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Research on vaccines during pregnancy: Protocol design and assessment of safety☆,☆☆

Flor M. Munoz[a,*], Jeanne S. Sheffield[b], Richard H. Beigi[c], Jennifer S. Read[d], Geeta K. Swamy[e], Indira Jevaji[f,1], Sonja A. Rasmussen[g], Kathryn M. Edwards[h], Kimberly B. Fortner[i], Shital M. Patel[j], Catherine Y. Spong[k], Kevin Ault[l], R. Philips Heine[e], Mirjana Nesin[m]

[a] Department of Pediatrics, Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA
[b] Department of Obstetrics and Gynecology, Division Maternal Fetal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[c] Department of Obstetrics, Gynecology and Reproductive Sciences, Magee-Women's Hospital of the University of Pittsburgh Medical Center, Pittsburg, PA 15213, USA
[d] National Vaccine Program Office, Office of the Assistant Secretary of Health, Office of the Secretary, Department of Health and Human Services, Washington, DC 20201, USA
[e] Department of Obstetrics and Gynecology, Division Maternal-Fetal Medicine, Duke University, Durham, NC 27710, USA
[f] Office of Research on Women's Health, Office of the Director, National Institutes of Health, Bethesda, MD 20817, USA
[g] Centers for Disease Control and Prevention, Atlanta, GA 30333, USA
[h] Department of Pediatrics, Vanderbilt Vaccine Research Program, Vanderbilt University, Nashville, TN 37232, USA
[i] Department of Obstetrics and Gynecology, Division Maternal-Fetal Medicine, Vanderbilt University, Nashville, TN 37232, USA
[j] Department of Medicine, Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA
[k] Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD 20892, USA
[l] Department of Gynecology and Obstetrics and the Emory Vaccine Center, Emory University School of Medicine, and the Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA 30303, USA
[m] Division of Microbiology and Infectious Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20817, USA

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ABSTRACT

The Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, National Institutes of Health organized a series of conferences, entitled "Enrolling Pregnant Women in Clinical Trials of Vaccines and Therapeutics", to discuss study design and the assessment of safety in clinical trials conducted in pregnant women. A panel of experts was charged with developing guiding principles for the design of clinical trials and the assessment of safety of vaccines during pregnancy. Definitions and a grading system to evaluate local and systemic reactogenicity, adverse events, and other events associated with pregnancy and delivery were developed. The purpose of this report is to provide investigators interested in vaccine research in pregnancy with a basic set of tools to design and implement maternal immunization studies which may be conducted more efficiently using consistent definitions and grading of adverse events to allow the comparison of safety reports from different trials. These guidelines and safety assessment tools may be modified to meet the needs of each particular protocol based on evidence collected as investigators use them in clinical trials in different settings and share their findings and expertise.

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☆ The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, National Institutes of Health, National Vaccine Program Office and the Food and Drug Administration.

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* Corresponding author at: Baylor College of Medicine, One Baylor Plaza, Suite 221-D, BCM-280, Houston, TX 77030, USA. Tel.: +1 713 798 5248; fax: +1 713 798 6802.
E-mail addresses: florm@bcm.edu (F.M. Munoz), nesinm@gmail.com (M. Nesin).
[1] Current address: Division of ESRD, Population and Community Health (DEPCH), Quality Improvement Group (QIG), Center for Clinical Standards & Quality (CCSQ), Centers for Medicare & Medicaid Services (CMS), USA.

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1. Introduction

Pregnant women and newborns are at increased risk for complications from infectious diseases. Vaccination during pregnancy can provide protection for mothers and infants against serious and potentially fatal infectious diseases. Worldwide, pregnant women routinely receive tetanus vaccine to prevent maternal and neonatal tetanus [1]. In the United States (U.S.) and other countries, vaccination against influenza is recommended during pregnancy to prevent complications in the mother and infants [2–4]. In 2012, the Advisory Committee on Immunization Practices (ACIP) to the Centers for Disease Control and Prevention (CDC) recommended vaccination of all pregnant women during each pregnancy with the adult formulation of the tetanus, diphtheria and pertussis vaccine (Tdap) [4–6]. In the U.S., other inactivated vaccines, such as pneumococcal vaccine, are recommended for pregnant women when the benefits outweigh theoretical risks (e.g., outbreaks, travel, high risk or occupational exposures). Live vaccines are generally contraindicated during pregnancy [7].

No vaccine has been licensed by the U.S. Food and Drug Administration (FDA) expressly for use in pregnant women. Recommendations for vaccination during pregnancy are based on risk versus benefit considerations. The American College of Obstetricians and Gynecologists (ACOG) and ACIP consider the following criteria when recommending vaccination of pregnant women: (1) An infectious disease poses a risk to the mother; (2) There is a risk to the fetus or infant; (3) A safe and effective vaccine is available to prevent the infection; and (4) Vaccination of the mother has the potential to benefit the mother and/or the infant, and is unlikely to cause harm [8,9].

Safety is a major priority when considering vaccination during pregnancy. FDA requirements and regulations for the administration of biological products in pregnant women are evolving based on the assessment of risk versus benefit [10]. Instead of the current classification in letter-risk categories (A to D and X), drugs and biological products will be required to include a narrative summary of the potential harm from using them during pregnancy based on available data [11]. Product labels also will include relevant clinical information on the use of the product during pregnancy and lactation. Per FDA regulations, human data may be derived from clinical trials, pregnancy exposure registries, large epidemiologic studies or small case series. Numerous observational studies, as well as Phase II clinical trials of viral and bacterial vaccines have been conducted since the early twentieth century, supporting the safety and potential benefit of vaccines used during pregnancy (Supplementary Table 1) [12,13]. More recently, the re-emergence of pertussis worldwide and the 2009 H1N1 influenza pandemic have brought pregnant women to the forefront as a population who benefits from inclusion in clinical research of vaccines.

The inclusion of pregnant women in clinical trials is essential to ensure a comprehensive evaluation of existing and future vaccines and biologicals. Most vaccines may directly benefit the pregnant woman (e.g., pneumococcal and influenza vaccines), and all vaccines have the potential to provide passive protection to the newborn. This is critical when no other effective disease prevention alternative is available (e.g., pertussis, respiratory syncytial virus, or group B streptococcus). Data generated from clinical trials can support the recommendation or licensure of a vaccine for pregnant women.

This document summarizes the recommendations of a panel of experts convened by the Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) to develop a reference tool and provide general principles to guide clinical investigators on protocol design and the assessment of the safety of vaccines in clinical trials in pregnant women.

2. Materials and methods

The panel consisted of experts in obstetrics, maternal–fetal medicine, infectious diseases, pediatrics, neonatology, genetics, vaccinology, epidemiology, teratology, pharmacology, statistics and clinical trial design, and constituted a partnership between government agencies, academia and industry.

Protocol design recommendations were based on current DMID/NIAID protocol development templates and the expertise of investigators who have conducted studies in pregnant women. Standard definitions of safety parameters were derived from the DMID Interventional Protocol Template, version 5.0, March 25, 2011 [14] and adapted to develop a grading system for adverse events (AE) in clinical trials enrolling pregnant women based on expert consensus. Serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSAR), and reporting requirements were defined by the Code of Federal Regulations (CFR) [15].

Local and systemic reactogenicity tables for pregnant women were generated using the grading described in "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Revised September 2007) [16], DMID Toxicity Tables [17], Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [18], Addendum 1 Female Genital Grading Table for Use in Microbicide Studies [19], and Cunningham et al. [20]. In addition, Medline Plus [21], Up-to-Date [22], 2011 CFR [23], and ICH Guidelines [24] were used as a source for definitions to assign clinical relevance and develop grading of clinical AEs occurring during pregnancy.

The content of this document is distinct from clinical care and regulatory reporting requirements. The tables are not all inclusive and may need to be modified as appropriate for use in specific trials.

3. Results

3.1. Protocol design

The panel recommended that each study team conducting trials in pregnant women include investigators with expertise in obstetrics, pediatrics and/or neonatology, and clinical research. Consultation with experts in subjects pertinent to the study during the protocol design phase is also advisable (e.g., epidemiology, safety assessments, pharmacology, and regulatory issues).

Vaccine candidates studied in pregnant women should meet the following minimum requirements:

- Pre-clinical studies have been performed.
- Reproductive toxicology testing demonstrated no fetal toxicity.
- Phase I–II clinical trials in healthy non-pregnant adults provide guidance on dosage, safety, and immunogenicity.
- There disease to prevent poses a special risk to the mother and/or fetus.
- The vaccine is unlikely to cause harm to the mother or fetus.

The study protocol should include the following items:

- Background with description of available data and rationale for the study.
- Inclusion and exclusion criteria for enrollment.
- Description of safety parameters to be assessed in the study (e.g., vital signs, laboratory values, local and systemic reactogenicity, and pertinent medical events in the mother and the infant).

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