicogenomic applications has the potential to offer significant benefit to women and infants.

ACKNOWLEDGEMENTS

This research was supported in part by grant # U01 GM092676 from the National Institute of General Medical Sciences and the National Institutes of Health and grant #U10 HD047892 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development and the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences, the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health.

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