Pediatric RESEARCH

COMMENT

Including pregnant women in clinical research: time to overcome the barriers

Scott C. Denne[1] the Pediatric Policy Council

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To fully benefit from medical advances, all populations need to be included in clinical trials. If particular populations are excluded from clinical trial participation, either actively or passively, the safety and efficacy of drugs, devices and other therapeutic approaches will remain unknown for individuals in these populations. Women, ethnic and racial minorities, and children have all experienced the consequences of exclusion from clinical trials. However, over the last two decades, federal legislation along with changes in Food and Drug Administration (FDA) and National Institutes of Health (NIH) policies have greatly improved the inclusion of women, ethnic and racial minorities, and children in clinical research.[1,2]

However, one important population that remains severely underrepresented in clinical trials is pregnant women.[3] Although there is understandable concern about protecting the developing fetus, the consequences of systematically excluding pregnant women from clinical trials is profound. Over 90% of women take at least one drug during pregnancy and lactation, but there is very little safety and efficacy information about their use in this circumstance.[4] This lack of safety and efficacy information is not only true of older drugs, but also for more recently approved drugs. For example no data were recorded about the risk in pregnancy of 73% of the drugs approved by the FDA between 2000 and 2010.[5] Without adequate information, clinicians are appropriately reluctant to utilize medications that may be of great benefit to pregnant women with a wide variety of conditions. As was true for children, protecting pregnant women and their fetuses from the possible risks of research has resulted in even greater harms. Millions of pregnant women each year are exposed to drugs without adequate safety, efficacy, or drug–drug interaction information, and potentially important new therapies are unavailable.

To be sure, appropriately including pregnant women in clinical research presents significant challenges and barriers.[4] Pregnancy is a short duration event with significant changes over the pregnancy interval. Any study design will need to account carefully for timing of exposure. The physiologic changes during pregnancy are also likely to alter the pharmacokinetics and pharmacodynamics of many drugs. The impact of external factors including obesity and the environment must also be considered. There is limited experience in conducting clinical trials in pregnancy, and the required expert clinical research work force is extremely limited. Currently, federal regulations classify pregnant women as a vulnerable population; this requires the Institutional Review Board to apply additional protections for trial approval.

Fortunately, there is now a strong consensus that including pregnant women in clinical research is critical, and the barriers to inclusion must be overcome. The 21st Century Cares Act, passed by congress in 2016, established a Task Force on Research Specific to Pregnant Women and Lactating Women (referred to as PRGLAC). Their report was issued to congress in September 2018 and provided 15 important recommendations to address the barriers of including pregnant women and lactating women in clinical research[4] (Table 1). Carrying out these recommendations will require the cooperation and sustained effort from multiple stakeholders, including the FDA, NIH, the pharmaceutical industry, academic clinical researchers (especially in obstetrics and pediatrics), families, and the public.

Sustaining dialog and collaboration among these diverse stakeholders will be an immense challenge and is an ambitious goal. Nevertheless, any progress toward this goal will deliver great benefit to pregnant women and breastfeeding infants. These comprehensive efforts toward including pregnant and lactating women in clinical research will not only provide important information about medication use, but also can provide a platform to pursue additional opportunities. For example, in this issue of Pediatric Research, Wagner et al. reviewed the science of prenatal maternal biomarkers for the early diagnosis of congenital malformations.[6] There is great potential for biomarkers to enhance prenatal diagnosis and to better understand pathogenesis of congenital anomalies. Both the FDA and the pharmaceutical industry are highly interested in developing and validating biomarkers for a variety of conditions, and biomarkers would be of particular use in studies of pregnant women.[7,8] As pointed out by Wagner et al., developing and validating biomarkers for the diagnosis of congenital anomalies will be challenging because it will require exceptionally large cohorts. One way to achieve large cohorts is to add a biomarker component to most clinical studies of pregnant women, including pharmaceutical trials. This will require active encouragement by the FDA and NIH, cooperation from the pharmaceutical industry, and development of international collaborations. As new clinical trials for pregnant women are now being designed, this is a particularly opportune time to make sure that a biomarker component is incorporated into these studies.

There is now a clear understanding of the critical need for including pregnant and lactating women in clinical trials, and the urgent necessity for overcoming the many barriers in the way of that goal. The pediatric community led the way to ensure that children were included in clinical research, and we now must also join the effort for pregnant and lactating women. Doing so will

[1]Department of Pediatrics, Indiana University, Indianapolis, IN, USA
Correspondence: Scott C. Denne (sdenne@iu.edu)

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Table 1. Recommendations of the task force (reference [4])

Task force on research specific to pregnant women and lactating women recommendations
1. Include and integrate pregnant women and lactating women in the clinical research agenda
2. Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women
3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics
4. Remove regulatory barriers to research in pregnant women
5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women
6. Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women
7. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model
8. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women
9. Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research
10. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women
11. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women
12. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women
13. Optimize registries for pregnancy and lactation
14. The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC task force when its charter expires in March 2019
15. Establish an advisory committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research

have a lasting impact on the lives and well-being of millions of mothers and their children worldwide.

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ADDITIONAL INFORMATION

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