Particular Patterns of the Influence of the Physiology of Normal Pregnancy on the Pharmacokinetics of Drugs in the Liver

ABSTRACT

Pregnant women are the most "untouchable" group of people in relation to pharmacological research due to ethical and legal aspects, as well as concerns for the health and integrity of the fetus. And that is why pregnant women practically do not participate in clinical, pharmacodynamic, or pharmacokinetic testing. The mechanisms of teratogenesis are unpredictable, and in this case mutations can occur regardless of the duration of pregnancy and at any level. In women during pregnancy, the activity of liver enzyme systems involved in drug metabolism changes completely, which affects their clearance. This should be taken into account when selecting drugs and dosages for the treatment of various diseases. Our study showed that during pregnancy, a significant decrease in the intrinsic hepatic clearance of the CYP1A2 substrate is enhanced by a decrease in the binding of theophylline to plasma proteins and an increase in the glomerular filtration rate.

Key words: liver enzymes, pregnancy, caffeine, proguanil, lamotrigine, phenytoin, methadone.

1. INTRODUCTION

1.1 RELEVANCE

Pregnant women are the most "untouchable" group of people in relation to pharmacological research due to ethical and legal aspects, as well as concerns for the health and integrity of the fetus. And that is why pregnant women practically do not participate in clinical, pharmacodynamic, or pharmacokinetic testing. This leads to the fact that all responsibility for assessing the risk and benefit of a particular drug in a particular clinical situation falls solely on the attending doctor. After all, reproductive scientific research on animals does not always allow us to predict the results in humans. The most dangerous and fraught reactions are drug-induced fetal malformations. The mechanisms of teratogenesis are unpredictable, and in this case mutations can occur regardless of the duration of pregnancy and at any level. In addition to this problem, women in the position are very often left without the necessary therapy, thus trying to mitigate all the risks associated with the use of medicines and avoid unnecessary effects on the fetus, sometimes even ignoring the patient's condition [1, 2]. Or another perspective: often doctors do not adjust the dosage and frequency of taking the drug and prescribe a standard scheme for adults, without taking into account the physiological changes in the body of a pregnant woman [3,4].

There are two important reasons to study individual medications and drug therapy during pregnancy. Firstly, the change in reproductive age. The realities of life are such that currently women from 10 to about 50 years old are considered to be of reproductive age, and even elderly women can become pregnant with the help of in vitro fertilization and donor eggs [5]. This expansion of the boundaries of pregnancy increases the number of women who may require therapy to treat diseases that occur during pregnancy and continue after its onset [6,7]

Secondly, these are physiological transformations during the gestation period. Adaptive metabolic settings can affect the pharmacokinetics of drugs, changing their peak concentration and the time it takes to reach it by reducing the binding of the compound to plasma proteins and increasing the volume of distribution. In addition, changes in renal and (or) hepatic clearance may occur [8]. When extrapolating pharmacokinetic data obtained from studies involving mostly non-pregnant women, physiological changes occurring during pregnancy are not taken into account for pregnant women. This may affect the effectiveness of the drug and, ultimately, the overall outcome of pregnancy [4,9].

The purpose of the study: to conduct a review analysis of the literature on pharmacokinetics of drugs on specific examples.

2. RESULTS AND DISCUSSION

During pregnancy, women completely change the activity of liver enzyme systems involved in drug metabolism, which affects their clearance. This should be taken into account when selecting drugs and dosages for the treatment of various diseases [10,11].

In pregnant women, the activity of liver enzymes involved in the metabolism of pharmacological drugs completely changes, which affects their clearance [12]. There is also an almost hundredfold increase in the level of estradiol compared to the initial concentration in non-pregnant women [13]. The hormone progesterone, responsible for maintaining the normal course of processes during pregnancy, also increases sharply from 30-40 ng/ml (in the luteal phase) to 100-200 ng/ml. These changes in the level of estrogen and progesterone, as well as other placental hormones and hormonal metabolites, can affect the enzymatic activity of the liver [14-16].

CYP3A4 substrates: in numerous studies involving women in the position, it has been proven that the clearance of CYP3A4 substrate drugs increases during pregnancy. Due to the fact that midazolam is eliminated exclusively through CYP3A4 metabolism [17], its clearance in the ratio of serum metabolites in concentration, 1-hydroxymidazolam/midazolam are recognized as markers of CYP3A4 activity [18]. In full-term pregnancy, the clearance of midazolam is 2.9 times greater than in non-pregnant women. The metabolic coefficient of cortisol, a non-specific marker of CYP3A4 activity, in pregnant women shortly before childbirth was increased compared to the same women one week and three months after childbirth [19]. In women in the third trimester of pregnancy, the clearance of nifedipine was increased by 4 times compared to the historical control. Methadone, which is used in the treatment of heroin addiction during pregnancy, is also a substrate of CYP3A4. In a study of the pharmacokinetics of methadone during pregnancy in the second trimester, its clearance doubled, but decreased slightly in the third. This change is both statistically and clinically very significant, since a decrease in the level of methadone in plasma can lead to the development of withdrawal syndrome (if the dosage is not adjusted). In the study of metronidozole with delayed release, which is mainly metabolized by CYP3A4, it was found that in the second and early third trimester, the total clearance of

the drug in pregnant women with oral administration was 27% higher than in non-pregnant women. The average maximum concentration of metronidozole was approximately 25% lower during pregnancy, and this difference in the values of the area under the concentration-time curve (AUC) in pregnant women compared with non-pregnant women was approaching statistically significant [17].

The factor stimulating the induction of CYP3A4 during pregnancy is still unknown. However, both estradiol, estran and (as well as natural progestins: progesterone, pregnenolone, 17-hydroxyprogesterone and 5ß-pregnan-3,20-dione), and have been proven to activate the nuclear pregnan X receptor (pxr of the pregnan X receptor) [20,21].

CYP1A2 substrates: the clearance of caffeine, a CYP1A2 substrate, decreases by two by the middle of pregnancy, and by the third trimester - by three times compared with the postpartum period [22,23]. Although theophylline's own hepatic clearance decreases during pregnancy (Fig.1), its hepatic clearance changes slightly due to a decrease in the binding of theophylline to various plasma proteins [24].

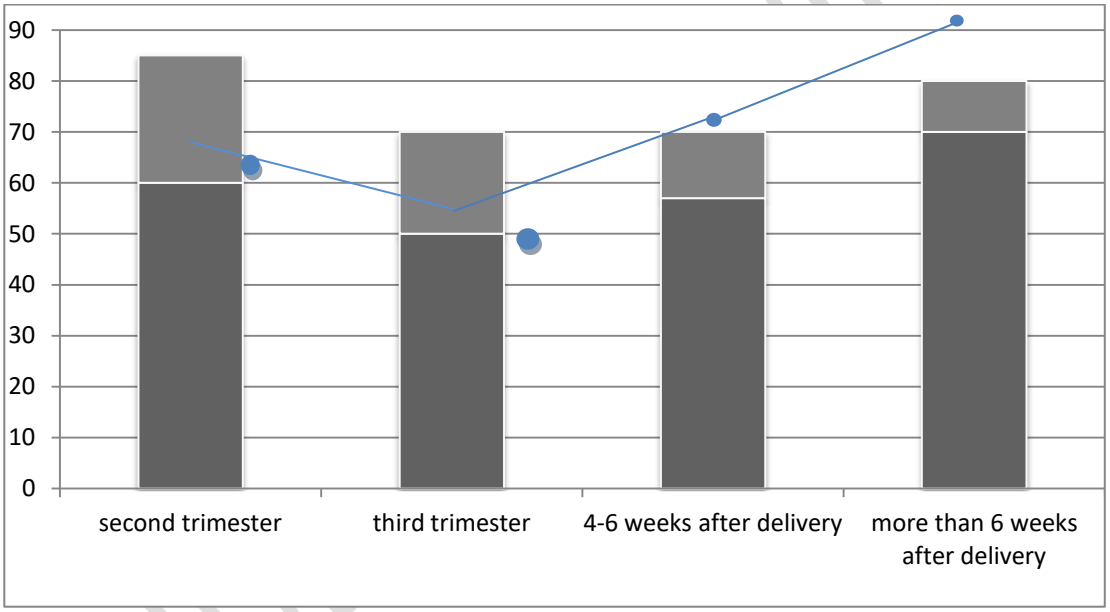

Figure 1. Clearance of theophylline in the second and third trimesters of pregnancy and in the postpartum period.

During pregnancy, a significant decrease in the intrinsic hepatic clearance (blue circles) of this CYP1A2 substrate is enhanced by a decrease in the binding of theophylline to plasma proteins and an increase in the glomerular filtration rate, so that the total clearance, consisting in total of hepatic (black bars) and renal clearance (gray bars), remains relatively unchanged.

As a result of compensating changes in hepatic and renal clearance, which were discussed above, in the third trimester of pregnancy in general, the clearance of theophylline remains unchanged.

CYP2D6 substrates: the activity of CYP2D6, which is known to be determined genetically, during pregnancy, oddly enough, increased in homozygous and heterozygous "fast metabolizers". However, the activity of this enzyme decreased in homozygotes with slow metabolism [25].

CYP2C9 substrates: the hepatic clearance of a limited metabolized phenytoin drug, which is mainly a CYP2C9 substrate, increases during pregnancy, which leads to a corresponding reduction in its total concentration in blood plasma [26]. This is largely due to a decrease in its binding to proteins, which is precisely confirmed for phenytoin, since the concentration of free substance in blood plasma has been shown to remain relatively constant until late pregnancy, when the internal clearance of this drug increases.

CYP2C19 substrates: The conversion of the antimalarial drug proguanil into its active metabolite cycloguanil occurs with the participation of CYP2C19. The metabolic coefficient of proguanil to cyclohuanil has been found to increase by about 60% during pregnancy [27]. In a population study, CYP2C19-dependent clearance decreased by 50% [28].

NAT2 substrates: using caffeine to study the transformation of liver enzymatic activity during pregnancy, both pregnant and non-pregnant women with epilepsy were examined. It was found that the activity of N-acetyltransferase (NAT - N-acetyltransferase) decreases during pregnancy. In some cases, caffeine was used to show that the normal activity of N-acetyltransferase in healthy women decreases during pregnancy [29, 30].

Glucuronidation process: the anticonvulsant and normotimic drug lamotrigine is metabolized by glucuronidation. It has been studied that its clearance [29] increases by more than 50% during pregnancy, which requires dosage adjustment. After childbirth, the clearance of lamotrigine quickly returns to the pre-pregnancy level, so the dose should be reduced during the first two weeks of the postpartum period [31, 32].

4. CONCLUSION

Betamethasone also undergoes glucuronidation in the liver, and, as it has been shown, its clearance in pregnant women is higher than in non-pregnant women. It was also found that in a two-pregnancy, the clearance of betamethasone is higher and, accordingly, its half-life is shorter than in a single pregnancy. This is believed to be caused by the increased metabolism of betamethasone with the participation of an additional fetoplacental system in a two-pregnancy pregnancy. A shorter half-life and a higher clearance can also explain the decrease in the effectiveness of betamethasone in reducing the incidence of respiratory distress syndrome in a two-pregnancy pregnancy.

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