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Modern Paradigm of the Pregnant-Involving Pharmacological Study: Risk Assessment, Ethical Principles and Regulatory Aspect

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This article is dedicated to the issue of studying drug efficacy and safety in pregnant women, i.e. to their participation in clinical studies. The authors emphasize that lack of evidence base on drug use makes physicians helpless against diseases and gestational pathological conditions. The authors demonstrate results of the completed clinical studies involving pregnant women. In this article, they analyze possible risks and ethical complications of pregnant women taking part in clinical studies, as well as modern possibilities of medicine and legislative base of a range of countries, which allow minimizing risks of taking part in a study both for mothers and their fetuses. The authors demonstrate that the international experience of resolving ethical and legal issues of clinical studies among children may facilitate settlement of many problems of this issue.
Keywords: *pregnancy, pharmacological study, ethics, regulatory process.*

Clinical practice indicates that the lack of evidence database on the effect of drugs and biological products on the course of pregnancy presents women and doctors in charge with a difficult dilemma, when prescription of the drugs, which have not undergone clinical studies, renders correct dosage and account of potential fetus-associated effects impossible. On the other hand, refusal to use drugs during pregnancy may result in harm to health not only of mothers, but also of their unborn r newborn children caused by the disease-associated pathological alterations [1, 2]. Risk/benefit balance of drug therapy is not always clear both for a mother and her fetus; it is circumstantial and specific in every woman [3]. In order to minimize embryofetal risk, it is necessary to identify and avoid using nonessential drugs, regulate dose, frequency and way of administration of the drug and duration of the essential treatment. It ought to be mentioned, though, that development of new drugs for treating pregnancy-associated pathological conditions present scientists with the challenges that only rarely occur in other populations. Any drug interventions awake in women fear of pregnancy- and labor-associated complications. This fact complicates clinical studies of drugs, because any risk assumption renders such clinical studies unacceptable for pregnant women. On the other hand, there is an obvious need in validating drug efficacy and safety data obtained in the clinical studies involving different populations of patients with respect to pregnant women, as their bodies undergo a range of functional changes during gestation [4]. Additional studies aimed at identifying the factors determining pregnancy-associated changes of pharmacokinetics (PK) and pharmacodynamics (PD) of drugs are required for women not to be barred from achievements of the modern pharmacotherapy. There is also an ethical dilemma of involving this particularly sensitive category of patients in randomized controlled studies of safe and efficacy of drugs [5]. At the same time, new discipline – obstetric-fetal pharmacology – may form the basis of extensive study of gestational use of drugs [6]. In order to enable pharmacological studies involving pregnant women, a model, which

allows considering not only the mother, but also her future child the study participant, has been offered [7].

NEED IN RESEARCH AND MODERN INSTRUMENTS OF REPRODUCTIVE AND PERINATAL MEDICINE

It is important to know and understand hormonal regulation of the reproductive function, the process of ovulation, early course of gestation, intrauterine growth and development of a future child, pregnancy complications, start of premature labor, occurrence and nature of various malignant reproductive tract tumors for rational approach to prevention and treatment of pathologies of women and fetuses. However, despite the palpability of the issue, a lot remains unstudied and requires explanation and data accumulation in order to understand these and other similar biological phenomena. At the same time, the modern medicine is characterized by synergy of fundamental and clinical research – the so called “translational research”- which provides bedside-to-bench resolution of clinical issues [8].Understanding of the molecular mechanisms underlying pathophysiological processes inevitably leads to the use of new techniques and instruments, such as genetic, genomic and preteomic markers, use of biomarkers, alternative designs of clinical studies of drugs and alternative methods of analyzing the obtained results. It is emphasized that translational research must include analysis of drug metabolism enzymes’ activity using pharmacological probes; moreover, it is necessary to define functions of transporters, receptors and ionic channels during pregnancy to ensure health protection of mothers and their children. This dictates the need in joining effort of obstetricians-gynecologists, pediatricians, clinical pharmacologists, molecular biologists and geneticists in order to develop and carry out an integrative clinical, translational and fundamental research program [6].

Use of omics technologies in obstetrics. Thanks to the progress of high-dimensional biology, development of omics technologies – genomics, transcriptomics, proteomics and metabolomics – allows identifying gene expression and other patterns that may be used for further identification of the population risk of undesirable side effects and/or lack of drug’s efficacy. Use of biomarkers to detect the disease, prove efficacy and assess toxicity or as surrogate clinical endpoints, though not a new concept in the development of pharmaceutical products, allows identifying the patients, who will most likely respond to the drug intervention; this allows identifying a population for involvement into clinical studies of drugs at lower cost. The growing use of omics technologies in various spheres of medical research is observed in obstetrics as well. It is estimated that technical and strategic issues may be overcome in the nearest future allowing omics strategies to implement results of experimental work in clinical practice [9]. Pregnancy is a unique physiological condition; pre-eclampsia, intrauterine growth restriction and premature labor are heterogenic processes. Meticulously planned experiments involving the use of standard protocols, appropriate analytical methods and statistical analysis are capable of contributing to resolution of many of these issues by generating reliable validated metabolic and proteomic data in order to determine answers to important biological matters. Identification of the key markers helps to understand the disease course better and allows developing new hypotheses, which may be used for developing efficient therapeutic interventions and serve as an instrument of developing new drugs. These biomarkers are capable of optimizing pharmacotherapy in the absence of alternative variants and when consequences of therapeutic failures are undesirable. E.g., tamoxifen produces positive therapeutic effect only in patients with postmenopausal estrogen-positive breast cancer.

The information collected by B. Wilffert et al. demonstrates direct correlation of pharmacogenetics with drug-induced congenital anomalies (folate metabolism and oxidative stress caused by influence of phenytoin and functioning of drug transporters in the placenta) [10]. Although there are no specific data in favor of the pharmacogenetics-associated malformations for nonsteroidal anti-inflammatory drugs, paroxetine, and fluoxetine, modification of teratogenic effects thereof by polymorphisms should be expected. A commonly

low spread of drug-induced congenital anomalies complicates demonstration of pharmacogenetics contribution; this requires large-scale studies, especially case-control studies.

Clinical studies involving pregnant women. V. Dominguez et al. performed a systemic review of publications of the clinical studies conducted in 2000-2009, which demonstrated that only 2% of the studies published in that period (29,378 publications) involved pregnant women. 69% of all the intranatal clinical interventions were associated with drugs [11]. Most studies concentrated on labor induction therapy with fetal drug exposure for a short period of time. Misoprostol, oxytocin and mifepristone were most often assessed as labor inducer or during the abortion procedure. Other frequently studied drugs included bupivacaine, which is used for epidural anesthesia both in and out of combination with fentanyl in order to provide intranatal anesthesia. It was revealed that only 3% (16) of the studies concentrated on gestational hypertensive conditions, which occur in ca. 5-10% of all pregnancies and lead to high risk of maternal and perinatal death. There were even fewer studies concerning treatment of gestational diabetes (< 2%), although its spread varies from 2 to 10%. Most analyzed antibacterial drugs for gestational use were penicillins, metronidazole and clindamycin, which are prescribed for treating sexually transmitted diseases and bacterial vaginosis.

What is the purpose of clinical studies of drugs? It is important to mention that before the drug is registered, its pharmacokinetic profile must be thoroughly analyzed (absorption, distribution, clearance and bioequivalence must be determined). The existing practice of analyzing PK and PD of drug intended for women appears illogical in groups of men or mixed populations and should be abandoned, as it may lead to erroneous recommendations regarding dosage regimens [12]. At the same time, the archaic notion that the data obtained in the first-in-man clinical studies may easily be integrated and extended to women continues to persist [13]. The study of the use of 300 new drugs in the period from 1995 to 2000 conducted in 2005 demonstrated that package insert even of the drugs with significant differences in absorption, biotransformation and excretion between men and women did not contain recommendations regarding the specific dosage regimen [14]. The need in joint involvement of men and women in clinical studies of drugs was complemented by the data analysis of 26 studies of bioequivalence submitted to the US Food and Drug Administration (FDA), which demonstrated significant gender differences in ca. 28% of cases [15].

Pregnancy is a dynamic condition incomparable with any other condition. It seems unlikely that the use of drugs in the critical period of a woman’s life will become safe and efficient without involving pregnant women themselves in the studies. Lack of information of gestational fetal safety of the drug poses a serious problem when an attending physician has to decide whether to start an alternative treatment or modify pharmacotherapy of pregnant patients. *Ex vivo* studies using human placenta demonstrated inefficiency of such an approach regarding the issues of transplacental drug transfer, especially in the first and the second gestational periods [16]. Therefore, only clinical studies may help to understand the drug’s action pattern during pregnancy. As ethical issues complicate the study of pharmacological safety, attention is drawn to the few clinical studies conducted in the last 40 years involving women with termination of pregnancy, which are concentrated on analyzing drug absorption and distribution in aborted fetuses. Only 5 works (23.8%) were conducted in the 2000s [17]. Due to the lack of ethical rules for such studies, they are primarily conducted outside of North America. However, polls of both specialists (researchers and attending physicians) and women themselves confirm reasonability of such studies [17, 18]. The population of the patients, who had suffered abortion, may also serve as a relevant pharmacological group and used as an analyzed population regarding study of gestational use of drugs without risk of any undesirable consequences for fetuses.

APPROACHES TO RISK EVALUATION OF PREGNANT WOMEN INVOLVEMENT IN PHARMACOLOGICAL STUDIES

Analysis of subpopulations of the patients who had not previously participated in pharmacological studies as research subjects is of crucial importance to practical medicine. E.g., before the legislative acts aimed at supporting clinical studies in pediatrics (Pediatric Research Equity Act 2007 and Best Pharmaceuticals for Children Act 2007) were enacted in the USA, children had been considered "therapeutic orphans" (just like pregnant women nowadays). After these laws had been adopted, researchers demonstrated that many previously made assumptions regarding dosage regimen, safety and efficacy of drugs in pediatric practice were either erroneous or only partially correct. This led to changes in labeling of 92 drugs used in pediatric practice. Moreover, such studies help to find optimal ways of studying other vulnerable populations, such as pregnant women. It has been recommended to develop and adopt the same legislation for pregnant women as for children if there are no other ways to involve them in pharmacological studies as research subjects [19].

Peculiarities of assessing drug vulnerability risk in pregnant women. Population of pregnant women may be described and analyzed with regard to their susceptibility, sensitivity or vulnerability to external agents, such as chemical compounds, pharmaceutical and natural products. On this premise we ought to define the abovementioned terms: *susceptibility* is a qualitative parameter characterized by biological (internal) factors, which may modify effect of the specific action leading to high risk for health in the event of a given level of exposure; in its turn, *sensitivity* is a tendency to high risk caused by a combined effect of susceptibility (biological factors) and differences in the level and duration of exposure; finally, *vulnerability* combines the notions of susceptibility and sensitivity with other factors, including social parameters (e.g., socioeconomic status and place of residence), which may contribute to increase in the risk for health [20]. When determining and assessing risk in order to minimize it in potentially sensitive populations, it is necessary to clearly understand the correlation of the drug exposure level with response thereto. However, there are no strategies that would allow adequately describing and assessing pregnant women as a vulnerable category regarding drug intervention; this requires various methodological approaches. At the same time, pediatric population may serve as an example of such assessment. R.H. Hines et al. reviewed the parameters used to classify children as a vulnerable population and presented a detailed discussion of the three most informative critical factors regarding risk qualification: pharmacodynamics, pharmacokinetics and pharmacogenetics. They also demonstrated promising potential of the sensitivity biomarkers incorporated in risk assessment models. The authors believe that the mode (pathway) of negative exposure, population-specific environmental factors and/or drug interventions ought to be taken into consideration along with the internal factors. They attract special attention to the existence of the so called critical susceptibility/sensitivity windows defined as the time intervals, when the analyzed subpopulation is most sensitive to the drug exposure than the population on the average. They outlined a three-stage assessment procedure of PK contribution to determining the susceptibility period in the pediatric population: problem formulation, data analysis and risk qualification. This procedure may be expanded by analyzing PD and specific modes (mechanisms) of action along with pharmacokinetic profile of the drug; this procedure may help to determine susceptibility periods in other populations as well [20].

With regard to the population of pregnant women, this concept must take into consideration system "mother-placenta-fetus" as a distinctive feature of pregnancy, in which safety of the uterine-placental barrier for protecting the fetus from toxic substances is not absolute. Any drug-induced side effects occurring in a developing body prior to its maturity are classified as developmental toxicity; teratogenicity may be represented by embryo- or fetotoxicity characterized by development of structural anomalies. At the same time, teratogen-induced

malfunctions of organs and systems in the fetal stage of ontogenesis in the absence of morphological alterations are defined as “functional teratogenesis” [21, 22]. Both maternal and feral genotype may affect sensitivity to teratogenesis; this may result in differences in cell sensitivity, fetal-maternal exchange, metabolism, protein binding and drug distribution in the body; even equivalent doses in the same periods of pregnancy may result in different outcomes. At the same time, sensitivity to teratogenic agents changes depending on the stage of development at the moment of exposure to a negative factor with the period of maximum sensitivity from the 15^{th} (3^{rd} week) to the 56^{th} (8^{th} week) day of prenatal development, when organogenesis. Teratogenic termination period is a time limit in prenatal ontogenesis, until which a teratogen may cause a certain maldevelopment of one or another organ. Teratogenic agents affect the developing cells and tissues with specific mechanisms and lead to four types of developmental disorder manifestations (death, congenital abnormality, growth impairment and malfunctions). The best known substances affecting development of the fetus (including drugs) do not pass to the fetus directly, but are metabolically altered in the mother’s body. At the same time, all teratogens have a certain limit, beyond which negative reactions do not occur [21, 23].

Medical and social risks of drug exposure during pregnancy. Information on PK and PD of the drugs used during pregnancy is often limited or absent. Marked physiological alterations during pregnancy regarding blood circulation, digestion, renal function and metabolic activity often render achievement of the therapeutic level of drug exposure impossible using the standard doses. Recommendations on the use of oseltamivir is an appropriate example: due to data limitations, the US Centers for Disease Control and Prevention recommended using the standard dosage regimen for adult patients in the event of suspicion or confirmation of a pregnant woman’s infection with an A virus subtype H1N1 strain [24]. However, failure to achieve efficient treatment of pregnant women with oseltamivir in clinical practice forced a range of experts to recommend doubling the drug dose in women with severe course of A/H1N1 influenza requiring artificial pulmonary ventilation. These recommendations were reasonable, as oseltamivir and active oseltamivir metabolite – carboxylate – are excreted from the body through the kidneys, whereas the glomerular filtration rate increases during pregnancy, which is why circulating blood should feature low metabolite concentration. Two recently published works on oseltamivir PK analysis in pregnant women illustrate common difficulties of conducting such studies [25, 26]. Interpretation of the obtained data is complicated by narrowness of our understanding of a drug’s PD and the correlation of oseltamivir carboxylate concentration with the clinical effect [24]. Thus, use of the modern antiviral drugs does not have an evidence-based correct dosage regimen (just like most drugs in the pharmaceutical market); this may lead to negative consequences for the mother and her child. A similar pattern is observed in the event of preventive use of amoxicillin, blood concentration whereof is incapable of preventing infection in the event of anthrax, or glibenclamide as an anti-glycemic agent in pregnant women [27, 28]. Use of peroral sugar-lowering glibenclamide and metformin drugs in pregnant women is based on randomized clinical studies, which yielded outcomes similar to the cases when insulin was used [29, 30]. Another important factor is accessibility of the mode of administration and prescription regimen. The authors demonstrated that the changes in the activity of such drug metabolism enzymes, as CYP2C9, CYP3A and CYP2C19, occurring during pregnancy modify glibenclamide’s PK and may probably affect the optimal dosage during pregnancy. Moreover, glibenclamide is susceptible to maternal-fetal exchange, therefore, any assessment of alternative dosage regimens exceeding the currently used rang (up to 10 mg BID) must be considered with regard to fetal and neonatal safety [28]. The change in metformin’s PK during pregnancy is also associated with transformation of renal filtration and active renal transport [31].

Along with physiological functions, the course of pathophysiological processes also changes during pregnancy. Thus, gestational hypertension may indicate development of pre-eclampsia manifested with the increase in blood pressure and development of proteinuria in the second half of gestation [32]. Clinical significance of differences in hypertensive disorders is a proof of

therapy selection. Common antihypertensive drugs are prescribed in the event of chronic or gestational hypertension, but not in the event of pre-eclampsia or intranatal treatment, when magnesium sulfate is used. Although dosage regimen of antihypertensive drugs is critical during pregnancy, there are few studies analyzing PK and PD thereof. The study of pharmacodynamic properties of metoprolol demonstrated 4-fold increase in the effect on heart rate and double – on systolic blood pressure during pregnancy (in comparison with the postnatal period). It was concluded that the change in cardiovascular response to metoprolol during pregnancy may be caused by high sensitivity or altered function of the beta-adrenergic system [33]. Studying metoprolol's PK in women during pregnancy and in the postnatal period, the authors observed a significant increase in gestational hepatic metabolism resulting in clearance increase [34]. Results of these studies illustrate the absence of any fixed state of PK- and PD-effects during pregnancy: they may vary considerably. The study of atenolol's PK and PD during pregnancy supports these observations, as it demonstrates increase in the drug's renal clearance; however, pharmacodynamic is yet to be defined [35].

As for social risks of drug exposure during pregnancy, they are closely associated with characterological peculiarities of the mother. Perception of risk/benefit ratio of prescription and over-the-counter drugs considerably influences the decision to use them, when the balance may be different for the mother and her child / future child. Making these decisions, pregnant women rely not only on professional knowledge of their attending physicians, but also on their own experience and sociocultural understanding, as they are affected by their families, friends, cultural and social norms [36].

Pharmacological study of risk perception, explanation thereof and nature of the risk/benefit ratio. New approaches are explicitly required to resolve the issue of determining the risk/benefit ratio of using drugs during pregnancy, particularly, establishment of an efficient system of surveillance over teratogenic effects of both new drugs and the drugs that have been present in the pharmaceutical market for a long time. Such a system is aimed at collecting basic information on the use of drugs during pregnancy in order to understand the correlation between their effects and outcomes [37, 38]. Two main approaches to determining teratogenicity in the period of postmarketing surveillance have been developed. Thus, the epidemiological studies conducted in clinical practice to obtain the necessary information on teratogenicity of drugs feature 2 standard designs: cohort and case-control studies. Moreover, appearance of international teratological information services in recent years has allowed conducting prospective observational studies. Pharmacovigilance is closely associated with the use of registers of pregnant women compiled by pharmaceutical manufacturers or research groups. Design of such registers allows researchers efficiently identifying drugs with high risk of teratogenicity (or other types of fetus-associated side effects, e.g. developmental delay) involving a small number of pregnant women. Databases compiled for administrative purposes may also be used to identify women, who have taken a certain drug during pregnancy, and outcomes of their pregnancies.

It is necessary to avoid both underestimation and overestimation of risks for the purposes of adequate pharmacotherapy. A potential underestimation of fetal risks associated with drug therapy, especially in the beginning of gestation, is a matter of concern among clinicians. At the same time, exclusive use of the classification proposed by the US FDA may lead to overestimation of drug risks and, therefore, withdrawal of a proper therapy or termination of a wanted pregnancy [39]. Development and use of programs for minimizing drug risks is a continuous process consisting of risk assessment, risk minimization and efficacy assessment for the purpose of the further improvement of the risk/benefit ratio [40]. Ideally, it is necessary to plan a birth control program (although it is only rarely feasible) in order to understand if the fetal risk is caused by intrauterine action of a specific drug. Goals of any risk minimization program must be prospective and clearly articulated. Example of such a goal may be the absence of fetal drug exposure, i.e. when a pregnant woman does not take a certain drug, whereas a woman of reproductive age does not get pregnant taking that drug. The information stated in the drug's

labeling may be considered one of the instruments of minimizing risks of its use, when modification of labeling of specific drugs regarding birth control may be useful for the purposes of the general risk minimization program. Historically, drugs with confirmed or potential fetal risk are marked in two different ways (FDA categories D and X) taking into consideration the mother's disease, use of drugs by the intended population, frequency and severity of the adverse fetal outcome. There are three types of category X drugs: (1) drugs with confirmed teratogenic risk for human use or (2) with suspected teratogenic risk for human use and (3) drugs not to be used by pregnant women (e.g., hormonal contraceptives). Proof of risk and benefit of use of a certain drug during pregnancy often does not exist, is controversial or difficult for interpretation and practical application. This is the main problem of balancing optimal management of the mother's health with the potential fetal risk. Other instruments of minimizing risks of the drug therapy requiring active participation of both women and medical personnel are pregnancy tests and the use of contraceptives. In the first case it is possible to prevent teratogenic impact on the fetus unless the pregnant woman initiates pharmacotherapy; in the second case, prevention of side effects presupposes deliberate use of efficient contraceptive methods.

ETHICAL PRINCIPLES AND MORAL IMPERATIVE OF CONDUCTING A PHARMACOLOGICAL STUDY INVOLVING PREGNANT WOMEN

As it has been mentioned above, any use of drugs during pregnancy involves assessment of the risk/benefit ratio; this requires understanding ethical principles of testing drugs' efficacy and safety. Biomedical progress is closely associated with development of ethical issues, which instilled such notions as genetics, genetic testing, study of stem cells, pharmacogenomics and personalized medicine with meaning. DNA databases and storehouses of biological specimens are considered the sphere of bioethics, which is involved in clinical studies along with medical ethics. With regard to medical practice and conduct of studies, ethical rules often rely on medical ethics, including such notions as protection of interests of research subjects, patient rights, informed consent and confidentiality of information.

Ethics for clinical studies. Fundamental ethical principles and codes adopted in order to protect human rights are contained in a range of key documents. The foundation of social interest to the protection of patients was laid by the adoption of the Nuremberg Code in the process of the Nuremberg trials after the case of Nazi doctors (found guilty) was closed in 1947; that Code became a prototype guarantee of ethical nature of research involving human subjects. The Declaration of Helsinki (full name – "Ethical Principles for Medical Research Involving Human Subjects") developed by the World Medical Association (WMA) in 1964 constituted the next stage. Despite frequent references to this document in judicial practice, it remains a "moral benchmark" rather than a regulatory instrument. It ought to be mentioned that neither the Declaration of Helsinki (2008 revision) nor the Convention on Human Rights and Biomedicine (Oviedo Convention 1997) nor the European Union Directive 2001/20/EU on clinical studies mention involvement of pregnant women in studies. Only the guidelines on ethical principles of conducting biomedical studies involving human subjects published in 2002 by the Council for International Organizations of Medical Sciences (CIOMS) contain recommendations (Guideline 17) intentionally dedicated to the studies involving pregnant women. The European Medicines Agency (EMA) and the US FDA recognize the need in collecting information on the drug effects observed during pregnancy and their correlation with outcomes regardless of the study design and in conducting clinical studies involving pregnant women in the framework of ethical and regulatory rules [41, 42]. At the same time, continuity with a conservative policy of non-involvement of pregnant women in clinical studies will never guarantee safe use of drugs neither to the fetus nor to the mother, especially in view of the influence of environmental factors (including drugs) on the fetal gene expression during pregnancy presupposing epigenetic programming (demonstrated by the most recent studies) [43]. Thus, ignoring this issue and postponing its resolution is very expensive for the society.

Ethical issues regarding approval of involvement of pregnant women in clinical studies. Unlike the Nuremberg Code, the Declaration of Helsinki leaves open the possibility to involve vulnerable persons (including children, who along with pregnant women require additional protection, which is why they either could not be involved in studies or could be involved to a limited extent only in different periods) in studies. At the same time, the Declaration of Helsinki clearly forbids conducting studies on vulnerable groups if they may be conducted on a different, better protected population. The ethical issues associated with studying the use of drugs during pregnancy are the same as the issues encountered by researchers in children [44, 45]. The experience obtained in pediatrics may be used for the pregnant women involved in pharmacological studies, especially in view of the moral imperative for promoting therapeutic management of pregnant women, which appeared after the American Academy of Pediatrics made a statement on the non-ethicality of avoiding studying drugs in children in 1997 [46]. Benefits of pharmacological studies must be accessible to all population segments regardless of gender, race, ethnicity, age and subpopulation. However, the absence of adequate ethical guidelines for the studies conducted during pregnancy causes concern [47]. Whereas the placebo-controlled or controlled studies of drugs may be ethically justified only for treating severe obstetric complications due to the lack of adequate therapy, stage I of clinical studies of new drugs must not involve pregnant women. The issue of fetal therapy is even more complicated and controversial due to an inevitable conflict of interest occurring when the mother is used as a conductor for the purposes of treating the fetus. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (USA, 1979) published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which has become a historical document and a moral basis for understanding the instructions concerning involvement of people in studies in the United States of America, summarized the basic ethical principles on the basis of the nature and definition of informed consent and presented assessment of the risk/benefit ratio criteria and adequate selection thereof for human studies. The basic ethical principles for human studies recognized therein were as follows: firstly, respect for persons (protection of pregnant women and their fetuses by informed consent and provision of additional guarantees); secondly, observation of a fundamental ethical principle “do not harm” (preliminary risk assessment of drugs and/or medical procedures in pregnant women and their fetuses); and justice (objectivity) – who is to benefit from the study or bear the burden of its failure? There are at least four arguments of involving pregnant women in pharmacological studies. Thus, women often require efficient treatment during pregnancy, which is difficult to prescribe due to the lack of adequate studies of PK and PD of specific drugs in the pregnant woman’s body. The next argument concerns the issues associated with fetal safety, when the lack of thoroughly structured studies of drugs’ safety renders making a decision whether to use them or not impossible. The third argument appears to be the most convincing: doctors often leave pregnant patients undertreated or women withdraw intake of life-saving drugs themselves due to the absence of proved data. And the fourth argument concentrates on resolving legal issues, where a permission to be involved in studies is not only a protection against risks, but also a considerable amount of ethical responsibilities regulating clinical studies [1]. Without any doubt, guidelines on conducting gestational studies should include carefully selected specific criteria for protecting fetal well-being. They should also include requirements of increased safety and correctness of risk/benefit ratio choice, just like guidelines for any other studies involving persons who are incapable or only partially capable of giving informed consent. Ignoring responsibility for the study involving pregnant women may have undesirable consequences for health and well-being of mothers of unborn or newborn children [48-50].

LEGISLATIVE AND REGULATORY REQUIREMENTS AND INITIATIVES REGARDING CONDUCT OF PHARMACOLOGICAL STUDIES INVOLVING PREGNANT WOMEN

Unfortunately, the available information on drug use in obstetrics is not based on thorough scientific evidence, which is why every patient becomes an object of research. Although a slight step forward has been made regarding involvement of non-pregnant women in studies, there is almost no progress even in the discussion of involvement of pregnant women in clinical studies of drugs. It ought to be especially mentioned that the thalidomide tragedy was not caused by the involvement of pregnant women in clinical studies, but resulted from at least partially inadequate regulatory standards of the studies preceding distribution and marketing of the drug [1, 41, 51]. As drugs may produce an irreversible effect on fetal development by means of fetal-maternal exchange, the existing practice of labeling drugs for use during pregnancy concerns only the issues of fetal safety and does not involve information on their PK, PD and efficacy. That is why if the drug's use has not been studied in pregnancy-associated conditions, such as premature labor and gestational asthma, its use for treatment during gestation is not considered an indication for regulatory purposes and is classified as "off label" [52]. At the same time, 2/3 of pregnant women take at least one drug with unconfirmed safety profile [53].

The most complete legislative and regulatory requirements to the studies involving vulnerable populations have been developed in the USA, where a unified range of regulations named the Federal Policy for the Protection of Human Subjects, commonly known as the Common Rule, was adopted in 1991 to protect subjects of research. The Common Rule delegates powers of authority to assess and observe protection of human subjects involved in the studies to Ethics Committees (Institutional Review Boards, IRBs). According to subpart B of this document (45 CFR46) modified in 2001, the fetal risk in the studies conducted to improve health of a pregnant woman should be minimized (not to be mistaken with minimum risk). It is necessary to recognize not only the mother, but also the fetus as subjects of the study [7].

In 1990, the US Government founded the Office of Research on Women's Health (ORWH) under the jurisdiction of the National Institutes of Health (NIH). An important factor was the publication of guidelines on involving women and ethnic minorities in clinical studies as subjects and establishment of the FDA Office of Women's Health (FDA-OWH) in 1994. The analysis of NIH and FDA policies conducted in the end of the 1990s in the framework of gender justice demonstrated higher activity of the former, who devote more attention to conducting clinical studies [54]. It is confirmed by the establishment of the Obstetric Pharmacology Research Unit Network (OPRU) under the legislation of the National Institute of Child Health and Human Development (NICHD) in 2004; this network pursues two goals: to prove the hypothesis that the pharmaceutical and biological products of therapeutic significance during pregnancy may be studied ethically and to obtain proofs of changes in drug distribution and effects by conducting studies during both normal and abnormal pregnancies [42]. Moreover, the studies of drug effect on pregnant women should be complemented by studies in the sphere of fetal pharmacology, as the level of unborn children's exposure to the drugs taken by their mothers is virtually unknown. Thus, the implemented measures will secure quality regulatory assessment of the drugs used during pregnancy in the nearest future and thus help specialists and patients to make informed decisions.

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