PREGNANT WOMEN AND THEIR FETUSES — ORPHAN POPULATIONS IN RESPECT TO THE SAFETY AND EFFICACY OF MEDICINES

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Pregnant women are a very special category of patients. The risk-benefit ratio of using various drugs in this case presents a significant medical, social and ethical problem. The increase in the age of onset of the first pregnancy is associated with the increasing prevalence of chronic pathology. Obesity, cardiovascular diseases, diabetes mellitus, hypo- or hyperfunction of the thyroid gland, as well as many other conditions contribute to the active use of drugs of various pharmacological groups throughout the entire period of pregnancy, including early periods. The current practice of pharmacotherapy in pregnant women is based mainly on the use of drugs with an uncertain teratogenic risk. Not including pregnant women in clinical trials is an ethical issue as significant as their potential inclusion. Previously, for a long time, vulnerable categories included generally all women of reproductive age, whose inclusion in clinical trials became possible only in the mid-1990s. Pregnant women were considered vulnerable until 2019. The orphan status of pregnant women in terms of inclusion in clinical trials limits their right to receive highly effective and safe medical care, which makes it relevant to review the existing ethical principles in relation to this category of patients and a to perform a detailed analysis of existing barriers for certain types of drug trials.

Keywords: pregnant women, clinical trials, vulnerable categories of patients, efficacy and safety of pharmacotherapy

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БЕРЕМЕННЫЕ ЖЕНЩИНЫ И ИХ ПЛОДЫ — ОРФАННЫЕ ГРУППЫ НАСЕЛЕНИЯ В ОТНОШЕНИИ БЕЗОПАСНОСТИ И ЭФФЕКТИВНОСТИ ЛЕКАРСТВЕННЫХ СРЕДСТВ

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Беременные женщины представляют собой совершенно особую категорию пациентов. Соотношение рисков и пользы применения различных лекарственных препаратов представляет в данном случае значимую медицинскую, социальную и этическую проблему. Увеличение возраста наступления первой беременности связано со все более широким распространением хронической патологии. Ожирение, сердечно-сосудистые заболевания, сахарный диабет, гипо- либо гиперфункция щитовидной железы, а также многие другие состояния способствуют активному применению препаратов различных фармакологических групп на протяжении всего периода беременности, включая ранние сроки. Существующая практика фармакотерапии беременных основывается преимущественно на применении препаратов с неопределенным тератогенным риском. Невключение беременных в клинические исследования является этической проблемой столь же значимой, как и их потенциальное включение. Ранее, в течение длительного времени, к уязвимым категориям относили в целом всех женщин репродуктивного возраста, чье включение в клинические исследования стало возможным лишь в середине 1990-х. Беременные женщины рассматривались в качестве уязвимых вплоть до 2019 г. Орфанный, с точки зрения включения в клинические исследования, статус беременных ограничивает их право на получение высокоэффективной и безопасной медицинской помощи, что делает актуальным пересмотр существующих этических принципов в отношении данной категории пациентов и детального анализа существующих барьеров для осуществления определенных видов исследований лекарственных препаратов.

Ключевые слова: беременные, клинические исследования, уязвимые категории пациентов, эффективность и безопасность фармакотерапии

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Despite all the advances in modern medicine, health of pregnant women is not improved, but even gets worse. Thus, the U.S. has experienced a rise in severe maternal morbidity and mortality for more than twice over the last 3 decades. This is partially explained by the aging of pregnant women and an increase in the prevalence of chronic diseases and obesity among them [1]. Obesity and maternal age above 35 and especially above 45 contribute to a wide specter of unfavorable outcomes of pregnancies, including intrauterine growth restriction, congenital abnormalities, higher risk of miscarriages, premature births, stillbirths, Caesarean sections, preeclampsia, pregnancy diabetes and other complications [2,3]. This risk is increased even more when a pregnant woman has concomitant diseases/conditions, including hypertensive disturbances and pregnancy diabetes [4]. Among women with multiple chronic conditions, deliveries have 3.8 times the rate of severe maternal morbidity and mortality compared to women without chronic conditions [1]. Out of 210 million annually

recorded pregnancies, an estimated 140 million only result in a live birth per year [5].

Women with chronic diseases not treated during the gestational period are at increased risk of postpartum complications, including cardiometabolic, renal [4,6] and mental ones [7]. In the U.S., cardiovascular diseases are responsible for 26% of pregnancy-related mortality during the first year postpartum [1]. In the perinatal period, suicide is committed by every 25th woman aged 20 to 35 [8], during the first year postpartum it is the reason for 20% of maternal mortality [9]. In depressive postpartum psychosis, the rate of infanticide is 4.5% [10].

Thus, many pregnant women with chronic diseases require pharmacotherapy throughout the entire period of pregnancy, including organogenesis associated with the risk of teratogenic effects. Moreover, pregnant women need drugs to treat acute diseases, including life-threatening ones, and obstetric disorders, and in some cases to prevent and treat fetal diseases. However, it is not always possible to compare the risk associated with a not treated disease and the risk related to the use of pharmacotherapy due to insufficient research of effectiveness and safety of drugs during gestation. Despite pharmacotherapy is obtained by at least 80–90% of pregnant women [11], data about effectiveness and safety of more than 90% of MPs present in the market in the period of gestation are not sufficient [12,13]. Data concerning pharmacokinetics and effectiveness of drugs among pregnant women are predominantly extrapolated from animal experiments or studies involving non-pregnant women and men, who still represent the majority in clinical trials. Fetal safety information is based on results of trials involving pregnant women in 5.2% of cases only; in other cases, it is obtained during animal experiments [13], though species sensitivity to the teratogenic effects was shown as early as the middle of the last century when thalidomide use was investigated. In this regard, almost all drugs that enter the market have an 'indefinite' teratogenic risk, whereas the interval required to select a more exact risk category is 27 years in average [14].

The majority of medicines are not officially approved for use during pregnancy. They are used off-label in doses and dosage regimens intended for non-pregnant women. At the same time, significant physiological changes in pregnancy induce alterations to all pharmacokinetic properties of medications. Development of new organs, such as placenta, uteroplacental blood flow and fetus, leads to significantly altered distribution, metabolism and excretion of various drugs. At the same time, maternal, fetal and placental activity of enzymes and transporters is dependent on gestational age. Dose adjustment can be required in various trimesters [15], whereas activity of some of them is subjected to genetic polymorphism [16]. During drugs biotransformation, novel metabolites not common for non-pregnant women can be formed in the placenta, including epoxides with teratogenic potential [15].

Thus, the ratio of risks and benefits of using various drugs in pregnant women remains unknown. It requires an urgent solution [17].

ETHICAL ISSUES OF STUDYING EFFECTIVENESS AND SAFETY OF MEDICINAL PREPARATIONS DURING PREGNANCY

Pregnant women are reluctant to be included in pre-marketing clinical trials and — in 95% of cases — in Phase IV clinical trials, where drugs are investigated in case of commonly occurring gestational conditions [18]. To a large extent, the reasons for these exclusions might be due to the two tragedies of the middle of the last century. Thalidomide used in 1957–1961 led to 8000–12000 children being born without limbs and with other birth defects, whereas diethylstilbestrol prescribed in the 1970s resulted in vaginal adenocarcinoma among women who were exposed to this preparation in utero.

In 1977, the FDA issued a guideline to exclude women of child-bearing age from Phase I and Phase II clinical trials, whereas pharmaceutical companies and research communities applied the exclusion to Phase III and Phase IV trials [14]. In 1979, the vulnerability concept has held a central place in research ethics guidance [19, 20]. Despite there is no unambiguous definition of the term and persons related to the category in scientific literature, it means that additional protection in clinical research is required and participation of vulnerable patients is restricted [21].

For a long time, vulnerable categories included generally all women of reproductive age, whose inclusion in clinical trials became possible only in the mid-1990s, when adequate safety measures have been followed (pregnancy testing, adequate contraception). Women who became pregnant during clinical trials were excluded. Pregnant women were considered vulnerable until 2019. So, the women and their fetuses have received the orphan status in terms of drug safety and effectiveness [22].

Meanwhile, concept analysis of women's vulnerability during pregnancy has shown that the patients are vulnerable only because in real medical practice they are increasingly under the growing risk of unfavorable effect due to limited science knowledge [23].

Owing to the lack of evidence data, the dose for pregnant women is equal to that obtained by non-pregnant women and men, which can result both in excessive blood concentrations or toxic effects, and insufficient concentrations that make therapy ineffective [17]. It puts the health and life of millions pregnant women and their fetuses/children at risk and raises the question of whether it is 'justifiable to include' pregnant women into randomized clinical trials (RCT) [21, 24].

Exclusion of pregnant women from the RCT violates fundamental principles of medical ethics, including the 'First Do No Harm' part of the Hippocratic Oath. It also violates the principle of respect for patient autonomy, which means that patients take an independent and informed decision about necessary methods of diagnostics and treatment, and the principle of justice, as it results in ignoring specific medical needs for this group of patients and slows down the affordability of the latest medical achievements [25]. The American College of Obstetrics and Gynecology (ACOG) suggests that pregnant women should be defined as 'scientifically complex' rather than a 'vulnerable' population. It means that a more frequent and targeted monitoring is required during the research [17]. The approach allows pregnant women to take an ethical decision for themselves and their fetuses [25].

CHALLENGES IN CONDUCTING CLINICAL RESEARCH INVOLVING PREGNANT WOMEN

Clinical research with participation of pregnant women can limit a number of factors on the part of drugs manufacturers, regulatory authorities and pregnant women themselves [11]. For manufacturers, such limiting factors include the risk of intense battles with the courts in case of unfavorable treatment outcomes, even if they weren't attributed to this exact drug; insignificant drug market size during pregnancy, and duration of use, which is pregnancy-limited in many cases. This can fail to

justify the costs for the drug registration and related regulatory burden [17]. Another limiting factor includes off-label use of medications: in real clinical practice pregnant women obtain drugs officially not approved for use during the gestational period. This is how a pharmaceutical company obtains financial income without being exposed to forensic risk.

Regulatory authorities also bear certain responsibility for the lack of adequate information on the use of drugs during pregnancy, as they do not require participation of pregnant women in clinical research during drugs registration and consider them vulnerable. Moreover, the research requires independent funding, which allows the regulatory authorities not to depend on manufacturers' drug registration fees [26].

It is frequently seen that pregnant women refuse to participate in research of novel drugs as they fear of the potential fetal risk, especially when there is no benefit for the women themselves (in the presence of alternative drugs to treat the pathology). Participation of pregnant women in pharmacokinetic research limits its duration. Thus, if an investigated drug has to be administered twice a day, a woman shall stay at the research center for 12 hours; ideally, the research should be conducted every trimester and in the postpartum period, which is even more complicated for breastfeeding women.

Another challenge is that clinical research involving pregnant women requires long-term follow-up to adequately assess not just outcomes for fetuses and newborns, but also potential effects on health and behavior of children [11].

Despite the abovementioned challenges, practicing physicians, researchers, professional communities and regulatory authorities are aware of the need in adequate clinical research of drugs during pregnancy [25]. In 2018, FDA and other American organizations engaged in development and control of drugs submitted a draft guidance for manufacturers that should be taken into account for scientific and ethical reasons while including pregnant women in clinical research [27]. To stimulate clinical research among pregnant women, it is recommended to use the experience of pediatric randomized clinical trials, which has resulted in significant progress within the last 15–20 years [11]. Thus, it is time to cancel the orphan status of pregnant women and their fetuses and allow mothers to exercise their ethical right to adequate medical aid, including the right for rational pharmacotherapy adjusted for the needs of this category of patients.

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