

Drugs In Pregnancy

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Variation in drug response may occur in pregnancy because of pharmacogenetic, pharmacokinetic and pharmacodynamic factors.

Pharmacogenetics [1]. The β_2 adrenergic receptor may have an arginine-to-glycine substitution at codon 16 (Arg16Gly) and a glutamine-to-glutamate substitution at codon 27 (Glu27Gln). Arg16 homozygotes given β_2 agonists for tocolysis had prolonged gestation and significantly better neonatal outcome. During spinal anesthesia for cesarean delivery, Gly16 homozygotes required less ephedrine for the management of hypotension compared with the Arg16 homozygotes and Arg16Gly heterozygotes. Glu27 homozygotes similarly required less ephedrine. The mu opioid receptor gene at nucleotide position 118 may have an adenine substitution by a guanine (A118G). In vitro, the G118 allele increases the binding and potency of β -endorphin, but clinical results have been conflicting. In laboring women, the AA homozygote had an increased intrathecal fentanyl requirement for effective analgesia. In women who received intrathecal morphine for analgesia after cesarean delivery, the AA genotype had less pain, required less morphine by patient controlled analgesia and had a higher incidence of nausea and vomiting.

Pharmacokinetics [2]. The metabolism of drugs via some cytochrome P450 (CYP) isoenzymes (CYP3A4, CYP2D6 and CYP2C9) and uridine diphosphate glucuronosyltransferase (UGT) isoenzymes (UGT1A4 and UGT2B7) is increased during pregnancy. Examples are phenytoin (CYP2C), midazolam (CYP3A4) and morphine (UGT2B7). In contrast, CYP1A2 and CYP2C19 activity is decreased during pregnancy and this reduces the metabolism of drugs such as caffeine and theophylline (CYP1A2). Infants of breastfeeding mothers taking codeine may have central nervous system depression, and even death from opioid poisoning has been reported. Codeine is metabolized to morphine by CYP2D6 and 1-16% of mothers may be ultrarapid CYP2D6 metabolizers. In addition, genetic variability in UGT2B7 may increase the formation of active morphine-6-glucuronide. It is estimated 1.4% of Western European women would have both the CYP2D6 and UGT2B7 variants promoting neonatal depression [3].

Pharmacodynamics [4]. Pregnancy reduces inhalational anesthetic requirements by 25-30%, and this is apparent from the end of the first trimester through to a few days after delivery. There appears to be less of a reduction in intravenous anesthetic requirements, but further research is required to separate the contributory pharmacokinetic from pharmacodynamic factors. Pregnancy also decreases sensitivity to pain, especially near term. Progesterone is likely to be mainly responsible for many of these changes because exogenously administered progesterone can produce most of these effects.

References

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