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Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments

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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, "Enrolling Pregnant Women in Clinical Trials of Vaccines and Therapeutics", to discuss enrollment and safety assessments of pregnant women in clinical trials of vaccines. Experts in obstetrics, maternal–fetal medicine, infectious diseases, pediatrics, neonatology, genetics, vaccinology and clinical trial design were charged with identifying normal ranges for vital signs and laboratory assessments in pregnancy. A grading system for adverse events was then developed

1. Introduction

The recent 2009 H1N1 influenza pandemic and the concomitant need for rapid evaluation of candidate vaccines in pregnant women prompted a much needed assessment of methods to implement vaccine-related research in this high-risk group. Prior to the pandemic, studies of therapeutics and vaccines during pregnancy were limited, in part due to investigator reluctance to enroll pregnant women for fear of medical liability and for theoretical safety concerns. However, with the risk of pandemic influenza believed to greatly outweigh expected adverse events (AEs) associated with the influenza vaccine, studies in pregnant women were initiated. Several of the major challenges encountered in the conduct of these trials involved defining and monitoring clinical and laboratory values during pregnancy. This is particularly challenging because clinical findings and laboratory values are often altered in normal pregnancy.

Pregnancy is associated with extensive functional and anatomical adaptations. Concomitant with the physiologic changes are alterations in baseline vital signs and laboratory parameters.

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Table 1
Grading system for adverse events.

Numeric grades		Descriptive grades	
1	Approximately 10% outside the normal range. Test is usually repeated to confirm the value, or to confirm resolution.	Mild	Transient or mild discomfort (< 48 h); no medical intervention/therapy required.
2	Approximately 10–20% outside the normal range, unless clinically relevant association was established to indicate otherwise. Usually does not require diagnostic work up and is followed to stabilization or resolution.	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
3	>20% outside of normal range, usually requires diagnostic work up and/or intervention.	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible. For IND studies, reported as a serious AE (SAE).
4	Usually requires an immediate intervention, even if not potentially or immediately life threatening.	Life threatening	In the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. For IND studies reported as SAE.

Note: The grading system presented in the table is based on clinical experience and consensus of experts. This table shows the description of numeric AE grades (grades 1–4) was developed. Numeric grades are not intended to match precisely the clinical severity or descriptive grades (mild, moderate, severe, life threatening) used in FDA Guidance for Industry.

Common laboratory values and the normal reference ranges across trimesters in pregnancy have recently been summarized by Abbassi-Ghanavati et al. [1]. While their list of laboratory values is not exhaustive, it is a useful reference for researchers enrolling pregnant women into clinical trials. However, values outside the normal range however are not graded, thus impeding a consistent assessment of AEs in pregnant women.

The Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), organized a series of conferences, "Enrolling Pregnant Women in Clinical Trials of Vaccines and Therapeutics", convening a panel of experts on three occasions during 2011 and 2012, to discuss enrollment and safety assessments of pregnant women in clinical trials of vaccines. Experts in obstetrics, maternal–fetal medicine, infectious diseases, pediatrics, neonatology, genetics, vaccinology and clinical trial design, were charged with identifying normal ranges for vital signs and laboratory assessments seen in pregnancy. The findings presented here are the result of these deliberations. The reference tables are designed to provide general guidance on parameters used for monitoring safety in vaccine trials involving pregnant women, to facilitate a consistent assessment of AEs in healthy pregnant women and, potentially, to assist in the enrollment of pregnant women with complications. These reference tables will also have broader applicability for other types of trials involving pregnant women e.g. drug studies.

2. Materials and methods

Publications by Abbassi-Ghanavati et al. [1], Williams Obstetrics [2], and Lockitch [3] were used as data sources. Unless otherwise specified, normal values for pregnant women were taken from the Abassi-Ghanavati et al. publication [1]. Reference ranges for healthy non-pregnant adults were obtained from Harrison's Principles of Medicine [4], MedlinePlus (www.nlm.nih.gov/medlineplus, accessed in December 2012), and DMID Adult Toxicity Tables [5]. The Food and Drug Administration (FDA) document "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" [6] was used as a source for assessment of local and systemic reactogenicity of parenterally administered vaccines and therapeutic agents.

According to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice [7], an AE is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be "any unfavorable and unintended sign(s), symptoms(s) or condition temporally related with the use of the investigational product". This definition was used in the development of the following tables.

The conference deliberations originated three tables regarding vital signs and laboratory assessments in pregnancy: (1) a table for a grading system for AEs; (2) a table for vital sign grading; and (3) a table of laboratory value AEs graded by trimester. The first trimester was defined as ≤14 0/7 weeks gestation, the second trimester as 14 1/7–28 0/7 weeks gestation, and the third trimester as 28 1/7 weeks gestation to delivery. The tables were developed to guide assessment of AEs in the context of a clinical trial rather than to guide clinical care. If an abnormality is identified prior to administration of study product or procedure, it should be considered a "baseline abnormality" and the subject's eligibility for enrollment should be assessed. Assessment tools were also developed for the evaluation of clinical adverse events and local and systemic reactogenicity–these tables are outside the scope of this manuscript and are the focus of a separate paper.

3. Results

Laboratory values and vital signs were graded from 1 to 4, based on the FDA "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" [6] and expert consensus (Table 1). Grade 1 or mild toxicity was defined as any event requiring minimal or no treatment and one that does not interfere with the patient's daily activities; values approximately 10% outside the normal range are included in this category. Grade 2 or moderate toxicity was defined as any event resulting in a low level of inconvenience or concern with the therapeutic measures, with values of 10–20% outside the normal range. Grade 3 or severe toxicity was defined as any event that interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Finally, Grade 4 or life-threatening toxicity was defined as any AE that places the subject, in the view of the investigator, at immediate risk of severe consequences, up to and including death from the reaction. Grade 3 and Grade 4 toxicity were matched to the "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" [6] when possible.

Table 2 depicts the grading changes of vital signs during pregnancy. Vital signs ranges were reported, with those outside the normal range graded using expert opinion for clinical relevance. The panel determined that vital signs values did not significantly differ between trimesters to warrant a table for each trimester. The resting pulse rate increases 10–20 beats/minute during pregnancy, peaking in the second trimester. Systolic and diastolic blood pressure decrease in pregnancy with the nadir occurring in the second trimester, and a return to baseline in the third trimester. The respiratory rate increases by 2–4 breaths/minute with a normal pregnancy range of 12–20 breaths/minute. Grade 4 toxicity