## **EDITORIAL**

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"The unique susceptibility of pregnant women and newborns to infections has been recognized for decades, and preventive interventions have been implemented, when available, based on their potential for benefit and the relatively low risk for the mother and fetus."

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# FUTURE SCIENCE

# The challenges of pregnancy in clinical trials for vaccines

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The study of vaccines during pregnancy is one of the most rapidly evolving fields in medicine today. Pregnant women and young infants are particularly at risk of acquiring and developing complications from infectious diseases [1]. Vaccines administered during pregnancy have the potential to benefit both the mother and her newborn infant [2,101]. Along with the active and ongoing development of safe and effective vaccines, the importance of including pregnant women in clinical research is increasingly recognized.

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The unique susceptibility of pregnant women and newborns to infections has been recognized for decades, and preventive interventions have been implemented, when available, based on their potential for benefit and the relatively low risk for the mother and fetus. Routine administration of tetanus vaccine during pregnancy was recommended by the WHO in the 1960s after a small study conducted in a high-risk region demonstrated a significant reduction in mortality from neonatal tetanus in infants born to vaccinated mothers. Tetanus vaccination during pregnancy has successfully reduced maternal and neonatal tetanus mortality worldwide [102]. Similarly, influenza vaccine was recommended for pregnant women in the USA after increased morbidity and mortality were documented in women who were pregnant during the influenza pandemics of the early twentieth century and during interpandemic periods [3]. However, it was the 2009 A/H1N1 influenza pandemic that served as a stark reminder of the severity of influenza in pregnancy, its impact on prematurity and fetal-neonatal mortality, and the need to improve influenza vaccine coverage in pregnant women [4]. More recently, the global resurgence of pertussis has resulted in risk-based recommendations to vaccinate pregnant women with tetanus-diphtheriapertussis vaccine in the USA and other countries, in order to provide protection during the period of highest vulnerability to pertussis by increasing the concentrations of maternally transmitted antibodies to the newborn [5].

While the impact of routine maternal immunization with influenza and pertussis vaccines remains to be determined, immunization during pregnancy is now a recognized and accepted strategy to provide protection against specific pathogens that are relevant to the mother and the newborn. These include tetanus, influenza and pertussis, and other infections for which vaccines are currently available, such as meningococcus and pneumococcus, or for which vaccines are in development, including group B streptococcus and respiratory syncytial virus [6,7]. The possibility to protect mothers and infants with vaccines against other relevant pathogens is evident. Maternal immunization is a high priority for research worldwide given its potential to significantly impact maternal and infant health.

As interest in maternal immunization as a desirable and feasible strategy to reduce maternal and child morbidity and mortality increases, the challenges associated with vaccinating pregnant women also continue to evolve. Probably the most

Keywords: challenges • clinical trials • maternal immunization • pregnancy • pregnant women • vaccines important change in the scientific community has been the transition from a culture where pregnant women were routinely excluded from clinical research to one where inclusion of pregnant women in clinical trials of vaccines and therapeutics is considered fundamental to ensure the health of mothers and their infants. Women who are pregnant deserve to have access to preventive and therapeutic interventions, as non-pregnant adults do. The challenge for scientists, physicians, vaccine manufacturers and regulatory agencies, is to develop acceptable methods to carry out research in pregnant women. These should take into consideration multiple factors specifically related to working with a vulnerable and high-risk study population, such as understanding ethical and cultural issues associated with conducting research during pregnancy, the potential risk versus benefit of the study interventions and the safety of the mother and fetus, as well the need to strictly adhere to scientific and regulatory requirements.

Until recently, guidelines on how to conduct clinical trials of vaccines in pregnant women have not been available, and a defined regulatory pathway to achieve approval for the specific indication for a vaccine to be administered to pregnant women has not been established. From a regulatory viewpoint, clinical trials in pregnant women are subject to human subject protection requirements as described in the Code of Federal Regulations in the USA, and by the Council for International Organizations of Medical Sciences worldwide [8,103-105]. The US FDA requirements for the use of vaccines and drugs in pregnancy is changing from one where biologicals were classified in pregnancy categories (A to D and X) based on whether studies had been performed in pregnant women, to one of acceptance of any available data (not restricted to clinical trials, and inclusive of observational, clinical and research data) to support or contraindicate their use in pregnancy [9,10].

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Clinical trials of vaccines in pregnant women must be carefully designed to ensure the safety of the mother and baby. Guiding principles on how to design and conduct pregnancy trials that conform with the requirements of the Division of Microbiology and Infectious Diseases of the National Institutes of Health have now been published [11]. Vaccines that are studied in pregnancy must comply with minimum requirements that include the completion of supporting preclinical studies, reproductive toxicology testing in animal models to

document a lack of fetal toxicity, and successful Phase I and II clinical trials in non-pregnant adults that show that the vaccine is safe and immunogenic. Guidance from regulatory agencies is also recommended early on in the process. Once a vaccine candidate is considered adequate for testing in pregnant women, special attention must be given to define inclusion and exclusion criteria for the study, as well as definitions of clinical and laboratory parameters to assess the safety of the vaccine in mothers and their offspring [11,12]. This is of particular importance in pregnancy studies given that pregnancy itself is a condition associated with potential complications, and that there is a possibility for adverse events to occur at all stages of pregnancy, at the time of delivery, and in the post-partum period, which should be assessed for their association with the study vaccine or lack thereof. A particularly challenging issue is that of determining the potential impact of maternal vaccination on the infant's ability to respond to pathogens or to active immunization in early life. However, when taken in the context of vaccination as a potential life-saving intervention for a period of time when active vaccination of the infant is not feasible, such as in tetanus or pertussis prevention, the value of maternal immunization is high. Furthermore, maternal antibodies are only present in the infant's circulation for the first few months of life, mostly disappearing by 1 year of age. Whether maternal immunization could result in late, long-term consequences to the child (presenting later in childhood, adolescence or even adulthood) is unknown.

With the rapid evolution of the field, clinical trials of vaccines in pregnancy face challenges, including the need to educate the public, healthcare providers, local and national authorities, and anyone involved in clinical research on the importance of carrying out these studies. Recruitment of women who are pregnant in clinical trials of vaccines must take into consideration the existing perception of the need to avoid any intervention or administration of medications or vaccines during pregnancy fueled by unfortunate historic experiences where administration of drugs for common symptoms seen in pregnancy resulted in birth defects. Also important, are cultural beliefs about factors (real or perceived) that might affect pregnancy and its outcomes, access to pre- and postnatal care, maternal level of education and previous maternity experience, involvement of the father and extended family, provider beliefs and reservations, particularly concerns of causing harm and of liability, local practices and adherence to recommendations of standard of care.

Investigators also realize that their understanding of the physiology of pregnancy and of the immunologic factors that affect the mother and the fetus is relatively limited. Research is needed to help decipher the intricate interactions between the mother and the

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fetus during different stages of pregnancy, fetal development, placental physiology, the effects of natural infections versus those of vaccines, maternal, fetal and early infancy immunology, and the potential short- and long-term consequences of immunizing women during pregnancy. In order to improve implementation of vaccination of pregnant women with existing vaccines and encourage the development of promising vaccines, it is important to describe and understand the epidemiology and impact of vaccine-preventable diseases in different populations and geographic regions, variations in local practices, and factors that might affect the knowledge and acceptance of maternal immunization as a critical health-sustaining strategy of global applicability.

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#### References

- Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg. Infect. Dis.* 12(11), 1638–1643 (2006).
- 2 American College of Obstetricians and Gynecologists (ACOG). Immunization during pregnancy. ACOG Committee Opinion Number 282. Obstet. Gynecol. 101, 207–212 (2003).
- 3 Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 59, 1–62 (2010).
- 4 Siston AM, Rasmussen SA, Honein MA et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. JAMA 303(15), 1517–1525 (2010).
- 5 Centers for Disease Control. Updated recommendations for use of tetanus toxoid, reduced diphtheria, and acellular pertussis vaccine (Tdap) in pregnant women – Advisory Committee on Immunization Practices (ACIP) 2012. MMWR 62(07), 131–135 (2013).
- 6 Johri AK, Paoletti LC, Glaser P *et al*. Group B streptococcus: global incidence and vaccine

development. *Nat. Rev. Microbiol.* 4, 932–942 (2006).

- Faber TE, Kimpen JLL, Bont LJ. Respiratory syncytial virus bronchiolitis: prevention and treatment. *Expert Opin. Pharmacother.* 9(14), 2451–2458 (2008).
- 8 Beigi RH, Goldkind SF, Jevaji I. Research on vaccines and antimicrobials during pregnancy: challenges and opportunities. *Vaccine* 31, 4261–4263 (2013).
- 9 Gruber MF. Maternal immunization: US FDA regulatory considerations. *Vaccine* 21(24), 3487–3491 (2003).
- 10 US Federal Drug Administration. Content and format of labeling for human prescription of drug and biological products: requirements for pregnancy and lactation labeling. *Federal Regis.* 73, 30831–30868 (2008).
- Munoz FM, Sheffield JS, Beigi RH *et al.* Research on vaccines during pregnancy: Protocol design and assessment of safety. *Vaccine* 31, 4274–4279 (2013).
- 12 Sheffield JS, Munoz FM, Beigi RH et al. Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments. *Vaccine* 31, 4264–4273 (2013).

#### Websites

- 101 Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Guidelines for vaccinating pregnant women. July 2012. www.cdc.gov/vaccines/pubs/downloads/b. preg.guide.pdf
- 102 World Health Organization. Maternal and neonatal tetanus elimination initiative 2013. www.who.int/immunization.monitoring/ diseases/MNTE.initiative/en/index.html
- 103 Code of Federal Regulations Title 21. www.acessdata.fda.gov/scripts/cdrh/cfdocs/ cfcfr/cfrsearch.cfm
- 45 CFR (Public Welfare) part 46 (protection of human subjects). DHHS (2005).
  www.access.gpo.gov/nara/cfr/ waisidx.10/45cfr46.10.html
- 105 The International Ethical Guidelines for Biomedical Research Involving Human Subjects. The Council for International Organizations of Medical Sciences in Collaboration with the World Health Organization. Geneva: CIOMS). www.cioms.ch/publications/guidelines/ guidelines.nov.2002.blurb.htm