ENROLLING PREGNANT WOMEN: PROBLEMS AND SOLUTIONS OF CLINICAL RESEARCH

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The article deals with the need of compulsory participation of pregnant women in clinical research of drugs. By the beginning of the 90-s of the last century, the majority of drugs prescribed to women was characterized by unsubstantial evidence of effectiveness and safety for women. Moreover, pregnant women almost did not participate in clinical research. Though pregnancy is a dynamic condition that can be compared with itself only. Then supervisory bodies created some documents regulating compulsory participation of the population in the research of drugs. However, until now, women are not sufficiently involved in the research of new original drugs, and pregnant women do the same very rarely. Possible scenarios of participation of pregnant women in clinical research have been reviewed. In particular, research of drugs used in therapy of abnormal conditions associated with pregnancy; drugs to treat chronic and acute pathological processes not related to pregnancy, and when a woman gets pregnant during the research have been distinguished. The importance of inclusion of pregnant women into the trials of effectiveness and safety of drugs in the presence of socially significant diseases, including the ones found during COVID-19 pandemics, is postulated.

Keywords: pregnant women, clinical trials, drug

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КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ У БЕРЕМЕННЫХ: ПРОБЛЕМЫ И РЕШЕНИЯ

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В статье рассматривается необходимость обязательного участия беременных в клинических исследованиях лекарственных препаратов. К началу 90-х годов прошлого столетия значительная часть лекарственных препаратов, назначаемых женщинам, имело недостаточную доказательную базу эффективности и безопасности их применения у женской популяции. Более того, беременные в клинических исследованиях практически не принимали участия. Хотя беременность — это динамичное состояние, которое может сравниваться только само с собой. Указанное послужило основанием для появления ряда документов контролирующих органов, регламентирующих обязательное участие данной популяции в исследованиях лекарственных препаратов. Тем не менее, до настоящего времени женская популяция включается в исследования новых оригинальных лекарственных препаратов недостаточно, а беременные крайне редко. Рассмотрены возможные сценарии участия беременных в клинических исследованиях. В частности, выделяются исследования лекарственных препаратов, применяемых для терапии патологических состояний, связанных с беременностью; лекарственных препаратов хронических и острых патологических процессов, несвязанных с беременностью; а также ситуации, когда женщина беременеет в процессе исследования. Постулирована важность включения беременных в исследования по эффективности и безопасности применения лекарственных препаратов при социально значимых заболеваниях, в том числе во время пандемии COVID-19.

Ключевые слова: беременные, клинические исследования, лекарственный препарат

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Approaches to the inclusion of women into clinical trials (CT) have undergone significant changes within the last thirty years. Until 1993, less active participation of women in CTs was actively supported by the Food and Drug Administration (FDA). It was associated with the tragedies of 1960-s and 1970-s, namely, the use of thalidomide and diethylstilbestrol in pregnant women. In 1977, FDA issued the 'General considerations for the clinical evaluation of drugs'. In accordance to it, women of reproductive age were suspended from early phase clinical trials (phase I and early phase II) and participated in late phase trials only, if the drugs were not intended to treat serious diseases. The limitations were possible because during the menstruation the endocrine profile undergoes significant changes. Then a significant effect can be produced on pharmacokinetics and pharmacodynamics of drugs. Moreover, any woman can get pregnant during research.

In 1992, all manufacturers of drugs with FDA approvals of new chemical entities from January 1988 to June 1991 were interviewed by the Government Accountability Office (GAO). Women were included into phase 2 or phase 3 CTs of 53 drugs. However, based on the GAO estimate, almost in 60% of cases it was not enough. Meanwhile, trials with 36 of 53 drugs (68%) included the minimum percentage of women in accordance with FDA recommendations. 25 of 53 entities (47%) were estimated for similarities and differences in reactions to drugs depending on sex [1].

Thus, by the beginning of the 1990s of the last century, many drugs administered to women had insignificant evidence of effectiveness and safety. The medical community couldn't help being worried because of that. That's why in 1993 'Recommendation to study and assess gender differences in

the clinical research of drugs' replaced the abovementioned FDA guidance [2]. It regulated participation of women in the early phase of CTs of drugs, biological products and medical devices. Medical researchers and ethics committees were significantly responsible for accomplishment of the acting standards and rules, and assessment of the possible risk for the participants.

However, insufficient research of drugs among women was still pressing. Analysis of 10 prescriptions medicines withdrawn from the market of the USA in 1997–2001 has shown that eight of them were related to 'an increased risk for female health' according to post-marketing trials (three drugs and five drugs were registered in 1993 and later, respectively). The drug was removed from the market due to unfavorable adverse drug reactions caused by pharmacodynamic differences (for instance, three drugs were withdrawn due to the risk of torsades de pointes, which is more frequently seen among women) or higher susceptibility of women to these drugs (four drugs were administered to a higher percentage of women as compared to men). There was no evidence of higher risk of adverse drug reactions for two drugs depending on the sex. Both were registered after 1993 [3].

The issue with CTs is more complicated when it concerns pregnant women. For decades, pregnant women were excluded from CTs because of potential teratogenicity of the studied drugs. Thus, data about effectiveness and safety of drugs used by pregnant women are very limited though they are widely applied [4]. When analyzing 172 drugs approved by the FDA from 2000 to 2010 it has been found out that 98% of them have an 'uncertain' teratogenic risk; and 73% lack safety-related data in pregnancy [5]. Thus, decisions to start or continue taking drugs are taken by the most pregnant women and their treating physicians without knowing much about the drug safety and effectiveness. At the same time, the risk of taking drugs can be exaggerated. In particular, while examining the cases of maternal mortality in the Great Britain it has been found out that some women died due to the drug withdrawal and non-administration [6].

There are two solid reasons to study drugs during pregnancy. The first reason is associated with the change in the reproductive health. Some time ago only healthy and young women could risk their health for that. Today, women aged 10 to approximately 50 are in reproductive age. That's why even elderly women can get pregnant with in vitro fertilization and donor cells. In developed countries, the age of women during the first pregnancy is steadily on the rise. A number of first pregnancies is increased for women elder than 30 years. Wider borders of the reproductive age and later pregnancy result in an increased percentage of women who may require drug therapy prior to pregnancy and its continuation during the pregnancy. To provide pregnant women who have concomitant diseases with an optimal treatment, it is necessary to know the peculiarities of drug-induced therapy of pregnant women with various abnormal conditions.

The second reason is associated with physiological changes while being pregnant: an increasing total body weight and structure of adipose deposits; the volume of plasma and cardiac output are increased; the rate of glomerular filtration is intensified; hypoalbuminemia is developed; gastrointestinal motility, regional blood flow and activity of hepatic metabolic enzymes are developed. As a result, pharmacokinetics and pharmacodynamics of drugs, their effectiveness and safety among non-pregnant and pregnant women can differ significantly [7].

A physician requires additional information while administering drugs to potentially pregnant women. If the woman suffers from diseases and takes medicines, data on how well the disease can be controlled with the current pharmacotherapy, reproductive/teratogenic risk of the administered drugs and how it was estimated should be available. In case of a danger, the drug can be replaced. The physician should find out whether the patient knows about the reproductive risk of the drug and discuss the risk and benefit ratio in every single case.

Some ethical principles should be followed when drugs are administered to pregnant women. Women, especially those with chronic diseases or pregnancy-associated conditions (nausea, vomiting, etc.), require effective treatment. To provide a compromise between a treated mother and safety of a child, therapy should be accompanied with data about drug fetal safety. Silencing of the need in pharmacotherapy is not permitted, as there are risks both for a mother, and a child, when treatment is not provided or not sufficient.

To obtain qualitative data about the drug, it is necessary to assess the risk/benefit of their use and an ability of pregnant women to take part in clinical trials [8].

Collecting drug-related evidence in strict adherence to scientific conditions is the main reason for inclusion and retention of pregnant women in a large number of biomedical trials. In this case, less women and their fetuses are subject to risk as compared with those after drugs have reached the pharmaceutical market [9]. Drug effectiveness/safety data are easier to assess if they are obtained from CT. However, in order to find some effects, drugs should be taken by a very large cohort of patients.

A pregnant woman should be suitable for a biomedical trial having a proper maternal/fetus/general state of health.

Though animal trial outcomes can't warrant the lack of risk for a human being, evidence of lacking teratogenicity and mutagenicity should be obtained during experiments with animals prior to the trial [10]. It should be remembered that except androgens, antiblastic drugs, valproate sodium and derivatives of vitamin A, all teratogenic substances in humans were discovered earlier than in animals; the majority of data were reported by physicians [11]. The protocol of a CT should necessarily include the plan of monitoring the pregnancy outcomes, including maternal health, short-term and long-term health of a child.

Two scenarios of participation of pregnant women in CTs are possible: a woman gets pregnant during a trial or a pregnant woman requires treatment but she can get it during a CT only. CT planning raises some questions that require answers. It is affordability of effective alternative therapy with the known less toxicity. The risk/benefit maternal/fetal ratio regarding a drug and abnormal condition, which is planned to be treated; possibility to use placebo-control or active control; whether pharmacokinetic assessment is suggested with the warrantied adequate systemic exposure and achieved effectiveness (for instance, pharmacokinetic trials included into third phase CTs).

If a CT participant gets pregnant during a trial, it should be taken into account whether she can continue the trial. In this case, an informed consent is taken from a nonpregnant woman; birth control methods and data regarding possible embryo- and fetotoxicity of drugs should be clearly stated herein. There are certain clinical situations when it is not efficient to make women who got pregnant during the CT continue the trial.

In this case, potential benefit of continued treatment should outweigh potential risks of continuing fetal exposure of the studied drug. It occurs when there are risks to terminate pharmacotherapy for a mother and/or risks of fetal exposure using additional drugs, if a mother is shifted to another

Table. Guidelines on participation of pregnant women in clinical trials and administration of drugs

Country	Legislative body	Guidelines on participation of pregnant women in clinical trials and administration of drugs
USA	Food and Drug Administration (FDA)	https://www.fda.gov/media/92565/download
Canada	Health Canada	canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html
European Union	European Medicine Agency (EMA)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500059887.pdf
Japan	Ministry of Health Labour and Welfare	http://www.nihs.go.jp/mhlw/yakuji/yakuji-e_20110502–02.pdf
Australia	Australian Drug Evaluation Committee (ADEC)	http://www.huidziekten.nl/richtlijnen/medpreg.pdf

therapy (in malaria, tuberculosis, oncological diseases). When a pregnancy occurs during a CT, the pregnant woman should sign a new informed consent, indicate the possibilities of an alternative therapy and compare therapeutic risks and benefits, namely, risk of continuing exposure of the studied drug on the fetus vs the risk of the alternative therapy, and danger of a non-treated disease. Meanwhile, consultation of the participant by an investigating physician, obstetrician and other medical specialists should be provided as needed on a constant basis.

Pregnant women with medical conditions that require treatment can be included into CTs if administration of the studied drug is accompanied with direct benefit for the pregnant woman and can't be achieved otherwise: the woman does not respond to the affordable therapy; alternative therapy is neither effective nor possible (allergy, increased sensitivity, stability). Meanwhile, the fetal risk does not exceed the minimal one. The CTs result in essential data, which can't be obtained otherwise. Thus, during CTs, drugs are administered with a therapeutic purpose mainly.

Trial endpoints and data about outcomes in a mother, fetus and newborn include as follows: gestational data, gestational time and duration of drug exposure; collection of ultrasound data and outcomes of other prenatal examinations; and registration of maternal complications. Gestational age in deliveries, complications in deliveries, condition of a newborn and conditions observed during the neonatal period should be taken into account separately.

In this century, regulatory authorities of many countries created guidelines to include pregnant women into CTs (table) [12].

In Russia, inclusion of pregnant women into CTs is regulated by Federal Law No. 61-FZ dated April 21, 2010 'On circulation of medicinal products' (edited as of April 28, 2023), where it is stated in par. 6, art. 43 that it is prohibited to conduct CTs of MP for human use involving 'pregnant and nursing women, except for cases, when a CT of drugs is intended for the abovementioned women, and when it is necessary to obtain data during respective clinical trials only and take all necessary measures to exclude the risk of harming a pregnant woman, a nursing woman, a fetus or a child' [13].

Five years ago, the FDA issued a Guideline regarding scientific and ethical approaches to the inclusion of pregnant women into CTs [14]. Inclusion of pregnant women into CTs of drug effectiveness and safety in case of socially significant diseases is of particular importance. The PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study) working group proposed three main points, in which conducting CTs within the cohort is compulsory. First, pregnant women and their children should be protected from narcotics-related risks just like all the others; second, their access to drugs during a CT should be similar to that of others; third, their own health and fetal outcomes should be equally respected [15]. While planning and launching CTs, the priority is given to the safety of infants due to a possible drug exposure but not to easier access of pregnant women to the trial.

However, the FDA explained recently that in the lack of safety precaution measures of using drugs among pregnant women, the drugs approved for use in adults are also approved for use during pregnancy. The open acknowledgement stating that drug safety data are incomplete was made to ensure that the HIV-infected pregnant women have access to antiretroviral drugs [16].

Exclusion of this cohort from CTs is associated with an unwillingness of pharmaceutical companies to take into account theoretical fetal risks (for instance, development of abnormalities). So, similar trials abroad are conducted mainly by clinical researchers using state funding received through competition. The regulating authorities in the sphere of circulation of drugs commonly display the same approach to avoid a possible risk. During all CTs, participants are insured against the risk of therapy adverse effects with the studied drug.

At the same time, sponsors of CTs can come across difficulties of getting insurance for CTs with pregnant women. Besides, this cohort requires additional communication (especially if the CT is conducted outside the maternity house) due to possible maternal and fetal risks. As a result, researchers suffer from an additional temporary and emotional load. In some cases, researchers can doubt their ability to discuss the assumed risks in an adequate way. There is a widespread and not supported view that pregnant women do not want to participate in CTs. In a wider medical community, there is no understanding of the fundamental role of the pregnant women included into the trials to ensure subsequent safe access to drugs.

During COVID-19 pandemics in 2020–2023, the problem of drug-related data, access of the pregnant women to CTs and progressive methods of therapy worsened. Besides, the infection was severe among these patients.

The RECOVERY (Researching COVID to enhance recovery) trial was a CT of drugs used in COVID-19 with involvement of pregnant women. Over 100 of pregnant or just delivered women participated in the trial. Effectiveness/safety of steroids, tocilizumab and casirivimab/imdevimab were assessed. Similar proportions of pregnant and non-pregnant women who decided to participate in CTs show that barriers for participation are mainly systemic, but not individual, with the role of governing authorities being critically important. Inclusion of pregnant women into the RECOVERY trial made it possible to transfer the trial results to clinical recommendations and practice [17]. Thus, if sponsor, regulatory and insurance barriers are overcome, pregnant women participate in CTs if they are offered to do so even under the conditions of a global pandemics.

In Britain and USA, target groups insisted that researchers and sponsors of CTs should explain why they exclude pregnant

and nursing women from trials that can be good for a woman and her fetus. Regulatory authorities are offered to request a plan of research and assessment related to pregnancy and nursing from drug manufacturers [18, 19].

Thus, pregnant and non-pregnant women can suffer from numerous diseases that demand short-term and long-term treatment. According to the available data, at least three-quarters of women take minimum one drug during their pregnancy. Pregnancy is a dynamic condition, which can be compared to itself only. Unfortunately, data about the use of drugs in obstetrics are based on deep scientific evidence. Thus, every woman is a study object. If no pregnant women participate in trials, safe and effective use of drugs during the critical period of a female life can hardly be real.

Clinical practice shows that women and treating physicians face a difficult dilemma due to the lack of evidence about the effects of pharmaceutical and biological products during pregnancy. Thus, administration of drugs that have not been tried during CTs does not enable their proper dosing or considering potential effects on an unborn child. But refusal to use the drugs during pregnancy will result in harming the health of both the mother, and unborn or newly born child. The risk/benefit of drug-induced therapy is not always clear both for a mother, and a future child. It should depend on circumstances and be individual for every woman [20].

Trials of drug consumption in this vulnerable group of patients confirm high rate of drug administration and enable characterization of their category.

Determining most frequently taken drugs (OTC and Rx drugs) during the first gestational trimester and more extensive knowledge about their embryofetal risks allow to optimize pharmacotherapy during pregnancy. Frequent administration of drugs by pregnant women indicates that post-approval (post-marketing) assessment of their benefit/risk profile during pregnancy [21].

The main obstacle, however, to successful decrease of morbidity and mortality within the essential group of patients is the discrepancy between the burden of diseases of pregnant women and their future infants, on the one hand, and investment in development and testing of pharmacological methods of treatment, on the other hand. A consequence of inability to develop drugs, which could be used during pregnancy, is that many drugs are not tested for use in obstetrical practice. Thus, prescribing information with extensive data about fetal safety includes no data about the dosage, respective treatment, maternal effectiveness and safety.

The distancing of pregnant women from the development of drugs and therapeutic knowledge creates a range of clinical problems for practicing physicians. In spite of numerous factors within the context of maternal and intrauterine environment, the available experience is simply evidence of a small number of prenatal effects with quantitative estimates of related risk of congenital defects. Subsequently, the global burden of congenital defects can be decreased with integrated trials in epidemiology, genetics and epigenetics through personalized and population oriented preventive strategies.

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