

EDITORIAL

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“As the inclusion of pregnant women in clinical trials has moved from ‘no’ to ‘yes’, ethical models and the informed consent process are guiding forces leading to medical answers and breakthroughs that improve the lives of pregnant women and their babies.”

From no to yes: the history and ethics of including pregnant women in clinical trials

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How often have you seen or heard ‘do not take this medication if you are pregnant (or nursing)’? Whether in media advertisements, pharmacies or provider offices, pregnant women are often warned to avoid many things. However, often the evidence behind these recommendations is not clearcut. The reason is that for a long time, pregnant women were excluded from participating in clinical trials. The ethical framework that led to telling women ‘no’ to participating in clinical trials continues to make it difficult to recruit women into research studies. However, the importance of including pregnant women and instead saying ‘yes’ is critical for the future of pregnancy therapeutics.

The last few decades have seen major changes in the landscape of research ethics. Very few areas have seen changes the scope of those seen regarding the inclusion of pregnant women in clinical trials, particularly medication trials.

In the wake of many revelations of unethical research, including problems arising from research involving drugs in pregnant women, children and the fetus, a protectionist research ethics model was adopted. Codified by the National Research Act in 1974, reproductive-aged women were excluded from many trials to avoid accidental early fetal exposure. Vulnerable populations such as pregnant women were given additional protections, such that unless there was a compelling reason for inclusion, pregnant women would not be included in research.

The general proscription model, however, was unsustainable as both clinicians and researchers realized that clinical trial data was not always generalizable from studied populations (usually men) to pregnant women. Pregnancy introduces an array of physiological changes that render dosing models from many clinical trials irrelevant. Owing to these changes, drug concentrations in pregnant women may be too low to be effective [1–3]. However, there was great concern about including pregnant women in clinical trials due to the often unknown effects drugs may have on the developing fetus. The lack of long-term developmental safety information for almost any drug further compounded this concern. In addition, animal model data had given false reassurance in the high-profile case of thalidomide.

During the late 1980s, however, a growing debate occurred about including pregnant women in clinical trials. Two landmark clinical trials helped push the ethical discussion forward and away from the strict protectionist model. The international studies demonstrating that prenatal vitamin supplementation (with folic acid) could reduce the incidence of recurrent and primary neural tube defects represented a departure from prior clinical trials that were centered on treating a condition [4,5]. These studies were about giving drugs (even if only prenatal

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vitamins) or placebos to healthy women to try and prevent a condition in the developing fetus. Ethics boards in several countries raised concerns at these study designs [6]. Even greater debate arose around the landmark international trial of giving azidothymidine to pregnant women with HIV infection to prevent maternal-to-child transmission [7]. The conduct of this trial broke new ethical ground [8]. It was one of only a few major clinical trials at the time giving a drug known to have some toxic side effects, that focused on pregnant women. This spurred intense ethical debates centering on reconciling the ethical perspectives of the mother and fetus.

In 1993, a major shift occurred in US regulatory policy; rather than excluding women and children from research, the NIH, through Public Law PL103-43, made clear its commitment to requiring that women be included in trials unless there was a reason not to. The NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended October 2001 is a clear statement on how to include vulnerable persons [101]. The paramount importance of the informed consent process is the focus and guides the inclusion of pregnant women in clinical trials. Challenges now lie at the level of quality and quantity of information [9]. This is particularly relevant in pregnancy, where the facts to populate informed consent risk–benefit discussions are not always known. Translating complex animal-based research or the difference between absolute risk and relative risk to the baby for a pregnant woman taking a drug can be challenging for both clinicians and researchers.

Luckily, there have been major efforts to include pregnant women in clinical trials over the last two decades. The Eunice Kennedy Shriver National Institute of Child Health and Human Development-funded Maternal-Fetal Medicine Units Network has been performing landmark clinical trials since 1986 [102]. Specific to clinical drug trials in pregnancy, the National Institute of Child Health and Human Development-funded Obstetric-Fetal Pharmacology Units Network focuses on basic, translational and clinical trials to characterize changes during pregnancy that affect drug disposition [103]. Attention is further being brought to the topics of pharmacotherapy in pregnancy through recent International Conferences on Individualized Pharmacotherapy in Pregnancy [10–12]. Many international groups also lead the way by including pregnant women in clinical trials.

When evaluating the ethical involvement of pregnant women in research studies, it is important to consider not only the potential effect of the drug on the pregnant mother and fetus, but also the impact the

condition itself may have on the mother and developing fetus. This becomes very important as the researcher chooses a control group. Placebo-controlled trials are not as common in pregnant populations as in nonpregnant populations. However several prominent recent clinical trials utilized placebo groups as controls [13,14]. The use of placebo groups in pregnancy clinical trials has been hotly debated. Placebo control groups allow for assessing outcomes from the condition itself. For instance, maternal conditions such as depression have been associated with neurodevelopmental issues in offspring. Thus, if a clinical trial of an antidepressant drug finds an association of the drug group with a certain neuro-developmental outcome, without a placebo control arm, it is impossible to ascertain if the adverse outcome is from the drug or the condition itself. In both pregnant and nonpregnant subjects, careful clinical trial design is the foundation of ethical clinical research.

Newer technologies and research strategies call for continued ethical discussions to safeguard the informed consent process. Recent trends in establishing biorepositories call for subjects to give consent for future unspecified use for their samples [15,16]. This often includes genetic analyses. The Genetic Information Nondiscrimination Act was a major step forward in protecting research subjects from downstream discriminatory ramifications of research participation. For pregnant women, these types of studies and safeguards are particularly important. Specimens and DNA obtained during research participation during pregnancy may be stored for years. Samples obtained at the time of delivery will contain the DNA of the baby, essentially enrolling that child in the biorepository at the time of birth and lasting for years into the future. This aspect of informed consent and adequately conveying the information to pregnant women highlight that informed consent is a process.

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As medical research moves through the genomic (and all other -omics) era, it is important to include pregnant women in clinical trials. It is not only ethical to do so, but there is an imperative to do so based on equity. As pregnancy is a unique biological condition complete with maternal and fetal physiological influences, it is necessary to understand the effects drugs have on the maternal and fetal conditions. Careful communication of the known and unknown risks and benefits to the pregnant woman are of the utmost importance. Knowledge and attitudes of the potential

subject, the research team and the clinical care team all have the potential to influence the informed consent process [17]. Researchers must use basic, translational and clinical research to provide data to populate the informed consent process. As the inclusion of pregnant women in clinical trials has moved from 'no' to 'yes', ethical models and the informed consent process are guiding forces leading to medical answers and breakthroughs that improve the lives of pregnant women and their babies.

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