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PHARMACOGENOMIC IN PREGNANCY

Clinical Research

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ABSTRACT

Aim: Pharmacogenomics (PGx) is part of personalized medicine, which is a fast-developing field of medicine. It is the study of how a patient's genetic makeup affects and how they react to drugs. In pregnancy the physiological and genetic changes will affect the drug efficacy and can cause side effects. The goal of this review is to outline the pharmacogenetics employed in current therapies, to outline recent results and research in obstetric pharmacogenetics, and to outline what is required to assure the future of pharmacogenetics and customized pharmacotherapy in pregnancy. **Conclusion:** Results from Pharmacogenomic tests may help ensure that medications are used safely during pregnancy and after delivery, and they may also provide mothers more assurance that their child will gain from breastfeeding. More efforts are needed to raise knowledge of testing, encourage informed decision-making, and ensure proper utilization and availability because Pharmacogenomic testing is still new many physicians and patients.

KEYWORDS

Pharmacogenomics, women, pregnancy, medications.

INTRODUCTION:

Pharmacogenomics (PGx) is the use of genomic and molecular data to better optimize the delivery of medical care, to speed up the development and clinical testing of novel medicines, and/or to ascertain a person's propensity for a given disease or condition[1]. The use of PGx knowledge may allow for the personalization of drug dosages and usage, as well as the reduction of side effects. Importantly, genetic information can be used to determine whether a medicine is hazardous or effective. PGx is part of personalized medicine, which is a fast developing field of medicine[2].The administration of the "appropriate dose of the right drug for the right patient at the right time" is the aim of PGx . Rapid innovations in genetic technology have led to an exponential rise in the identification of number of diseases that have been linked to specific genetic variables, which has sped up the development of genetic factors as biomarkers.Also genetic variations in individuals decide their capacity for metabolism[3]. Different subsets of patients have different levels of drug metabolizing capacity with implications for drug effectiveness and toxicity risk depending on the type of drug.

The value of PGx in clinical practice is being studied through randomized clinical trials and other experimental methods. Over 85–95% of the population has an actionable PGx variant that could affect dose or treatment, and more than 350 drugs currently have PGx information in their FDA-approved labelling. There are 88 drugs that now have CPIC[The Clinical Pharmacogenetics Implementation Consortium (CPIC] Level A evidence, which means that at least one moderate or strong action change in prescribing is advised based on the high-quality evidence in favor of doing so[4] . Different people can respond differently to the same medication, which is a well-known phenomenon in the medical field for which PGx gives insights.

PGx testing arguably falls somewhere between the definitions of predictive testing and predisposition testing because, when exposed to a particular drug[5] the phenotype may or may not appear depending on the degree of clinical and genetic heterogeneity. PGx testing after ADR could be regarded as diagnostic.

Pregnancy Status In Pharmaceutical Research

The majority of treatments lack pregnancy data for a variety of reasons Due to many medical dangers, ethical problems, and the fact that pregnant women make up a small portion of the patient population, pharmaceutical companies have also shown little interest in including pregnant women in their drug development studies.Schonfeld discovered that pregnant women were excluded from more than 75% of all research protocols and from more than 90% of all protocols including pharmacological studies[6] in an examination of all protocols submitted to a single institutional review board (IRB).

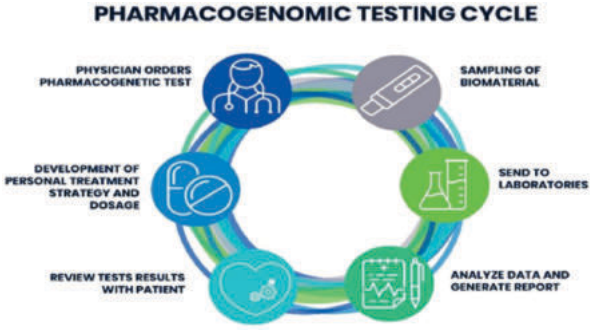

Figure 1: Pharmacogenomic Testing Cycle [https://www. mdpi. com/1999-4923/12/12/1240]

Physicians rely on dose regimens in package inserts, which are typically derived from research in healthy males, because pregnancy-specific dosing of medicines is nearly universally lacking .In order to prevent unintentional early drug exposure to fetuses, the US National Research Act of 1974 legislated the exclusion of women of reproductive age from numerous trial . It wasn't until the early 1990s that the FDA started requesting gender specific analysis of safety and efficacy data on all new drug applications and the National Institutes of Health started asking for the inclusion of women in human subjects research[7].

The US NIH-funded Obstetric-Fetal Pharmacology Research Units Network and other international organizations are working to overcome the gap in prenatal pharmacokinetic and pharmacodynamic data[8] . The goal of this review is to outline the pharmacogenetics employed in current therapies, to outline recent results and research in obstetric pharmacogenetics, and to outline what is required to assure the future of pharmacogenetics and customized pharmacotherapy in pregnancy .

Drug Metabolism And Pregnancy

The idea that pregnant women are a unique population is supported by hormonal changes, increased plasma volume, increased renal clearance, modifications in protein binding, and changes in hepatic metabolism. Glucuronidation and chemical modification by cytochrome P450 enzymes are two important metabolic routes for drug metabolism, which largely take place in the liver[9].The

metabolism of many drugs depends on one or both of these enzymes, and hormonal factors during pregnancy might cause changes in enzyme activit Lamotrigine, for instance, is metabolized mostly by the process of glucuronidation. Lamotrigine concentrations decrease during pregnancy, a powerful inducer of glucuronidation (uridine diphosphate-glucuronosyltransferase (UGT)1A4), is increased during pregnancy[10]. Also, low activity has been associated with CYP1A2 and CYP2C19 during pregnancy.

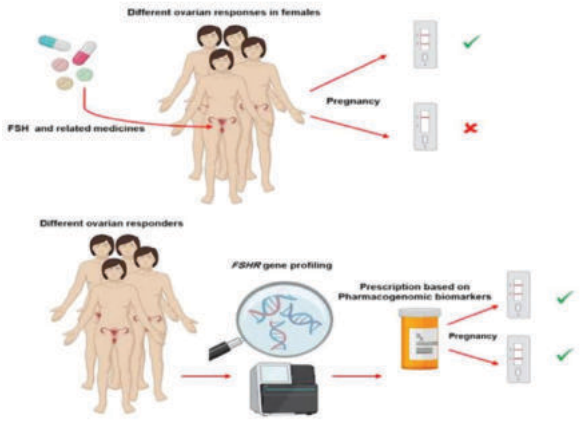

Figure 2 : Pharmacogenomic Biomakers Of Follicle- Stimulating Hormone Receptor [https://www.mdpi.com/2077-0383/10/2/170]

Pharmacogenomic Liability Of Medications Commonly Prescribed During Pregnancy

MEDICATION CLASS	MEDICATIONS	BIOMARKERS	ASSOCIATED PHARMACOGENETIC LIABILITY
Antimicrobials	Nitrofurantoin	Glucose-6-phosphate dehydrogenase	Hemolyticanemia risk
Antidepressants	citalopram/escitalopram	CYP2C19	Ultrarapid metabolizers have lower plasma concentrations, increasing likelihood of treatment failure
	Paroxetine	CYP2D6	Ultrarapid metabolizers have lower plasma concentrations,increasing likelihood of treatment failure
Antiepileptics	Carbamazepine	HLA	HLA-B is associated with greater risk of stevens-johnson syndrome (SJS)toxic epidermal necrolysis
	Oxcarbazepine	HLA	HLA-B is associated with greater risk of stevens-johnson syndrome (SJS)toxic epidermal necrolysis
Antihypertensives	Metoprolol	CYP2D6	Poor metabolizers and extensive metabolizers who concomitantly useCYP2D6 inhibiting drugs will have increased metoprolol levels
Gastroenterology	Metoclopramide	CYP2D6	Poor metabolizers are at potentially increased risk of dystonic and other adverse reactions. Lower maximum daily dose recommended in CYP2D6 metabolizers
	Omeprazole	CYP2C19	Systemic exposure to omeprazole varies withpatient's metabolism status at CYP2C19
	Ondansetron	CYP2D6	Increased metabolism inCYP2D6 ultrarapid metabolizers; associated with decreased response to medication
Opioids	Codeine	CYP2D6	Ultra -rapid metabolizers may have higher levels of morphine in breast milk, leading to infant respiratory depression.
	Codeine	UGTB7*2	Infants who are breastfeeding and have the UGTB7*2 genotype have potentially reduced activity. In a combination with the mother who has is a an ultra-rapid metabolizer, this may lead to toxicity of morphine in the infant

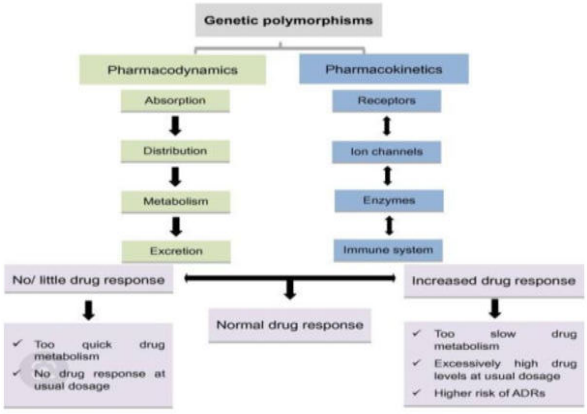

Figure 3: Genetic Polymorphisms [https://www. semanticscholar. org/paper/pgx-of-drug-metabolizing-enzymes-and-ahmed-zhou/c62e15dff525140f6fa03b71802a71a977f60ebc]

Physiologic And Metabolic Changes That Could Have An Effect On Medication During Pregnancy

CHANGE	EFFECT ON PREGNANCY
Slower gastric emptying reduced, intestinal mortality	May effect drug absorption
Increased in gastric pH	May effect drug absorption
Increased glomerular filtration rate	Enhanced renal drug elimination Decreased steady state concentration of many drugs
Increased in total volume of distribution	Altered drug distribution Decreased peak serum concentration of many drugs
Hypoalbuminemia	Decreased protein binding and increased free drug fraction
Change in metabolic enzyme activity	Altered drug metabolism: -CYP1A2,CYP2C19 activity/expression is decreased -CYP2A6,CYP2C9,CYP2D6,CYP3A, uridine glucuronyl transferase activity/ expression is increased
Presence of placenta	Additional metabolism and transport of some drugs

Need Of Pharmacogenomic Application In Pregnancy

Pregnant women commonly use over-the-counter and prescription drugs which should be stopped by the various physiological changes that occur during pregnancy have an impact on medication efficacy, and these changes may also be influenced by hereditary factors[11]. Monitored drug therapy is frequently required for pregnant women . During pregnancy, more than 95% of women use a prescription medication or dietary supplement. This covers more than 65% of women who take prescription medication in addition to prenatal vitamins and iron. Utilizing developing genomics technologies can assist in the introduction of PGx in perinatology.

Over the past three or four decades, there has been a steady rise in the

usage of drugs during pregnancy .The frequency of underlying medical comorbidities, changes in the demographics of pregnant women, and the emergence of maternal disorders requiring medication during pregnancy are the main causes of this. Also most therapies and biologics were never tested in pregnant women during development, these drugs are still regarded as **Therapeutic orphans**[12].The pharmacokinetic and secondary pharmacodynamic properties of medicines are impacted by the physiological changes in pregnant women.In an effort to highlight the importance of the latter, the goal of this study is to present a broad overview of the epidemiology of medication , usage and the current state of drug research in pregnancy.

Following reasons can brief the need of PGx in Pregnancy:

1. Given the prevalence of and growing importance of pharmaceutical usage during pregnancy, it is essential to understand pharmacogenetic liability
2. 80% of women use at least one drug throughout the first trimester, whether it be prescription or over-the-counter (excluding vitamins and iron).[13]
3. Nearly 30% of pregnant women experience poly-pharmacy, which is the use of four or more drugs, whether prescribed or over-the-counter
4. Among the most prevalent prescription drugs during pregnancy include antibiotics, antiemetics, and medications for chronic diseases like asthma, depression, anxiety, hypothyroidism, and pain.
5. As per FDA drug labelling and CPIC standards, many of these drugs have documented pharmacogenomic risks[14]
6. FDA labelling is intended to educate physicians of any treatment issues that may arise based on pharmacogenomic data .

CONCLUSION:

By gaining a better understanding of how to properly treat women throughout pregnancy, research studies like OPTI-MOM will contribute to lowering the burden of maternal sickness and, by extension, reducing rates of drug-related foetal and infant illness. Pharmacogenomic and pharmacokinetic studies of medicines during pregnancy will continue to guide clinical decision-making and prescription practices.

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