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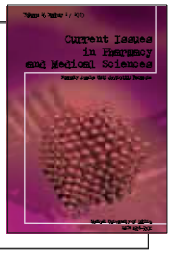

State of knowledge about drugs used during pregnancy and their toxicity to the fetus – preliminary report

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ABSTRACT

Most drugs pass through the placenta because of its small weight. What remains inadequate, is patients' awareness of pharmacotherapy during pregnancy. There are not so many experiments showing the knowledge about pharmacotherapy during pregnancy among women. In the present study authors wanted to demonstrate what is the knowledge of women about drugs toxicity in FDA pregnancy categories, the use of prescription drugs and biological products, and what kind of drugs, supplements of diet and herbal products were used by patients during pregnancy. The aim was also to reveal knowledge about drugs toxicity on fetus. Questionnaire survey was anonymous, and done by a midwife 1-3 days after parturition. Patients were women from region of Lower Silesia (Poland), who chose to give birth in the Clinic of Gynecology and Obstetrics, Chalubinskiego Street in Wroclaw. Research resulted in 60 questionnaires received from women. Percentage of patients, who had been taking supplementation with folic acid and vitamins reached 77%. As much as 45% of women who took part in research had used pharmacotherapy during pregnancy. From all women, 17% declared to have taken herbal preparations for common cold, fever, cough. Result of the study revealed that 23% of women who took part in the study knew about the FDA division of drugs used during pregnancy. The knowledge about possible teratogenic effect of the drugs is not yet well established among women after parturition. Special observations have to be done among pregnant women for broadening the knowledge about pharmacotherapy in pregnancy and women's treatment habits during pregnancy.

Keywords: drug therapy, herb-drug interactions, drug toxicity, pregnancy pharmacology

INTRODUCTION

The general idea of the placenta being a wall that blocks all substances potentially harmful for the fetus from entering the fetal blood was refuted years ago. Most drugs of low molecular mass pass through the placenta. In some cases pharmacotherapy in pregnancy is necessary because of illnesses that have been acquired before pregnancy, sometimes because of one that appears during pregnancy, and drugs may also be used to help with proper development of e.g. the central nervous system of the fetus. What should be taken into consideration, according to Rubinchik-Stern and Eyal, is that the placental barrier can also limit the delivery of drugs targeted to treat the fetus, sometimes targeted to prevent maternal-to-fetal disease transmission [15]. All these cases should be treated with proper understanding.

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To understand the potential consequences of uncontrolled therapy in pregnancy, the best example is provided by a drug popular in the 1950s and early 1960s. Thalidomide was a widely used antiemetic drug produced by a German company. The target patients were pregnant women from Europe and Canada, who could buy thalidomide without a prescription for treatment of pregnancy--related morning sickness. Before entering the USA pharmaceutical market its clinical trials were questioned. At the time the first cases of newborns with limb reduction, malformations of the inner and outer ear, congenital heart diseases, and ocular irregularities were observed [11, 12]. Thalidomide is, therefore, for all clinical pharmacologists a symbol of how dangerous therapy during pregnancy may be to the fetus. This tragedy was also the cornerstone of focusing the importance of stringent and well-performed testing of drugs before their introduction to the pharmaceutical market.

What still remains inadequate is the knowledge of patients' awareness of pharmacological treatment during pregnancy. The patients' knowledge about the possible

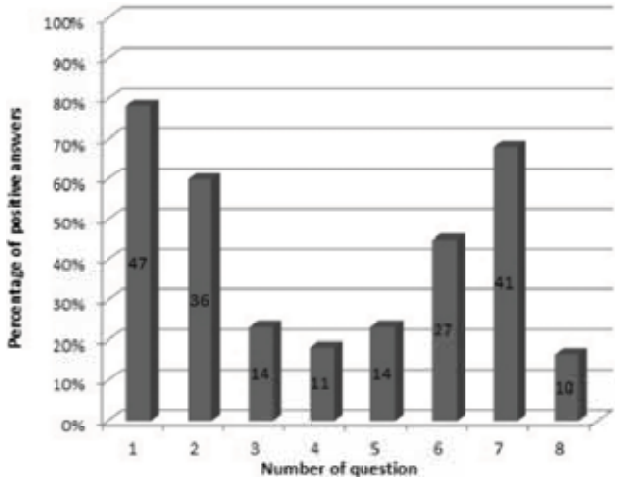
side effects of drugs on pregnant women's health and health of the newborn was the main target of our study. The aim was also to determine the familiarity of women with drug toxicity according to the Food and Drug Administration (FDA) classification on the use of prescription drugs and biological products in pregnancy [8].

MATERIALS AND METHODS

The research was done with the voluntary, informed participation of Polish women from the region of Lower Silesia (Poland), who had chosen to give birth in the Clinic of Gynecology and Obstetrics, 3 Chalubinskiego Street in Wroclaw. There were assigned 60 women in research . All questionnaires were taken from patients by a midwife 1-3 days after the parturition, after informing the patient about the goal of the research. The questionnaire was anonymous, and the bioethical committee approval for the research was obtained.

RESULTS

As a result of the study questionnaires were received from 60 women after parturition (Fig. 1). In the questionnaire survey conducted by the co-author, 47 pregnant women had been taking dietary supplements in combination preparations containing folic acid, vitamins from the B group (B1/B2/B6/B12), vitamin E/D/C, magnesium, iron, zinc, iodine, and manganese. From these, 60% of patients were taking supplementation of the kind that was suggested by the leading gynecologist.



1. Have you been taking dietary supplements in combination preparations containing folic acid, vitamins from the B group (B1/B2/B6/B12), vitamin E/D/C, magnesium, iron, zinc, iodine, and manganese?; 2. Have you been taking supplementation of the kind that was suggested by the leading gynecologist?; 3. Do you know the classification of drugs according to their toxicity to the fetus (pregnancy category A, B, C, D, X according to the FDA)?; 4. Can you distinguish which groups of drugs are considered safe according to previously mentioned classification?; 5. Have you been interested in the toxicity of drugs besides the FDA category to which the drug was assigned?; 6. Have you used pharmacotherapy during pregnancy (drugs given on prescription) such as antimicrobial agents and others?; 7. If you had to take a drug during pregnancy, what would be the most important factor? With answer: the best interests of the child, if it was harmful to the pregnancy, presence of possible side effects, and whether the drug was recommended by the doctor; 8. Have you used herbal preparations instead of medicines while treating cough, fever or common cold during pregnancy?

Fig. 1. Results of questionnaire survey among women after parturition

The number of patients who did not know about the classification of drugs according to their toxicity to the fetus (pregnancy category A, B, C, D, X according to the FDA) and were not able to answer the question about which groups of drugs are considered safe arrived at 77%. Women who knew the described classification and correctly answered the question mentioned before reached 18% of all questioned patients, and 72% of these were university graduates. Among all patients with higher education, 33% knew about the FDA classification of drugs used in pregnancy. From all women, 23% described their interest in the toxicity of drugs besides the FDA category to which the drug was assigned.

In total 27 out of 60 women who took part in the questionnaire survey had used pharmacotherapy during pregnancy (drugs given on prescription) such as antimicrobial agents and others, and only 33% among 27 patients described that they were interested in the potential toxicity of the drug to the fetus. All drugs used by patients are listed in Table 1.

Table 1. Description of active substances used during pregnancy by participants of the research

Active substance	Medicinal purpose	Group toxicity according to FDA / possible contraindications
Levothyroxine	Treatment of inert goiter. Prevention of recurrence after surgical removal of the goiter.	Category A
Amoxicillin	Infections of the upper and lower respiratory tract.	Category B
Furazidin, Akritoin	Antimicrobial agent, chemotherapeutic agent used to treat infections of the lower respiratory tract.	Do not use in the first trimester of pregnancy.
Progesteronum	Recurrent and threatened abortions against progesterone deficiency.	Category B
Iron fumarate	Iron deficiency based on anemia.	Category N
Cefuroxime axetil	Acute tonsillitis, acute sinusitis.	Category B
Nystatin	Polyene antifungal medication.	Category C
Nifuratel	Synthetic chemotherapeutic activity against trichomoniasis, antifungal and antibacterial action.	
Chlorchinaldol	In gynecology use in the prevention of reproductive tract infections and its treatment.	Pregnancy and lactation are contraindications to the use of the drug.
Metronidazole	Demonstrates bactericidal activity against protozoonicidal and anaerobic microorganisms.	Category B
Drotaverine	Antispasmodic drug.	Do not use during labor. Drug passes through placenta.

From all patients 68% declared that if they had to take a drug during pregnancy, most important for them would be the best interests of the child, if it was harmful to the pregnancy, presence of possible side effects, and whether the drug was recommended by the doctor.

Among patients who took part in our study, 17% preferred to take herbal preparations instead of medicines while treating cough, fever or common cold. All these herbal products are described in Table 2 [2-6].

Table 2. Herbal products used by women in the research during pregnancy instead of medicinal treatment, and evaluation of possible contraindications [2-6]

English name	Latin name	Traditional and medicinal purpose	Contraindications
Black elder	Sambucus nigra	In flu it is used as a diaphoretic; also to medicate symptoms of coughs and colds.	There are insufficient data on the safety of pregnant women. However, there is no increase in frequency of malformation or other harmful effects on the fetus from limited use of elder flower in women.
Large--leaved linden	Tilia cordata, Tilia platyphyllos	As a diaphoretic in febrile states, in tonsillitis, flu.	There are insufficient data on the safety of pregnant women.
Liquorice root	Glycyrrhiza glabra	Anti-inflammatory activity.	Licorice should not be used during pregnancy and breastfeeding. Studies in animals have shown reproductive toxicity.
Common marsh-mallow	Althaea officinalis	Inflammation of the mucous membranes of the upper respiratory tract (inflammation of the throat and larynx), dry cough.	There are insufficient data on the safety of pregnant women.
Scots pine	Pinus sylvestris	To increase the amount of mucus produced in the respiratory tract, facilitate bronchial purification.	There are insufficient data on the safety of pregnant women.
Weeping downy birch	Betula pendula, Betula pubescens	Alternatively as a diuretic.	The European Medicines Agency is currently developing information about Betula.
Fennel	*Foeniculum vulgare*	As an expectorant in cough associated with cold symptomatic treatment of mild, spasmodic gastro-intestinal discomfort, including bloating.	There are insufficient data on the safety of pregnant women; should be avoided in pregnancy.

DISCUSSION

In present research majority of women took dietary supplements during the pregnancy. Patients have been taking supplements with combination preparations the aim of which was to help prevent folic acid deficiency. These dietary supplements contain additional vitamins and minerals that help to make up the shortfall and cover the increased demand for these components. Prevention of muscle cramps and premature uterine contractions was the aim of taking magnesium with vitamin B6. The possible great potential of the gynecologist at the moment of choice of the drug is without question, seeing the results of this study (60%). What should be underlined, in the authors' opinion, is that this great influence on patients' health choices could be also utilized for broadening patients' horizons in the case of drug toxicity, whose results were poor in the present study.

As mentioned above, among all patients who took part in our study, 10 women (17%) preferred to take herbal remedies instead of medicines during light pathological conditions. Even if the number is not statistically significant, it shows that some patients consider herbal products as safe. The FDA Division of Drug Information in answer to the author's question stated that these are not FDA-approved medicines, and therefore it was impossible to give any information on their safety or efficacy during pregnancy. The European Medicines Agency (EMA) has proposed the Evaluation of Medicines for Human Use, where all herbal products that have been used by our patients were discussed [2,3,4,5,6]. Safety of usage of most herbal products during pregnancy has not been established. In the absence of sufficient data, the EMA suggests, in most cases, that the use of these products during pregnancy is not recommended. According to Fakeye et al., the conclusion should be made that herbal products should not be prescribed by physicians, and special care should be taken if the pregnant patient uses herbal products as self-treatment [7]. The multiplicity of drug interactions with herbal products and also side effects and lack of knowledge about the teratogenic potential of most herbal products makes it prudent to dissuade patients from using herbal products during pregnancy.

All processes of well-known drug's LADME (Liberation, Administration, Distribution, Metabolism and Excretion) may be changed under the physiological conditions of the body of a pregnant woman [9,10]. To give one from among many possible examples, high concentrations of progesterone in women's blood, especially in the last trimester of pregnancy, are the cause of delayed intestinal motility. This has an effect of time-delayed emptying of the stomach and intestines in about 30-50% of women [16]. This may have had consequences for the use of levothyroxine by one of our patients, 50-80% of the dose of which is absorbed in the small intestine.

Different effects of the drugs on the function of the fetus in later stages of pregnancy may be observed. Immaturity of organs metabolizing and excreting drugs (liver, kidney) in the fetus may cause accumulation and toxicity for the fetus [13, 14]. The knowledge about possible teratogenic effects of drugs is not yet well established. There are, however, indications showing whether the drug has already been tested on pregnant animals, or if there are any other clinical trials showing its toxicity to the fetus, e.g. the descriptions of the FDA and EMA, so the low status of pregnant women's knowledge about existence of these descriptions should be discussed. From all 60 women, 77% did not know about the FDA categories, and only 42% were interested in the toxicity of the drug that they were supposed to take. It should be underlined that 65% of women who were aware of the possible toxic action of drugs on the fetus had a higher education degree. In the light of the present results, and knowledge that different factors may influence the action of drugs on the human fetus [9, 10], more observations have to be made to broaden the knowledge about pharmacotherapy in pregnancy.

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