

## **PARTICULARITIES OF PHARMACOTHERAPY DURING PREGNANCY**

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### **REZUMAT**

Consumul de medicamente în cursul sarcinii nu este deloc neglijabil. Între 20-40% dintre femeile gravide necesită pe perioada celor nouă luni de sarcină o terapie medicamentoasă, în cursul căreia terapeutul trebuie să țină seama de doi pacienți: mama și fătul. Departe de a juca rolul unei bariere, placenta se lasă ușor traversată de medicamente: substanța medicamentoasă administrată mamei ajunge și la făt, iar unele medicamente aparent bine tolerate de femeia gravidă pot fi responsabile de apariția unor anomalii embrio-fetale, fără a avea nici un marker predictiv pentru această evoluție. Diferiții factori care influențează susceptibilitatea produsului de concepție față de unele medicamente sunt: 1) vârsta sarcinii în momentul administrării medicamentului; 2) factorul maternal; 3) susceptibilitatea proprie a embrionului/fătului față de medicament (dependentă de factori genetici); 4) factorul placentar. Pentru a reduce riscul toxicității fetale induse medicamentos, se impune cunoașterea principalelor reguli generale de conduită terapeutică practică, la femeia gravidă: a) limitarea la maxim a consumului de medicamente în cursul sarcinii; b) evaluarea atentă de către terapeut a raportului beneficiu/risc; c) evitarea recomandării medicamentelor recent comercializate, unde nu avem o experiență cunoscută la femeia gravidă; d) consilierea gravidei cu privire la riscurile automedicației, inclusiv pentru medicamentele aparent anodine.

**Cuvinte cheie:** sarcină, medicamente, risc fetal și matern

### **ABSTRACT**

The use of drugs during pregnancy is a major risk. Twenty to 40% of pregnant women need medication during the 9 month of the pregnancy; the doctor has to know that he/she deals with two distinct patients: the mother and the fetus. Far from being a real barrier, the placenta is sometimes very easily crossed by some drugs, affecting in the same time the mother and the fetus, but in different manners. Some drugs, well tolerated by the mother, might be responsible for the development of some embryo-fetal anomalies, without having any predictive marker for this evolution. The factors that might affect the susceptibility of the fetus for some drugs are: 1) The age of pregnancy; 2) The maternal factor; 3) Embryo's susceptibility for drugs (depending on genetic factors); 4) The placenta. With the goal of reducing the drug-induced fetal toxicity, we must be aware of the most important general rules of therapy for pregnant women: a) The limitation of drugs consumption during pregnancy. b) The benefits/risk ratio must be evaluated very carefully by the physician. c) New drugs must be avoided, when the risk in pregnancy is not documented. d) Pregnancy counseling, concerning all the risks of self medication, even in case of apparently harmless drugs.

**Key Words:** pregnancy, drugs, fetal and maternal risk.

Medication during pregnancy, for different maternal diseases or symptoms, chronic or acute, is a very common situation in medical practice. Up to 40% of the pregnant women resort to drug therapy by their own will (especially before knowing they are pregnant), or after therapist's (physician/pharmacist) advice.

Some of these drugs, apparently well tolerated by the mother, might be responsible for the development of embryo-fetal anomalies, without having any predictive marker for this evolution. The dramatic situation caused by thalidomide in 1961 (responsible for phocomelia) and dyethylstilbestrol in 1971, responsible for the development of vaginal adenocarcinoma in little girls whose mothers had been treated with this drug during pregnancy, was a warning for the medical and pharmaceutical personnel, and is still in their memory, underlining the risks of medication during pregnancy.

This risk still exists, because pregnancy doesn't protect the young women against different diseases, by contrary, it might expose them to other conditions, directly related to the stage of pregnancy. So, the becoming mother might use different drugs during pregnancy, while in her body a lot of metabolic and

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physiologic changes are taking place. All these changes might influence in different ways the drugs' pharmacokinetic properties and by consequence their clinical effects. That's the reason why we must know as well as possible what is happening with the drugs administrated during the 9 months of pregnancy.

## **PHARMACOLOGICAL CHANGES IN PREGNANT WOMEN**

### **1. DRUGS ABSORPTION**

#### **Gastro-intestinal absorption varies:**

- Gastric evacuation time is often prolonged in pregnancy, with about 30-50%
- Intestinal motility and intestinal peristaltis are diminished, as result of a higher plasma concentration of progesterone;
- Acid gastric secretion is diminished with about 40% during the first two semester of pregnancy; peptic activity is reduced, while gastric mucus secretion and pH are increased (pH increase influence the drugs ionization and by consequence their gastro-intestinal absorption);

All these changes interfere especially with drugs' speed of absorption, resulting in a delaying.

#### **Muscular Absorption**

At the muscular level, drugs absorption depends of regional blood flow, which rises as a result of general vasodilatation, after the decrease of peripheral vascular resistance. However, at the end of pregnancy, the presence of edema might decrease the blood flow at the limbs level.

The drugs administrated i.m. in buttocks and hips have a very irregular absorption, very often unpredictable, as a result of the hemodynamic changes that occurred.

#### **Pulmonary Absorption**

Respiratory flow and alveolar ventilation are increased during pregnancy. The absorption of drug aerosols (anti-inflammatory, bronhodilatatory) is accelerated; they penetrate very fast, crossing the respiratory ways through alveolar level, therefore the absorption of the drugs administered this way is improved.

#### **Other levels of absorption**

The increase of regional blood flows facilitates lotions and pomades penetration at cutaneous level; at vaginal mucosa level drugs absorption is higher.

### **2. THE DISTRIBUTION**

#### **2.1. In mother**

##### **Hemodynamics changes**

In pregnant woman:

- total blood flow increases with about 30%,

reaching the maximum between weeks 30 and 34 of pregnancy

- cardiac flow increases with 50%
- renal and pulmonary flow are increasing in parallel with the cardiac flow, while hepatic flow remains unmodified
- uterine blood flow also increases, reaching a maximum of 600-700 ml/min, 80% for placenta and 20% for myometer.

#### **Changes in drugs binding of plasma proteins:**

Plasma albumins concentration decreases progressively during pregnancy, at the end of the 9<sup>th</sup> month reaching the value of 2.5 g% while its normal concentration is about 4 g%; this modification causes a diminished binding between plasma proteins and some drugs (non-steroidal anti-inflammatory, glucocorticoids, etc) and the augmentation of their free ratio, pharmacologically active.

The concentration of  $\alpha_1$  glycoproteins (which bind basic drugs as:  $\beta$ -blockers, prazosine, lydocaine) also decreases during pregnancy.

#### **Body hydric compartments are significantly modified during pregnancy:**

Plasma volume increases with about 50%, reaching its maximum between weeks 30 and 34 of pregnancy;

Total body water increases very much; 60% of this amount is designated for the fetus, placenta and amnion, and the remaining 40% refers to the body of the mother.

**Table 1.** Water distribution for pregnant and non-pregnant woman

<b>Non -pregnant</b>	<b>Pregnant</b>	<b>Fetus + annexes 5 l</b>
Plasma water 3 l	Plasma water 4 l	
Interstitial water 11 l	Interstitial water 16 l	
Intracellular water 28 l	Intracellular water 30 l	

Hydric spaces expansion during pregnancy modifies drug's distribution, especially for the hydrosoluble ones.

Body composition also changes during the nine month of pregnancy. Lipids accumulate especially as subcutaneous stores; adipose tissue content might grow from 3-4 kg to about 19 kilos at the end of pregnancy.

This fat tissue accumulation during pregnancy explains the raise of distribution volume for liposoluble substances (e.g. diazepam, petidine, thiopental) and the persistence of a high drug concentration after anesthesia (thiopental, bupivacaine).

Drug distribution in pregnant body is also influenced by the presence of fetus and placenta (new distribution compartments) which might play a very important role concerning drugs' quantity and trans-

port speed, from mother to fetus.

As we know, placenta can not be considered a barrier that protects the fetus against any drugs used by mother.

Most of them cross the placenta by passive diffusion. The smaller the drug molecular weight (less than 400 daltons, for the large majority of therapeutic substances), the more lipophilic and the higher ionized, the easier it crosses the placenta.

Drug's transport speed at placental level might be defined as follow:

$$V = K \cdot A/X (C_m - C_f)$$

Where K = diffusion constant, depends of molecule's physico-chemical traits (molecular weight, liposolubility, ionization)

A/X = surface/thickness ratio for interface membrane (placenta) varies with the age of pregnancy (its surface increase progressively with the age of pregnancy, while its thickness decreases; placenta becomes thinner, facilitating the trans-placental passage and increasing the quantity of drug that reaches the fetus)

$C_m - C_f$  = concentration gradient between mother and fetal circulation

The fetus has a limited capacity of hepatic metabolism and renal excretion, due to the immaturity of the organs involved in excretion processes. Drug elimination is realized mostly through mother's body.

At delivery, the newborn must eliminate alone the drugs recently administrated to his mother (few hours before delivery), only by his clearance functions, only partially mature. This situation might lead to a prolonged drug impregnation for the newborn and the occurrence of undesirable effects.

Depending on their transplacental transfer, the drugs might be classified in three categories: drugs with limited transfer, raised transfer and excessive transfer. (Table 2). The majority of molecules are included in the first two categories.

### 3. METABOLISATION

#### Mother's metabolism

Hepatic metabolism depends on: drug binding of plasma proteins, blood hepatic flow and intrinsic hepatic clearance.

Furthermore, progesterone (which has a raised hepatic excretion during pregnancy) is susceptible to stimulate the activity of hepatic microsomal enzymes ( $P_{450}$  cytochrome) and therefore accelerates the metabolism of some drugs (e.g., fenitoin, valproic acid, carbamazepine etc).

#### Fetus Metabolism

The fetal liver contains many enzymes, but incom-

**Table 2.** Drugs transplacental transfer

Group of drugs	Placenta transfer		
	Limited	Raised	Excessive
<b>ANTIBIOTICS</b>		Ampicillin	
Penicillins		Amoxicillin	
Cephalosporins	Cefotaxime		
	Cefuroxime		
Aminoglycosides	Gentamycin		
	Kanamycin		
	Amykacine		
<b>CNS MEDICATION</b>			
Anticonvulsants	Carbamazepine	Phenobarbital	Valproic acid
		Phenitoin	
Benzodiazepines		Lorazepam	Diazepam
		Medazepam	
Antidepressives		Fluoxetine	
		Lithium	
Analgesics/ anti-inflammatories	NSAI	Paracetamol	
	Dexamethasone		
	Betamethasone		
<b>ANTIHYPERTENSIVES</b>			
$\beta$ -blockers	Propranolol	Betaxolol	
	Clonidine	Sotalol	
	Methylodopa		

CNS= central nervous system

pletely matured. Their enzymatic activity is only 2% of mother's, thus fetal hepatic biotransformation has few effect on the maternal plasmatic concentration.

### 4. RENAL EXCRETION

#### Particularities of renal excretion in pregnant women:

-renal blood increases during pregnancy, becoming double at 26<sup>th</sup> week of pregnancy;

-glomerular filtration increases from 120 to 170 ml/min;

-creatinine clearance (Clcr) increases with about 50%;

-tubular secretion remains unchanged.

As a result, the renal excretion of drugs during pregnancy is much accelerated, due especially to the weak bindings between drugs and plasma proteins, as result of hypoalbuminemia caused by hemodilution.

#### In fetus

Renal excretion capacity for drugs is diminished; their excretion depends mainly of the mother.

Pharmacokinetic changes that occur during pregnancy might determinate unpredictable evolutions of biodisponibility and pharmacodynamic activity for the drugs used by the future mother. That's the reason why we must very carefully survey maternal plasma concentration and very often adjust the posology, for maintaining the optimal level of efficiency.

### **Clinical situation imposing drugs administration during pregnancy**

Drugs administration in pregnant women may be needed in two important circumstances: *to continue the therapy for a chronic disease acquired before pregnancy* (diabetes, bronchial asthma, epilepsy etc.), *or for the treatment of new disease or symptom*, developed during pregnancy, related or not to this (pains of different etiology, infections, nausea, constipation, etc.).

In this situation, therapist often deals with a serial of questions:

- Is the drug therapy indispensable or not?

-What kinds of risks involve the interruption of drug therapy? (very often stopping the drug therapy during pregnancy might expose both mother and fetus to serious risks and might have negative consequences for the fetus)

- What therapeutic agent do we recommend? For how long? What is the dose?

The answer must be always individualized, adapted to each patient. It is not enough to state that a drug is or is not recommended during pregnancy, we also must evaluate the risks of "to treat /not to treat" attitude in any particular situation.

One of the most important rules when choosing a drug for a pregnant patient demands for that compound to be very efficient and very well studied during pregnancy. It is obvious that, a new drug, without having any available studies concerning pregnancy, is contraindicated for a pregnant woman, except the situation when we don't have any other effective treatment available.

### **Drug therapy and embryo-fetal risks**

The evolution of an embryo-fetal anomaly after drug therapy depends on the simultaneous action of several factors: the nature of drug, time of exposure, posology, the intrinsic susceptibility of embryo/fetus for the drug (depending of genetic factors) and the stage of pregnancy when the drug was administered.

#### **Stages of pregnancy**

Concerning fetal toxicity, the most important fact we must consider is the stage of pregnancy, because during the nine months of intrauterine life, the product of conception is passing through several stages, each of them having its specific traits regarding the possible toxicity induced by medication.

#### **1. The stage of blastogenesis: first 14 days of gestation, following the law "all or nothing"**

In the first two weeks of pregnancy, the product of conception obeys the law "all or nothing". This signifies that medication in this stage either determines

the death of blastocyst, by stopping its evolution, or has no effect at all (it is the stage of differentiation, when the mass of cells might regenerate after such an aggression and allows cells' multiplication).

#### **2. Embryonary stage (organogenesis) = maxim vulnerability (week 3-12 of pregnancy)**

First 2 to 3 months of pregnancy are essentials in the evolution of post-medicamentous malformations, because in this period fetus organs are forming. The major risk for embryo malformations is between weeks 13-56 of pregnancy, when organs formation occurs. In this stage, each organ passes through a critical stage of maxim vulnerability, corresponding to its stage of differentiation. So, the heart is particularly vulnerable between the days 15-25 of pregnancy, the eye between days 20-40, the limbs between days 24-36 and the nervous system between days 20-40.

Depending on the moment when the drug is administered, one might predict, at less partially, what organ has been injured (only partially, because it exists a particular tropism of some compounds for particular tissues- i. e. tetracycline for bones and dental enamel).

This stage is particularly risky, because very often women don't even know they are pregnant; even more, she takes medication by her own for the first signs of pregnancy (nausea, for instance), more or less aggressive for the fetus.

#### **3. Fetal stage (months IV-VII of pregnancy): low vulnerability. Functional Risks.**

In this stage, all organs, except brain and external genital organs, are differentiated and continue their maturation.

The risks induced by medication are smaller, but still exist. The administration of a drug with a fetotoxic potential in this stage might alter the differentiation of genital apparatus, inducing pseudohermaphroditism, or induce brain lesions, resulting in different encephalopathies or delayed fetal intrauterine evolution.

Drug's toxic effects depend of how advanced the pregnancy is. The drugs are affecting the fetal physiology (organs' normal functions), respecting their morphology.

#### **4. Perinatal stage**

Theoretically, this stage corresponds to the 9<sup>th</sup> month of pregnancy, but it's better to be considered the end of the 7<sup>th</sup> month (when the fetus is viable), the risks being even higher for the prematures.

Drugs used at the end of pregnancy:

a) Might interfere with the normal evolution of labor, triggering it too early (i.e., derivatives of ergotamine used as self-medication in the treatment of mi-

graine have an ocytotic effect, inducing a hyperkinetic labor and a premature delivery) or by contrary, delaying it (i.e., drugs with a tocolytic effect: NSAIDs,  $\alpha_2$  simpatomimetics, diazoxide, magnesium sulphate).

b) Might have negative effects on the fetus and the newborn.

NSAIDs (nonsteroidal antiinflammatory drugs). As their use might present some risks for mother, fetus or newborn, they might be recommended in obstetrical pathology for two situations:

- in the imminence of premature delivery (the dose of 100-200 mg/day, for a three days continuous cure, or discontinuous: indomethacin has imposed as a reference molecule for this category of pregnant women, having a tocolytic efficiency almost as good as the one obtained by using  $\alpha_2$ -simpaticomimetics – 70-80%.

- treatment of hydramnios.

All NSAIDs administrated to the becoming mother, within 4-6 weeks before delivery, might expose the newborn at:

-Cardio-pulmonary toxicity (manifested by respiratory distress, signs of right heart insufficiency, renal, hepatic and intestinal stasis, peripheral edema) secondary to the premature closure of the arterial channel, as result of their antiprostaglandinic effect.

The risks of arterial channel narrowing (characteristic for fetal circulation) depend of the age of pregnancy. Its apparition can be observed for more than 50% of cases observed, between weeks 32-35 of pregnancy. For this reason, it's not recommended the administration of this drug 4 weeks before delivery.

-Fetal renal function disturbance, as result of the inhibition of PGE<sub>2</sub> synthesis, has clinical signs ranging from oliguria, hydro-saline retention, (weight growth) to renal insufficiency; fetus renal function degradation also determine a decrease in the volume of amnions (which is mostly the result of urine produced by the fetus).

-Prolonged bleeding time, as result of the anti aggregant and anti plachetar effect (aspirin); this fact might complicate the normal labor evolution or might determinate hemorrhages of variable gravity for the newborn.

c) Effects on the newborn:

-Drug overdose. The newborn might be exposed to a high drug concentration, used by the mother a few hours before delivery; having a limited capacity of hepatic metabolisation and renal excretion, due to the immaturity of these organs. Thus, the newborn will be prolongedly impregnated with the drug, so being exposed to several adverse effects (this risk is higher for the premature). For instance, sedatives determine som-

nolence, even lethargy, leading to some severe respiratory troubles, imposing the specialized assistance in a special infantile care unit.

-Abstinence syndrome, a few days after delivery, has been described in newborns whose mothers used large doses of benzodiazepines or opioids in the days prior to delivery.

### 5. Post delivery stage

It doesn't have a determinate time. It corresponds to the evolution of different troubles induced by the drug used by mother during her pregnancy; they emerge immediately or after a variable period of time (even years) after delivery, and manifest as follow:

a) Extra-uterine life adaptation troubles:

#### $\beta$ -blockers

Cardio-vascular effects induced by beta-blockers are well known; but we know less about their consequences on maternal and fetal physiology. The blockage of  $\alpha$ -adrenergic receptors usually induces: maternal bradycardia, slows the fetal cord beatings, decreases the blood flux at umbilicus, while in newborn induces bradycardia, hypotension and hypoglycemia (in about 40% of cases). The variety of these pathological incidents might be explained by the pharmacokinetic properties of  $\beta$ -blockers, especially by their plasma proteins binding and liposolubility. That is why it is recommended the surveillance of the newborns with mothers treated with  $\beta$ -blockers in a specialized medical care unit for the newborn, for 3-5 days after their delivery. The surveillance is longer for the prematures, because they present more intense and prolonged posttherapy side effects. Despite favorable outcome in the majority of cases, some  $\beta$ -blockers are more recommended: (propranolol, atenolol, metoprolol, sotalol, labetalol) than others. For the rest of  $\beta$ -blockers caution its recommended, because of lack of information concerning their maternal and fetal consequences. These restrictions will be removed once proof becomes available that our concerns about their effects were unjustified.

b) Post delivery troubles for the new born

- Here are included the troubles occurring a few days after delivery in newborns exposed in uterus at antidepressive drugs, imipraminic or inhibitors of serotonin reuptake (fluoxetine, fluvoxamin, sertraline); the most frequently reported symptoms are: agitation, convulsions, hyperreflexia, muscles tonus alterations (hypotonia or hypertonia), suckling disorders, etc.

-The most dramatic case was reported for diethylstilbestrol, a drug which exposed the feminine descendents of mothers that used this medication during pregnancy, at vaginal cancer, at puberty.

## **CONCLUSIONS**

Prescribing a drug during pregnancy involves the entire therapist responsibility, because he/she has multiple attributions: to establish and argue the therapy and also to evaluate the clinical situation, concerning the risks for both patients (mother and fetus).

In all cases, the following must be taken into consideration: the exact stage of pregnancy, the fact that placenta is not an impermeable barrier for the large majority of drugs, and the particularities of any pregnant. We must not deprive the becoming mother of an efficient therapy because of excessive prudence.

Once decision to use a drug is made, it is recommended the administration of minimal effective doses, for the shortest period as possible, using the best known drugs (it is recommended to avoid the use of molecules recently introduced in therapy, which were not the object of a detailed study concerning their risks during pregnancy).

It's also indispensable the counselling of the pregnant woman concerning the risks of self-medication, even in the case of apparently harmless drugs.

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## PARTICULARITIES OF PHARMACOTHERAPY DURING PREGNANCY

**Carmen Cristescu**

1. Which of the following drugs have an excessive transplacental transfer:
  - a) clonidine
  - b) valproic acid
  - c) gentamycin
  - d) fluoxetine
  - e) carbamazepine
2. Non-steroidal anti-inflammatory drugs, (NSAIDs), administered to the mother, during perinatal period can:
  - a) provoke to the newborn extrauterine adaptive troubles
  - b) have a marked oxytocic effect
  - c) disturb fetal renal function
  - d) delay fetal intrauterine development
  - e) expose the newborn to cardio-pulmonary toxicity
3. The development of a postmedication cardio-pulmonary embryo-fetal anomaly depends on:
  - a) the exposure to the drugs of the conception product
  - b) the stage of pregnancy when the drug was administered
  - c) drug's galenic form
  - d) drug's administration rhythm
  - e) administered doses
4. The administration of a potentially fetus-toxic drug, during the IV- VI month of pregnancy, can determine:
  - a) ocular congenital malformations
  - b) cardio-pulmonary toxicity
  - c) pseudohermaphroditism
  - d) various encephalopathies
  - e) congenital malformations of the limbs
5. Among the drugs which can interfere with the normal delivery evolution, having a tocolytic effect, are included:
  - a) salbutamol
  - b) ergot derivatives
  - c) theophylline
  - d) indomethacin
  - e) sotalol
6. During pregnancy, the following changes occur in the mother:
  - a) the tubular secretion is diminished at the end of perinatal period
  - b) renal blood flow increases
  - c) creatinine clearance diminishes with about 50%
  - d) tubular secretion remains unmodified
  - e) glomerular filtration increases
7. Placenta is easier penetrated by the drug:
  - a) less ionized
  - b) having a molecular weight over 400 Daltons
  - c) less lipophilic
  - d) more ionized
  - e) hydrophilic
8. Which of the following drug groups presents the risk of fetal arterial channel narrowing, when administered during perinatal period:
  - a) beta-blockers
  - b) NSAIDs
  - c) ergot derivatives
  - d) benzodiazepines
  - e)  $\beta_2$ -sympathomimetics
9. Among the antibiotics with a raised transplacental transfer are included:
  - a) cefuroxime
  - b) amikacin
  - c) kanamycin
  - d) amoxicillin
  - e) cefotaxime
10. Which of the following affirmations concerning the haemodynamical changes occurred at a pregnant is/are correct/s:
  - a) total blood flow increases
  - b) renal flow increases
  - c) uterine blood flow is reduced
  - d) cardiac flow diminishes with about 50%
  - e) hepatic blood flow remains unmodified

**To complete the examination for CPhE evaluation turn the page for instructions and the response form.**

Correct answers for CME: Polyglandular autoimmune syndromes. (TMJ 2004; 1:86-90):

1 - abc; 2 - acd; 3 - ac; 4 - acd; 5 - bc; 6 - abcd; 7 - ac; 8 - acd; 9 - ab; 10 - cd