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BEZBEDNOST PRIMENE LEKOVA U TRUDNOĆI

SAFETY OF DRUG USE DURING PREGNANCY

Aleksandar Rašković[1], Olga Sič Horvat[1]
1 Katedra za Farmakologiju i Toksikologiju, Medicinski fakultet, Univerzitet u Novom Sadu

SAŽETAK

Prioritet farmakoterapije u trudnoći predstavlja primenu onih lekova čija bezbednost garantuje da korist njihove upotrebe značajno prevazilazi rizik izazvan lekom.Sa druge strane, osnovni etički principi kliničke farmakologije nas upozoravaju da se lek može primenjivati u nekoj populaciji samo ukoliko su u njoj ispitani i potvrđeni njegova bezbednost i efikasnost. Kako se klasične kliničke studije na populaciji trudnica ne sprovode iz etičkih razloga, saznanja o bezbednosnom profilu leka u trudnoći proizilaze na osnovu rezultata ispitivanja na laboratorijskim životinjama, registara pojedinačnih slučajeva primene leka u trudnoći, retrospektivnih i observacionih ispitivanja.

U cilju sagledavanja bezbednosti upotrebe lekova u trudnoći, nacionalna regulatorna telasu formirala kategorizacije sigurnosti primene lekova u trudnoći. Ipak, nedostaci postojećih klasifikacija su posledica činjenice da su kategorije kojima lek pripada primarno utvrđene na osnovu rezultata pretkliničkih, a ne na osnovu studija na ljudima. Isto tako, postojeće klasifikacije lekova su često dovodile do zabune i lošeg informisanja o stvarnom značenju kategorije i pretpostavljenom riziku za upotrebu leka u trudnoći.

Zbog toga se od 2015. godine predlaže novi sistem kategorizacije lekova, koji podrazumeva da svi registrovani lekovi treba da imaju sažeti prikazdostupnih podataka o bezbednosti primene u trudnoći (PLLR – pregnancy and lactation labeling rule., tj. da se realan bezbednosni profil nekog leka u smuslu primene u trudnoći ne može proceniti samo na osnovu pripadnosti nekoj od kategorija u okviru postojećih klasifikacija).

Bezbednost primene lekova u trudnoći se razmatra sa stanovišta njihovog uticaja na trudnicu, placentu, plod ali i na dužinu i tok trudnoće. Organizam trudnice se tokom trudnoće fiziološki menja pod uticajem hormona, zbog čega se menjaju farmakokinetske i farmakodinamske osobine lekova. U drugom i trećem trimestru se povećava količina vode, čime se menja distribucija lekova tj. hidrosolubilni lekovi se raspoređuju u većoj količini tečnosti i postižu niže koncentracije od očekivanih. Povećanje masnog tkiva trudnice će sa druge strane smanjiti koncentracije liposolubilnih lekova.

Pored farmakokinetike, promenjena je i farmakodinamija tj. odgovor organizma trudnicena lek, kao i osetljivost organa na lekove. Bezbednost primene lekova u trudnoći zavisi i od njihovog uticaja na placentu. Izlaganje placente ksenobioticima poput fibrinolitika ili kadmijuma, dovodi do odlubljivanja i smrti njenih ćelija, a time i do potencijalno fatalnog ishoda po plod. Štetna delovanja leka na plod uslovljena su lekom i vremenom njegove primene.

Sam plod je najosetljiviji na ksenobiotike, a time i na primenu lekova, u periodu organogeneze – tj. od 20. do 60. dana gestacije, jer je tada najveća verovatnoća da primena leka dovede do malformacija ploda. Primenjeni u drugom i trećem trimestru, lekovi najčešće ne dovode do malformacija i teratogenog delovanja, ali mogu ispoljiti farmakološka neželjena delovanja na plod i uticati na trajanje trudnoće.

Na kraju, svaka trudnica ima pravo na adekvatnu terapiju, a iz grupa postojećih lekova za određene indikacije potrebno je odabrati one koji se dovoljno dugo nalaze u prometu i za koje smo sigurni da su bezbedni za plod.

Ključne reči: farmakoterapija u trudnoći, teratogeni rizik, farmakokinetika i farmakodinamija u trudnoći

ABSTRACT

The priority of pharmacotherapy during pregnancy is the use of medications whose safety ensures that the benefits of their use significantly outweigh the risks associated with the drug. On the other hand, the fundamental ethical principles of clinical pharmacology remind us that a drug can only be used in a particular population if its safety and efficacy have been studied and confirmed within that population. Since classical clinical studies on pregnant women are not conducted for ethical reasons, knowledge about the safety profile of drugs in pregnancy is based on data from animal studies, registries of individual cases of drug use during pregnancy, retrospective, and observational studies.

To better assess the safety of drug use during pregnancy, national regulatory bodies have established safety categorization systems. However, existing classifications have limitations because drug categories are primarily determined based on preclinical studies rather than human studies. Moreover, current drug classifications often lead to confusion and misinformation about the actual meaning of the category and the presumed risk associated with drug use during pregnancy.

Therefore, since 2015, a new categorization system has been proposed, requiring all registered drugs to include a summarized review of available data on their safety during pregnancy (PLLR – Pregnancy and Lactation Labeling Rule). This approach emphasizes that a drug's actual safety profile regarding pregnancy use cannot be evaluated solely based on its category under existing classification systems.

The safety of drug use during pregnancy is evaluated from the perspective of its effects on the pregnant woman, the placenta, the fetus, and the duration of the pregnancy. The pregnant woman's body undergoes physiological changes under hormonal influence during pregnancy, altering the pharmacokinetics and pharmacodynamics of drugs. In the second and third trimesters, the increase in body water changes drug distribution — hydrophilic drugs distribute into a larger volume of fluid and thus reach lower concentrations thanexpected. An increase in maternal adipose tissue, on the other hand, reduces the concentrations of lipophilic drugs.

Besides pharmacokinetics, pharmacodynamics also changes — the pregnant woman's response to drugs and the sensitivity of organs to drugs are altered. Drug safety during pregnancy also depends on the effect of the drug on the placenta. Exposure of the placenta to xenobiotics such as fibrinolytics or cadmium can lead to detachment and death of placental cells, potentially resulting in fatal outcomes for the fetus.

Harmful effects of a drug on the fetus depend on the drug itself and the timing of its administration. The fetus is most sensitive to xenobiotics, including drugs, during the period of organogenesis — from the 20th to the 60th day of gestation — when there is the highest likelihood that drug use will cause fetal malformations. When administered in the second and third trimesters, drugs usually do not cause malformations or teratogenic effects but may have pharmacological adverse effects on the fetus and influence the duration of pregnancy.

Ultimately, every pregnant woman has the right to appropriate therapy, and from the available drug options for specific indications, it is necessary to choose those that have been in use for a sufficiently long time and whose safety for the fetus is well established.

Keywords: pharmacotherapy in pregnancy, teratogenic risk, pregnancy pharmacokinetics and pharmacodynamics