Study could prove beneficial to improving drug therapy during pregnancy

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More than 50% of pregnant women take at least one medication, and the average number of prescriptions per patient during pregnancy ranges from three to five. Pregnancy is known to alter the rate and extent of drug elimination posing a challenge to prescribers. At the same time, current obstetric guidelines promote the use of appropriate (i.e., "lowest effective") doses of drugs to prevent adverse outcomes in fetuses. However, determining "appropriate" dosing has been difficult as very little is understood about what causes these changes in drug disposition during pregnancy. A better understanding of altered drug disposition during pregnancy and its underlying mechanisms is critical to determine optimal dosage regimens in pregnant women.

Hyunyoung Jeong, an associate professor at the University of Illinois at Chicago, uses human liver cells to identify factors causing changes in the rate of hepatic drug elimination. Previously, her work highlighted important roles of multiple pregnancy hormones such as estrogens and progesterone in such changes. What she discovered is that most pregnancy hormones alter the expression of many enzymes involved in hepatic drug metabolism—but not an enzyme called CYP2D6. CYP2D6 is an important drug-metabolizing enzyme that is responsible for the elimination of 20% of marketed drugs. Jeong's latest study is the first to identify factors that govern CYP2D6 induction during pregnancy.

The study first established "CYP2D6-humanized mice" as a model to study CYP2D6 induction during pregnancy. These mice carry the human CYP2D6 gene so that the well-known interspecies difference in the

genes of drug-metabolizing enzymes could be overcome. In the mice, a transcription factor called SHP was shown to exhibit decreased expression in the liver during pregnancy. Follow-up mechanistic studies revealed that SHP is a negative regulator of CYP2D6 expression, suggesting that decreased SHP expression may explain CYP2D6 induction during pregnancy. To identify upstream regulators of SHP that trigger the phenomenon, different factors that are known to alter SHP expression were screened. Hepatic levels of retinoic acid, a bioactive product of dietary vitamin A and an inducer of SHP expression, was decreased in mouse livers during pregnancy.

The identification of factors underlying CYP2D6 induction during pregnancy would be a major advance in improving drug therapy during pregnancy.

More information: Dr. Jeong presented the findings during the Experimental Biology 2014 meeting on Sunday, April 30 from at the Effects of Drugs, Genetics and Pregnancy on Drug Metabolism poster session in the Sails Pavilion (Poster #W417) of the San Diego Convention Center.

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