

## SAFETY OF OVER-THE-COUNTER MEDICATION IN PREGNANCY. SOMETIMES A DILEMMA

IRINA CAZACU<sup>1</sup>, ANDREEA FARCAȘ<sup>1</sup>, CRISTINA MOGOȘAN<sup>1</sup>,  
MARIUS BOJIȚĂ<sup>1</sup>

<sup>1</sup>Drug Information Research Center, School of Pharmacy,  
University of Medicine and Pharmacy „Iuliu Hațieganu” Cluj-Napoca

### Abstract

*Over-the-counter (OTC) drugs are a category of medication which can be consumed by patients without a medical prescription. Because many drugs are available as OTC products and are considered safe to use, pregnant women are using more and more these drugs without medical advice and without knowing the risks to the fetus. The availability of these products and the publicity encourage drug consumption and self-medication, giving patients total control of their complaints. The number of drugs used during pregnancy is continuously increasing and the most used drugs are: analgesics, antipyretics, decongestants, antihistamines, antitussives and expectorants, antacids, antidiarrheal and laxative agents. Most of them don't have a well established safety profile if used during pregnancy. While some can be considered safe to use due to clinical experience, others are considered teratogenic or should be avoided in the first period or last period of pregnancy. Before using any drug in pregnancy the risk-benefit ratio should be assessed and the benefits of the drugs for the mother should always outweigh the risks to the fetus.*

**Keywords:** over-the-counter medication, pregnancy, safety, risk factor.

## SIGURANȚA MEDICAȚIEI OTC ÎN SARCINĂ. UNEORI O DILEMĂ

### Rezumat

*Medicamentele OTC sunt medicamentele ce pot fi eliberate fără prescripție medicală. Datorită faptului că o multitudine de medicamente sunt disponibile OTC fiind considerate sigure, femeile însărcinate le utilizează din ce în ce mai mult fără un consult medical prealabil și fără să cunoască riscurile pe care le pot avea asupra lor și asupra fetoșilor. Disponibilitatea acestor produse OTC și publicitatea încurajează consumul de medicamente și automedicația, oferind pacientului control absolut asupra simptomatologiei. S-a observat o creștere considerabilă a consumului de medicamente în timpul sarcinii, cele mai utilizate medicamente OTC fiind: analgezice, antipiretice, decongestionante, antihistaminice, antitusive și expectorante, antiacide, antidiareice și laxative. Marea majoritate a produselor OTC nu au un profil al siguranței bine stabilit în sarcină. În timp ce unele medicamente OTC pot fi considerate sigure în urma datelor obținute din utilizarea pe scară largă la gravide, altele au demonstrat a avea potențial teratogenic sau au recomandări clare de a nu fi utilizate în prima perioadă sau în ultima perioadă a sarcinii. Înainte de utilizarea oricărui medicament în sarcină trebuie stabilit raportul beneficiu-risc, iar beneficiile tratamentului pentru mamă trebuie să depășească întotdeauna riscurile pe care le are medicamentul asupra fătului.*

**Cuvinte cheie:** medicația OTC, sarcină, siguranță, factori de risc.

## 1. Introduction

Over the years, over-the-counter (OTC) medication has become more and more controversial, mainly because of its misuse, safety issues and the lack of information concerning self-medication. Over the counter drugs are a category of medicines that can be consumed by patients without medical advice, unlike prescription drugs which are required by law to be prescribed to patients by a physician.

Lately a lot of OTC drugs have been approved containing so-called "safe drugs". Moreover, drugs released only on medical prescription for many years have been switched to the OTC status. Consequently patients tend to have more self treatment possibilities, but most of the time the chosen one is not the best suited. Some OTC drugs are not available only in pharmacies, but also in supermarkets, general stores, gas stations etc., therefore they can be purchased without professional advice and the inappropriate use and safety are the main concerns. Commercial clips that advertise OTC drugs have and will continue to change the public perception about these drugs often giving inadequate or incomplete information, allowing the patients major autonomy regarding their complaints.

Of course, OTC drugs and drugs switched to OTC status have evidence of safety, but in some special population categories (children, elderly, pregnant woman) there's a lack of clinical studies and evidence of effects to support their use.

Inadequate use, especially in pregnancy, is due to the general perception that these drugs are safe. Drugs taken by the mother generally cross the placenta reaching various concentrations in the embryo [1]. So, even if a drug is safe to use for the mother that doesn't mean that it cannot affect the unborn child. Since the discovery of thalidomide's teratogenicity on the fetus, by using it during pregnancy, the care for the safety of drugs used in pregnancy has increased. A large number of OTC drugs have undetermined safety and this is because pregnant women are excluded from clinical studies, for ethical considerations, while the results of trials conducted on animals cannot always be assigned to humans, especially in case of pregnancy. Other drugs have already been proven to have teratogenic effects on the fetus and they are contraindicated in pregnant women [2,3,4,5].

### Before recommending OTC medication to pregnant women:

1. propose lifestyle changes
2. evaluate the gravity of the complaints and the need of medication
3. evaluate the risk-benefit ratio

related problems trying to establish connections between drug exposure and adverse events [6]. The spontaneous reporting system is the main method to collect information referring to drug safety and emphasized after the tragedy with thalidomide. Collecting spontaneous reported adverse events which occur during pregnancy and after may help decide if a drug can affect the unborn or the mother, in which manner, and to establish the risk-benefit balance.

**The spontaneous reporting system needs an active implication from all parties involved in the prescribing and consumption of drugs!**

The major problem is the low level of reporting in all the countries despite the well-developed pharmacovigilance systems. This means that the real number of adverse effects related to drugs and the real incidence of these effects that appear during pregnancy are unknown, therefore previous experience with drugs can't always be used in medical practice.

The U.S. Food and Drug Administration (FDA) has assigned risk factors (A, B, C, D, X) to all drugs, depending on their risks to the fetus based on the various studies existing about these drugs [1].

### FDA Risk Factors in pregnancy [1]

**CATEGORY A:** Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

**CATEGORY B:** Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

**CATEGORY C:** Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other), and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

**CATEGORY D:** There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

**CATEGORY X:** Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Pharmacovigilance has an important role in drug-

## 2. Over-the-counter preparations used by pregnant women

Studies have showed that the number of drugs used in pregnancy is continuously increasing. Various groups of OTC drugs are used in pregnancy, some of them potentially harmful for the mother or the fetus or both. Pregnant women commonly use analgesics and antipyretics, treatments for colds, antihistamines, antacids and laxatives [7].

### 2.1. Analgesics and antipyretics

**Avoid nonsteroidal anti-inflammatory drugs during the third trimester of pregnancy!**

#### 2.1.1. Aspirin

**Aspirin** is a nonsteroidal antiinflammatory drug (NSAID) and it is the most frequently ingested drug in pregnancy either as a single agent or in combination with other drugs. It is usually used to treat premature labor (alone or in combination with  $\beta$ -mimetics), systemic lupus erythematosus (80 mg/day in combination with prednisone to reduce the incidence of pregnancy loss), preeclampsia, eclampsia. Low-dose aspirin (40-150 mg/day) is used to prevent pregnancy-induced hypertension with firm requirements to assess the risk-benefit ratio. Aspirin consumption during pregnancy may produce adverse effects in the mother: anemia, antepartum or postpartum hemorrhage, prolonged gestation and prolonged labor. To the fetus or newborn it can produce increased perinatal mortality, intrauterine growth retardation, congenital salicylate intoxication and depressed albumin-binding capacity [1]. Aspirin used in the latter period of pregnancy should be avoided due to the possibility of fetal premature closure of the ductus arteriosus [8]. During the first two trimesters of pregnancy aspirin should be given only after assessing the risk-benefit ratio.

The use of aspirin during pregnancy, especially of chronic or intermittent high doses, should be avoided. If an analgesic or antipyretic is needed, acetaminophen should be considered [1].

#### 2.1.2. Ibuprofen

**Ibuprofen** is an NSAID used to relieve pain and to decrease fever. The use of ibuprofen as a tocolytic agent in one study has been associated with reduced amniotic fluid volume. If used in the 3<sup>rd</sup> trimester, ibuprofen can cause persistent pulmonary hypertension of the new born or premature closure of the ductus arteriosus *in utero* as a consequence of prostaglandin synthesis inhibition. Other studies have shown that ibuprofen may inhibit labor and prolong pregnancy and it has been associated with spontaneous abortions [1]. In other study which evaluated maternal medication use and risks of gastroschisis and small intestinal atresia (SIA), ibuprofen was not observed to increase gastroschisis risk, despite previous studies which

connected them, but that it might affect the development of SIA by fetal vascular disruption [9]. No increased risk has been found for malformations and no evidence of developmental abnormalities was observed in reproduction studies in rats and rabbits for ibuprofen in human therapeutic doses [1]. Ibuprofen should be used only when necessary and not at all in the 3<sup>rd</sup> trimester.

#### 2.1.3. Acetaminophen

**The selective pain reliever is acetaminophen. Do not overdose!**

**Acetaminophen** is the selective pain reliever and the most used analgesic-antipyretic drug during pregnancy. The major risk of acetaminophen in pregnancy in any trimester usually appears with overdosage inducing fetal hepato-renal toxicity. Various studies on pregnant women who had received acetaminophen in different stages of pregnancy did not suggest a causal relationship between congenital anomalies and the drug [1,14,15]. Unlike aspirin, acetaminophen does not affect the platelet function and does not cause hemorrhage. In a retrospective study which evaluated the relation between the use of cough, cold and analgesic medication and the risks of gastroschisis and small intestinal atresia, the risk for gastroschisis was increased for the use of acetaminophen and acetaminophen combined with pseudoephedrine [9]. An observational study on 47.400 live-born singleton sons associated maternal intake of acetaminophen for more than 4 weeks, especially during the first and second trimesters, with an increase in the occurrence of cryptorchidism [10].

In order to avoid the overdosage, it is important to inform pregnant women about the risks of using toxic doses and to highlight the use of acetaminophen only when necessary, in therapeutic doses.

**Table no. 1.** Risk factors for analgesics and antipyretics.

Drug name	FDA Pregnancy Risk Factor
Aspirin	C *D if full-dose aspirin used in 3 <sup>rd</sup> semester
Ibuprofen	B *D if used in 3 <sup>rd</sup> trimester or near delivery
Acetaminophen	B *analgesic/antipyretic of choice

## 2.2. Treatments for colds

There are a lot of OTC preparations for the treatment of the common cold and they contain only few substances but in many combinations. They are used mainly to relieve symptoms like cough, nasal congestion, sneezing and rhinorrhea [11].

Besides analgesics and antipyretics, cold medication during pregnancy usually includes decongestants, antitussives, expectorants and antihistamines.

### 2.2.1. Decongestants

**Decongestants** are sympathomimetics which can be administered orally (pseudoephedrine) or by the nasal mucosa using nasal sprays (oxymetazoline, xylometazoline). These drugs activate alpha-adrenergic receptors having vasoconstrictive effects which can cause increased maternal blood pressure with a decrease in blood flow to the fetus and can result in impaired fetal blood supply [12].

#### 2.2.1.1. Pseudoephedrine

**Pseudoephedrine** is one of the most commonly used medication in pregnancy due to the large experience with the drug during pregnancy [13,14]. Studies indicate that the use of pseudoephedrine and pseudoephedrine combined with acetaminophen in the 1<sup>st</sup> trimester has been associated with gastroschisis, with major risk for the combination. Underlying illnesses might also increase the risk for gastroschisis [1,9].

Sympathomimetic amines are teratogenic in some animal species, but human teratogenicity has not been suspected [1]. It is important for pregnant women to know that they should avoid this drug during the 1<sup>st</sup> trimester and if necessary they should use it with caution in a low-dose, short-acting preparation [15].

**Avoid pseudoephedrine during the 1<sup>st</sup> trimester of pregnancy!**

In a study involving 2474 women who had reported the use of oral decongestants (mainly phenylpropanolamine) during early pregnancy and 1771 women who used prescription oral decongestants later in pregnancy, no teratogenic effect of oral decongestants was found [16].

#### 2.2.1.2. Oxymetazoline

**Oxymetazoline** is used as a long-acting vasoconstrictor agent in nasal congestion. No previous experiences associating oxymetazoline with congenital abnormalities are known. Oxymetazoline and xylometazoline should be administered with caution due to their adrenergic effects on alpha uterine receptors [1]. Other caution to consider is the overdosage with tachyphylaxis and the fact that in overdosage the drug can be absorbed systemically with increased risk to the fetus [15].

**Tabel no. II.** Risk factors for decongestants.

Drug name	FDA Pregnancy Risk Factor
Pseudoephedrine	C *risk of gastroschisis with 1 <sup>st</sup> trimester use
Oxymetazoline	C *caution to overdosage

### 2.2.2. Antitussives

#### 2.2.2.1. Dextromethorphan

**Dextromethorphan** is commonly used as a cough

suppressant in over-the-counter preparations and many authors consider it safe to use during pregnancy [15]. In therapeutic doses, it doesn't produce nervous system depression or dependence. Data from a study which examined the effects of dextromethorphan on chick embryos suggested that this drug should not be used in pregnant women because of the risk of fetus malformations. The authors published evidence that the receptors blocked by dextromethorphan in the chick are analogous to receptors in other animals, including humans [17]. Applying this information to humans is not possible because of the dose used and the absence of maternal and placental metabolizing systems in chicks. There's no agreement regarding the comparative assessment of chick models and human models.

**Dextromethorphan is considered the safest antitussive to use during pregnancy.**

Many studies aimed at evaluating the possible teratogenic risk in humans found no clear associations between dextromethorphan and congenital malformations [1]. Although studies provide evidence that dextromethorphan is safe to use during pregnancy [18], it is advised to be reserved for significant maternal need, when benefit justifies the potential risk to the fetus [15].

### 2.2.3. Expectorants

#### 2.2.3.1. Guaifenesin

**Guaifenesin** is an expectorant commonly used as an over-the-counter drug during pregnancy. In a study monitoring 197 pregnant women with 1<sup>st</sup> trimester exposure to guaifenesin, an increase in the expected frequency of inguinal hernias was found. For the use in any trimester of pregnancy, no malformations were observed [1].

Guaifenesin use in pregnancy may also be associated with an increased risk of neural tube defects, although no significant results were obtained. Despite the weak evidence of data to support an association between guaifenesin and congenital defects, the use of this expectorant should be avoided during the 1<sup>st</sup> trimester and recommended only if benefits to the mother exceed the risks to the fetus [19].

**Table no. III.** Risk factors of antitussives and expectorants.

Drug name	FDA Pregnancy Risk Factor
Dextromethorphan	C *teratogenicity reported in animal studies
Guaifenesin	C *should be avoided in 1 <sup>st</sup> trimester

### 2.2.4. Antihistamines

Chlorpheniramine is the most used antihistamine in cold treatments to reduce nasal secretions.



**Chlorpheniramine is recommended as the antihistamine of choice.**

Studies showed no association between **chlorpheniramine** and congenital defects [20]. Chlorpheniramine was recommended by the American College of Obstetrics and Gynecologists and the American College of Allergy, Asthma and Immunology in 2000 as the antihistamine of choice [14]. Reports suggested that the intake of antihistamines during the last two weeks of pregnancy could be associated with retrolental fibroplasias in premature infants [1]. Chlorpheniramine has B risk factor.

### 2.3. Antacid and antisecretory agents

**The use of antacids and antisecretory agents is usually recommended when diet and lifestyle changes are not sufficient for controlling gastrointestinal symptoms.**

#### 2.3.1. Antacids

Antacids including aluminum, magnesium and calcium salts or sodium bicarbonate are commonly used to relieve heartburn particularly during the second and third trimesters of pregnancy [15]. Heartburn appears in pregnancy due to an increase in lower esophageal sphincter pressure caused especially by progesterone [23].

Aluminum, magnesium and calcium salts are generally regarded as safe in pregnancy. However in a case study, a mother reported a daily intake of 15 g **aluminum hydroxide** during the entire pregnancy and her daughter was diagnosed at four months with neurodegenerative disorder with profound mental retardation, multifocal seizures, spastic tetraplegia, growth retardation and spasticity and died at the age of nine years [21]. **Sodium bicarbonate** used frequently can cause metabolic alkalosis and fluid overload both in mother and fetus [15].

Preparations with limited intestinal absorption (e.g. aluminum hydroxide, magnesium hydroxide) are usually used in pregnancy because they reduce the exposure of the fetus [15]. However, **calcium** and calcium-magnesium based antacids are the general recommended ones due to their safety and because they do not cause bowel upset at the recommended doses. They also may have a beneficial effect by reducing the risk of pre-eclampsia in pregnant women with a calcium deficient diet [22].

#### 2.3.2. Antisecretory agents

##### 2.3.2.1. Histamine H2 receptor antagonists

Gastrointestinal antisecretory agents such as histamine H2 receptor antagonists are also available for the improvement of heartburn, gastroesophageal reflux disease or for the control of acid secretion in pregnant women with Zollinger-Ellison syndrome.

Studies on animals with **ranitidine** at doses up to 160 times higher than human doses showed no evidence of impaired fertility or fetal harm. Ranitidine has no anti-androgenic activity so it is considered a safer choice in pregnancy than cimetidine. **Cimetidine** has not been studied in *in utero* exposure, therefore it is recommended not to be used in pregnancy due to the possibility of feminization, as observed in animals and in nonpregnant humans [1]. In rabbits treated with **nizatidine** in doses 300 times higher than human doses, abortions, low fetal weights and fetal death occurred. There's a single case report with a mother who had taken nizatidine during the 14-16 post conception weeks who delivered a healthy newborn [1,23].

In a study based on a computerized database of medications dispensed between 1998 - 2007 to all women registered in a health maintenance organization, which was linked with computerized databases containing maternal and infant hospitalization records from the district hospital, exposure to histamine H2 receptor antagonists was not associated with an increased risk for congenital malformations, perinatal mortality, premature delivery, low birth weight or low Apgar scores [24]. Apgar score is the first test given to the newborn right after the birth and it evaluates the physical condition after delivery and the need for extra medical care.

##### 2.3.2.2. Proton pump inhibitors

Proton pump inhibitors (PPIs) suppress gastric acid secretion, being used to treat gastro-oesophageal reflux, erosive esophagitis, Zollinger-Ellison syndrome, peptic ulcers or in combination with antibiotics to eradicate *Helicobacter pylori*. A multicentre prospective controlled cohort study following 410 pregnancies with exposure to PPIs suggested that PPIs do not present a major teratogenic risk in human pregnancy [25]. Differing by country, PPIs including omeprazole, pantoprazole, lansoprazole are either available as OTC drugs or as prescribed drugs or have been proposed to be switched to OTC status.

In reproductive studies, **omeprazole** caused dose-related embryo and fetal mortality in rats and rabbits with no evidence of teratogenicity and also caused dose-independent increase in gastric cell carcinoid tumors in rats. The U.S. FDA have received reports with birth defects from exposure to omeprazole during pregnancy, including anencephaly and hydranencephaly [1]. Various other studies found no significant association between omeprazole and increased risk for malformations [25,26]. Yet, congenital heart defects including ventricular septum defect, ductus arteriosus have been observed [1].

**Lansoprazole** showed no evidence of impaired fertility or fetal harm in rats and rabbits but like other PPIs, carcinogenicity was observed in mice and rats causing dose-related gastric, testicular and liver tumors. Birth defects including cardiac defects have been reported to have unclear causal relationship with lansoprazole [1].

New PPIs like **pantoprazole** or **esomeprazole** have safety evidence in animal studies but there's a lack of evidence for their use during human pregnancy [23].

PPIs should be avoided during 1<sup>st</sup> trimester of pregnancy and be used only when necessary when diet changes, antacids and histamine H2 receptor antagonists are not efficient.

#### Steps to treat heartburn in pregnancy:

1. modify lifestyle and diet
2. if no improvements, use antacids (calcium based antacids are the preferable ones)
3. if antacids are inefficient, use histamine H2 receptor antagonists (ranitidine is the safest choice)
4. in case of significant medical need, use proton pump inhibitors (omeprazole, lansoprazole)

**Always evaluate the risk-benefit ratio!**

**Table no. IV.** Risk factors for antisecretory agents.

Drug name	FDA Pregnancy Risk Factor
Ranitidine	B *safer choice in pregnancy
Cimetidine	B *still to avoid because of the antiandrogenic activity
Nizatidine	B *still to avoid because of the adverse effects in animal studies
Omeprazole	C *adverse effects in animal studies and reports with human birth defects
Lansoprazole	B *still to avoid because of the carcinogenicity observed in animal studies
Pantoprazole	B *lack of data for the use during pregnancy

## 2.4. Antidiarrheal, laxative and antiflatulent agents

**The use of antidiarrheal, laxative or antiflatulent agent is rarely justified in pregnancy. Dietary measures should be taken firstly in consideration.**

### 2.4.1. Antidiarrheal agents

**Antidiarrheal** agents include usually loperamide, bismuth subsalicylate, kaolin and pectin. **Loperamide** is an antidiarrheal agent available in OTC preparations. Reproductive studies with loperamide on rats and rabbits showed no evidence of impaired fertility, teratogenicity or other fetal harm. Other surveillance human studies associated exposure to loperamide during the 1<sup>st</sup> trimester with cardiovascular defects, therefore the drug should be avoided if possible in early pregnancy [1,27].

**Bismuth subsalicylate** is hydrolyzed in the organism to bismuth salts and sodium salicylate. Due to the presence

of salicylate, this drug should be used carefully because, like aspirin, chronic exposure could cause congenital defects, increased perinatal mortality from premature closure of ductus arteriosus, intrauterine growth retardation, salicylate intoxication and hemorrhage. No clear evidence for congenital abnormalities was noticed for the exposure to bismuth salts during pregnancy. Because of salicylates, bismuth subsalicylate should be avoided in the first period of pregnancy and if necessary should be administered only in therapeutic doses [1,12,13,15].

**Kaolin and pectin** are antidiarrheal agents which are not absorbed into the systemic circulation. They were not associated with fetal abnormalities. Reports showed that kaolin may have caused iron deficiency anemia with preterm delivery and low-birth-weight infants. In a study on female rats, supplementing the kaolin diet with iron avoided anemia or low-birth-weight [1,13].

**Table no. V.** Risk factors for antidiarrheal agents.

Drug name	FDA Pregnancy Risk Factor
Loperamide	B *cardiovascular defects with 1 <sup>st</sup> trimester use
Bismuth subsalicylate	C *avoid because of salicylate absorption
Kaolin and Pectin	C *still they are considered safer because they are not absorbed

### 2.4.2. Laxative agents

Constipation appears usually in the last period of pregnancy. In a study regarding the treatment of constipation during pregnancy, stimulant **laxatives** showed to be more effective than bulk-forming laxative but causing more side effects. In case of constipation, before seeking help from laxatives, patients should change their diet habits by eating more fiber products [28]. Only when patients fail to respond to dietary changes, the use of laxatives should be taken into account, weighting the risk-benefit ratio [29].

**Lactulose** is an osmotic laxative biodegraded in the colon which hasn't been associated with fetal harm in mice, rats and rabbits at doses higher than human doses. There are no reports for human pregnancies [1]. Lactulose has B risk factor.

Bulk laxatives are based on fibers which attract water as for example **Psyllium** which has not been associated with malformations [15]. Stimulant laxatives including **senna** and **castor oil** should be used only postpartum because they can also stimulate uterine contractions causing premature labor [12].

### 2.4.3. Antiflatulent agents

**Simethicone** is an antiflatulent agent available over-the-counter. In a surveillance study it has been associated with cardiovascular defects, but with other factors being

involved: mother's disease, concurrent drug use and chance. There are no reports on fetal toxicity [1,12]. Simethicone has C risk factor.

## Conclusions

A vast number of OTC drugs are available to patients and many of them can raise serious concerns, especially when they are used in conditions like pregnancy. Various types of drugs taken by the mother are generally transmitted to the fetus across placenta during pregnancy and they can influence the normal development of the fetus and affect the process of giving birth. That is why it is very important before the intake of a drug in pregnancy to evaluate first the necessity of the drug, to establish if lifestyle changes could or could not improve the evolution of ailments and last, but not least, to evaluate the risk-benefit ratio.

There are risk factors for each drug established by the U.S. Food and Drug Administration indicating the risks posed to the fetus based on different studies involving these drugs. There is a lack of clinical studies and medical information concerning the use of drugs in pregnancy, so it is better to avoid their use in any trimester of this period. Pharmacovigilance and adverse events reporting systems need more attention from medical staff and patients because they can provide valuable information concerning drug safety.

## Acknowledgements

The documentation made for this study was supported by a research grant financed by the Romanian Ministry of Education and Research – PNII Partnership in priority issues 12-102 / 2008

## References

- Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Sixth edition, Baltimore. Lippincott Williams & Wilkins 2002.
- Kacew S. Effect of over-the-counter drugs on the unborn child: what is known and how should this influence prescribing? *Paediatr Drugs* 1999;1(2):75-80.
- Schjøtt J, Frost Widnes SK. Advice on Drug Safety in Pregnancy: Are there Differences between Commonly Used Sources of Information? *Drug Safety* 2008;31(9):799-806.
- Haramburu F, Miremont-Salamé G, Moore N. Good and bad drug prescription in pregnancy. *Lancet* 2000;356(9243):1704.
- Bond C, Hannaford P. Issues related to monitoring the safety of over-the-counter (OTC) medicines. *Drug Saf* 2003;26(15):1065-1074.
- Bojita M, Farcas A, Macavei C, Farah C. Drug Information Research Center – promoting the rational use of medicines from 2004. *Ann Acad Ro Sci* 2010;1(1):109-120.
- Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *American Journal of Obstetrics and Gynecology* 2005;193(3):771-777.
- Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME.

- Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother*. 2006;40(5):824-829.
- Werler MM, Sheehan JE, Mitchell AA. Maternal Medication Use and Risks of Gastroschisis and Small Intestinal Atresia. *Am J Epidemiol* 2002;155(1):26-31.
- Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology* 2010;21(6):779-785.
- Erebara A, Bozzo P, Einarson A, Koren G. Treating the common cold during pregnancy. *Can Fam Physician*. 2008;54(5):687-689.
- McKenna L, McIntyre M. What over-the-counter preparations are pregnant women taking? A literature review. *J Adv Nurs*. 2006;56(6):636-645.
- Werler MM. Teratogen update: pseudoephedrine. *Birth Defects Res A Clin Mol Teratol*. 2006;76(6):445-452.
- Black RA, Hill DA. Over-the-counter medications in pregnancy. *American Family Physician* 2003;67(12):2517-2524.
- Conover EA. Herbal agents and over-the-counter medications in pregnancy. *Best Pract Res Clin Endocrinol Metab* 2003;17(2):237-251.
- Källén BA, Olausson PO. Use of oral decongestants during pregnancy and delivery outcome. *Am J Obstet Gynecol* 2006;194(2):480-485.
- Andaloro VJ, Monaghan DT, Rosenquist TH. Dextromethorphan and other N-methyl-D-aspartate receptor antagonists are teratogenic in the avian embryo model. *Pediatr Res* 1998;43(1):1-7.
- Einarson A, Lyszkiewicz D, Koren G. The safety of dextromethorphan in pregnancy: results of a controlled study. *Chest* 2001;119(2):466-469.
- Silva R, Lee Jay H, Tweed E. Is guaifenesin safe during pregnancy? *Journal of Family Practice* 2007;56(8):669-670.
- Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy. Safety considerations. *Drug Saf* 1999;20(4):361-375.
- Reinke CM, Breitzkreutz J, Leuenberger. Aluminium in Over-the-Counter Drugs. *Hans Drug Safety* 2003;26(14):p1011-1025.
- Heading RC. Heartburn in pregnancy. *British Journal of Midwifery* 2004;12(2):112.
- Richter JE. Review article: the management of heartburn in pregnancy. *Aliment Pharmacol Ther* 2005;22(9):749-757.
- Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Uziel E, Levy A. The Safety of H2-Blockers Use During Pregnancy. *Journal of Clinical Pharmacology* 2010;50(1):81-87.
- Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, Tonningen MR, Clementi M. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. *Alimentary Pharmacology & Therapeutics* 2005;21(3):269-275.
- Källén BA. Use of omeprazole during pregnancy--no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001; 96(1):63-68.
- Källén B, Nilsson E, Olausson PO. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatrica* 2008;97(5):541-545.
- Jewell DJ, Young G. Interventions for treating constipation in pregnancy. *Cochrane Database Syst Rev* 2001;(2):CD001142.
- Prather CM. Pregnancy-related constipation. *Curr Gastroenterol Rep* 2004;6(5):402-404.