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VACCINES IN PREGNANT WOMEN & INFANTS (D SCHWARTZ AND C KRUBINER, SECTION EDITORS)

Pregnant Women, Vaccine Development for Emerging and Epidemic Viral Infections and Maternal Immunization: Human Rights and the Global Survival of Mothers and Infants

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Abstract

Purpose of Review Pregnant women, their fetuses, and infants are at a high risk of exposure to infectious diseases, especially in low-income regions of the world where vaccine-preventable diseases are prevalent. Vaccines administered during pregnancy can protect not only pregnant women against infection-related morbidity and mortality, but also their fetuses and infants against preterm delivery, perinatal death, and disability. This article analyzes current issues related to maternal vaccination with a focus on emerging and epidemic viral infections and human rights.

Recent Findings Historically, pregnant women have not been considered in the development of vaccines and have been excluded from participating in clinical trials and vaccination campaigns. Because of risk for injury and death of mothers and fetuses/infants during infectious disease outbreaks, it is important to consider their rights to receive any potential form of prevention or therapy available to non-pregnant individuals in order to enhance their well-being.

Summary It is unacceptable to ignore the needs of pregnant women and infants in pharmaceutical and vaccine development, clinical trials, and biomedical research. International agencies and organizations are beginning to realize the importance of involving pregnant women in these studies, as well permitting vaccinations of pregnant women during outbreaks of life-threatening infections.

Keywords Pregnancy · Maternal vaccination · Human rights · Vaccines · Immunization · Maternal and infant mortality · Vaccine preventable disease · Maternal immunization · Ebola virus

Introduction

Vaccines save lives—their development and implementation have been one of the most successful triumphs in modern public health and medicine. The World Health Organization estimates that between the years 2010 and 2015, a minimum of 10 million lives have been saved by global vaccination programs, and that many millions more have avoided illness and disability caused by such infections as diphtheria, polio, pneumonia, meningitis, diarrheal disease, measles, and pertussis, to name just a few. Despite these successes, maternal mortality remains unacceptably high—approximately 830 maternal deaths occur every day, a total of between 291,000 and 349,000 annually, with greater than 99% occurring in the resource-poor countries of the world [1, 2]. It is also estimated that as many as 1.5 million infants and children die each year due to diseases that could have been prevented by vaccination, and that approximately 29% of deaths in children 1–59 months of age are vaccine preventable [3•]. However, for many epidemic infections that are associated with high case fatality rates, the development of vaccines has not been as timely. In particular, and with the exception of yellow fever, vaccine development for arthropod-borne viral infections that fall into the general category of hemorrhagic fevers has significantly lagged the development of other, less deadly, infections. This is most unfortunate, as vaccines are critically

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important tools in the public health response to infectious diseases. Immunization of pregnant women has the potential to significantly improve maternal and infant health by reducing morbidity and mortality associated with pathogens that are especially important in the perinatal period and in early life, and for which no alternative effective preventive strategies exist. Recent outbreaks of viruses including influenza [4, 5], Lassa fever [6], Ebola and Marburg viruses [7, 8], Zika virus [9], and hepatitis E [10] have illustrated the higher risks for poor outcomes experienced by pregnant women and their infants during epidemics of certain infectious diseases. Sadly, exclusion of pregnant women from both experimental vaccine clinical trials as well as administration of highly effective vaccines during epidemics has been most recently exemplified during a series of Ebola virus epidemics and outbreaks in Africa [3, 11]. But the African Ebola outbreaks are only the most recent and high-profile examples of the unfair exclusion of pregnant women from participating in the design, preclinical trials and clinical distribution phases of vaccination development and implementation [12••, 13••]. Many believe that excluding pregnant women from vaccine trials and usage is an unfortunate decision, as the majority of vaccine-preventable diseases can cause devastating injuries to the fetus and the mother [14, 15].

Pregnancy and Vaccines

Pregnant women, their fetuses, and infants are at a high risk of exposure to infectious diseases, especially in the resource-poor and low-income regions of the world where vaccine-preventable diseases are prevalent. Because of this, vaccines administered during pregnancy offer the potential to protect not only pregnant women against infection-related morbidity and mortality, but also their fetuses and infants against preterm delivery, perinatal death, and disability. The potential benefits of providing immunization to pregnant women and their infants to protect against infection are not a novel concept—even during the early development of vaccines, their usage during pregnancy was considered potentially beneficial. It was observed as early as 1879 that pregnant women that were given smallpox (Jennerian) vaccination against smallpox had infants who were protected from infection. [16] Additional research on vaccine administration during pregnancy included evaluating the administration of whole cell pertussis vaccine (DTP) in the 1940s, influenza vaccine following the global pandemics in the 1950s, and tetanus toxoid vaccine in preventing maternal and neonatal tetanus worldwide since the 1960s [17]. Maternal immunization research was supported by National Institutes of Health in the United States for decades, including basic science, clinical, epidemiological, and translational research.

However, progress in maternal vaccination slowed during the 1950s and early 1960s, when a syndrome of congenital limb malformations, termed phocomelia, developed in many thousands of infants born to mothers who were given the drug thalidomide as a treatment for hyperemesis gravidarum (morning sickness) during pregnancy [18]. This association had the result of increasing restrictions of exposures to medications and vaccines for pregnant women, including exclusion of pregnant women from bioresearch protocols [3•]. Fortunately, decades of subsequent experiences with global administration of a wide spectrum of vaccine products since those times has changed the way that maternal immunization is practiced. The availability of additional data on the benefits of vaccine administration to pregnant women, as well as the absence of increased risk for adverse outcomes following vaccination during pregnancy, has increased attention to the life-saving benefits of maternal immunization.

The evolution of the use of the inactivated influenza vaccine during pregnancy provides an example of this change in attitude based upon increasing clinical experience and investigational studies. Although the inactivated influenza vaccine was first distributed in the late 1940s in the United States, it was not until 1960 that the Surgeon General of the United States first recommended administration of the influenza vaccine to pregnant women due to heightened risk for viral complications in this population. However, many others did not support this recommendation [19•]. In 1990, the Advisory Committee on Immunization Practices (ACIP) recommended that the vaccine be given only to pregnant women with underlying conditions, and then only after the first trimester to minimize potential teratogenicity. Then, in 1995, ACIP changed their immunization recommendations to include pregnant women without underlying problems but restricted to the third trimester. A study demonstrating increased hospitalizations for women in their 2nd and 3rd trimester of pregnancy due to influenza infections in interpandemic periods, the ACIP once again changed their recommendations to add vaccination in the 2nd trimester. Following the severe 2003–2004 influenza pandemic in which many pregnant women developed life-threatening infections and missed opportunities for immunization were identified, ACIP recommended in 2004 that pregnant women could receive the influenza vaccine any time during gestation, including the 1st trimester [19•].

Another highly lethal pandemic also provided impetus to allow pregnant women to receive potentially life-saving medicines. During the development and spread of the acquired immunodeficiency syndrome (AIDS) pandemic in the 1980s, it was recognized that pregnant women could become infected and vertically transmit the human immunodeficiency virus (HIV) to their fetus and infant with a high fatality rate and no cure. As a result, pregnant women were permitted to enroll in the early phases of anti-retroviral drug trials—even prior to the completion of experimental animal studies. This decision was based upon the life-threatening nature of AIDS and was believed to justify an unknown risk to the fetus in order to potentially extend the life of the mother [3•, 20].

This conservative approach to the vaccination of pregnant women, which has resulted in their exclusion from enrollment in drug and vaccine trials, has continued to persist up to the present times. [3•] The participation of even non-pregnant women in experimental trials remained restricted until 1993, when the policy was modified so that both sexes were recruited into drug studies in order to determine gender-based differences [21]. This change in policy did not include pregnant women, however. Moreover, fewer than 20 years ago, the United States Food and Drug Administration (FDA) still maintained their policy of excluding those women "of childbearing potential" from experimental drug trials [3•, 22]. However, this has undergone more recent modification in that women are being permitted to enroll in drug trials for non-obstetric conditions with the following restrictions—that they are not pregnant at the time of enrollment, and that they do not intend to become pregnant, including the use of birth control [23]. Possibly, the most permissive clearance for the participation of pregnant women in experimental studies originates with the Joint United Nations Programme on HIV/AIDS/World Health Organization (UNAIDS/WHO) ethical guidance for HIV prevention trials [3•, 24]. Guidance Point 9 from this document states, "Researchers and trial sponsors should include women in clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention interventions. During such research, women's autonomy should be respected and they should receive adequate information to make informed choices about risks to themselves, as well as to their fetus or breast-fed infant, where applicable".

In contemporary times, pregnancy continues to be viewed as a potentially dangerous period for the administration of immunizations and medications. It can be very challenging to be completely certain of the safety to the mother and developing embryo and fetus of drugs and vaccines, and thus caution has traditionally guided their usage during pregnancy. There was always the possibility of side effects occurring in the mother that could be deleterious to the normal progress of the pregnancy, labor, and delivery; transplacental passage might result in teratogenic, developmental, and toxic effects to the fetus; intrauterine fetal demise could occur; and there was the danger of passage of the medicant to the newborn infant following delivery through breastmilk [3•, 25]. In addition, pregnancy can affect the manner in which a drug or vaccine interacts with the host—alterations in the maternal immune response, believed to permit the mother to tolerate a semi-allogeneic fetus, can potentially interfere with the specific immune response to pathogens and alter susceptibility of the maternal-fetal pair to infections [3•, 26, 27]. Gender-based differences can also be seen in the non-pregnant state—the hormonal, genetic, immunological, and environmental differences between females and males can have an effect on their immune responses and the sex-related outcome of vaccination.

This traditional fear of vaccinating pregnant women has not just existed in the realm of outbreaks and epidemics—physicians and travel medicine clinics have historically been hesitant to provide pregnant travelers with the appropriate vaccines for their destinations, even though this has placed them at increased risk for acquiring an infection [28].

Reluctance to Include Pregnant Women in Design, Trials, and Administration of Vaccines

From a historical perspective, the needs of pregnant women have never been prioritized in either the development or clinical testing of vaccines or pharmaceutical products. Even when new biomedical products reach the marketplace, information on their safe use for pregnant women and the fetus is usually incomplete, or in many cases, lacking. All vaccine formulations that are currently in use in pregnant women were, in fact, initially developed and tested for in non-pregnant persons [3•, 26]. There are no vaccines that are currently approved or licensed specifically for use in pregnant women.

The basis for the exclusion of pregnant women to participate in clinical trials and immunization programs is, for the most part, based upon the avoidance of risk and liability. Following the arrival of new vaccines onto the marketplace, information on their safe use for pregnant women and the fetus is usually incomplete, or even lacking. For the large majority of vaccines and drugs, there is a lack of evidence to guide their evaluation for use in pregnant women—this is especially true with medications as there is a dearth of information on the potential teratogenicity of greater than 98% of drugs approved by the FDA since 2000, and 91% approved since 1980 [13]. In almost 75% of drugs approved for use since 2000, no pregnancy-specific data appears at all. In addition to this deficiency of knowledge, for greater than 98% of pharmacokinetic studies, there exists no information to guide drug dosing in pregnant women [13, 29, 30].

Potential issues involving both national and international legal liability also have been important factors in delaying and even prohibiting the clinical testing and evaluation of vaccines and drugs in pregnant women. The pharmaceutical companies who are responsible for the design, evaluation, and distribution of the majority of vaccine products face concern not only for adverse outcomes for pregnant women and their fetus exposed to vaccines during clinical trials and following approval, but also for development of post-natal complications for vaccinated neonates and infants. Vaccine manufacturers also have concern for legal liability in cases where previously approved vaccines were not tested or initially recommended for use in pregnancy, but there has been subsequent need for vaccine administration in

pregnant women as in the case of a humanitarian crisis. Another factor that inhibits knowledge of the safety of vaccine use during pregnancy lies in the methodology of vaccine development and testing. Cost efficiency has dictated that until it appears likely that a newly developed vaccine candidate will be approved and licensed that testing for mutagenicity, teratogenicity, and toxicology are conducted, result in delays in important pregnancy-specific safety data. As a result, most of the safety data on vaccine use during pregnancy are available through post-marketing observational studies, passive surveillance methods, and anecdotal reports. Contributing to the hesitancy of pharmaceutical companies, institutions, and agencies to permit vaccine administration to pregnant women is their emphasis and fear of potential adverse outcomes from the vaccine, while simultaneously deemphasizing the consequences and risks of infection to non-immunized mothers and their fetuses. This phenomenon was most recently exemplified in the West African epidemic and DR Congo outbreaks of Ebola virus, in which non-immunized mothers had a fatality rate of greater than 50% and their fetuses close to a 100% case fatality rate [3•, 7].

As a result of these and other issues, a vicious cycle has developed in which pregnant women have been excluded from receiving vaccines during mass vaccination campaigns and humanitarian crises due to insufficient data regarding safety to the mother, fetus, and infant because they were not originally included in clinical trials, and pregnant women have been excluded from vaccine development and clinical trials due to fear of adverse outcomes and legal liability.

Despite these misgivings, no maternal vaccine has been proven to result in birth defects [3•]. Although live attenuated virus vaccines have generally not been recommended for use during pregnancy, their inadvertent administration to pregnant women during mass vaccination campaigns has been documented [31]. During the West Africa Ebola epidemic, pregnant women had unintentionally and unknowingly been included in the vaccine trials—this occurred because pregnancy tests were not typically performed, and pregnancy status of women was identified on the basis of self-reporting. During this time, more than 20 pregnant women were administered the experimental rVSV-ZEBOV vaccine as part of the Ebola Phase 3 cluster-randomized ring vaccination trial in Guinea (*Ebola ça suffit!*) [12••, 32]. Dr. Severine Caluwaerts, an obstetrician with Medecins sans Fronteres (MSF), discussed these cases with a representative of the World Health Organization who stated that the inadvertently vaccinated pregnant women have apparently suffered no ill-effects [33].

Human Rights of Pregnant Women to Receive Vaccines

Pregnancy is a unique physiological situation in which two (or more in the case of multifetal pregnancy) individuals may share the risk of perinatal morbidity and mortality resulting from exposure to an infectious disease. As a result of the increased probability of potential harm and even death of mother and infant during certain infectious disease outbreaks, it is important to consider the rights of pregnant women and the fetus to receive any potential form of therapy available to non-pregnant individuals in order to enhance their well-being. To not do so would represent an ethical dilemma, depriving them of their human right for survival. Unfortunately, the accepted principles of justice—fairness, equity, and the maximization of benefit—have been mostly overlooked in the exclusion of women and infants from clinical research, and in particular, vaccine testing and distribution [34].

Even after the West African Ebola epidemic brought worldwide attention to the plight of infected pregnant women and their infants, it was the Zika virus pandemic that began in 2015 that propelled interest in the development of vaccines for pregnant women. Initially coming to attention due to the unexplained preponderance of newborns with microcephaly in northeastern Brazil, the new mosquito-borne virus was found to produce the bulk of its damage during pregnancy. When infecting mothers, it was transplacentally passed to the fetus where it causes a syndrome of fetal malformations including brain damage, microcephaly, and perinatal death. [9, 35] According to Ruth R. Faden, PhD, MPH, founding director of the Johns Hopkins Berman Institute of Bioethics, "Zika galvanized the imagination of the vaccine community," "There you had a context where it was pregnant women and their soon-to-be babies that bore the brunt of the global concern. We would not be worrying that much about Zika as a threat, but it was precisely because of congenital Zika syndrome that we became globally aware." [36].

The rights of pregnant women to be included in both the design, clinical trials, and administration of vaccines have been recently addressed by the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group, a group of multidisciplinary experts based at the Johns Hopkins Berman Institute of Bioethics and the Center for Global Development [13]. PREVENT has made several recommendations to ensure the needs of pregnant women and their infants during epidemics and attempting to correct the inequalities suffered by these individuals in previous outbreaks. These include (1) pregnant women are not unjustifiably excluded from participating in vaccine studies; (2) pregnant women and their offspring benefit from advances in vaccine technologies and are not left behind as new vaccine products are developed; and (3) pregnant women have access to safe and effective vaccines to protect them and their offspring against emerging and re-emerging pathogenic threats. [13] Because of the increasing recognition by the global community that it is unacceptable to ignore the needs of pregnant women and infants in pharmaceutical and vaccine development and testing and biomedical

research, governing and advisory agencies are calling for inclusion of the interests of pregnant women and infants in both current and future development [13]. The suggested guidelines also include recommendations for the equitable inclusion of pregnant women in public health preparedness, starting from the ground up with basic research on maternal and fetal immune system function, consideration of pregnant women when designing vaccine development and investment, and permitting pregnant women to participate in clinical trials when the benefit of the vaccine outweighs the potential risk. In particular, PREVENT has made the following four recommendations for ethical principles governing biomedical research involving pregnant women: (1) pregnant women deserve an evidence base for the prevention and treatment of their illnesses equal to others as a matter of justice; (2) pregnant women should not be categorized as a "vulnerable population" for purposes of human subject research review; (3) it is ethically permissible to conduct research with pregnant women that meets specific risk standards; and (4) justice requires that pregnant women have fair access to research that offers the prospect of direct benefit [13].

Vaccinating a Pregnant Woman Saves More Than One Life

An example of the wide-reaching global medical and public health impact of immunization of pregnant mothers is illustrated by decades of success with prevention of maternal and neonatal tetanus (MNT) infection. In the early 1990s, between 15,000 and 30,000 women died from maternal tetanus, representing approximately 5% of all maternal deaths; there were 787,000 neonatal deaths from congenital tetanus in the 1980s. Immunization of pregnant women with a tetanus toxoid-containing vaccine has been a significant component of the worldwide reduction of maternal deaths from tetanus, as well as a global reduction of neonatal deaths to 34,000 in 2015—a 96% decline in newborn mortality [37]. Together with other forms of therapy, maternal vaccination has been so successful that 35 countries were successful in eliminating maternal and neonatal tetanus infection—these included South Africa, China, Egypt, and Turkey. In addition, 24 of the 36 states in India, 30 of the 34 provinces of Indonesia, and the majority of Ethiopia have eliminated MNT as a public health problem [38].

Fortunately, the attitudes of an increasing number of highly respected international agencies and organizations, including World Health Organization, Pan-American Health Organization, American College of Obstetricians and Gynecologists, Council for International Organizations of Medical Sciences, and the Office of Research on Women's Health of the National Institutes of Health have come to realize the importance of involving pregnant women in research studies. Similar to the biologically unique aspects of incorporating the pediatric population into the design of research studies, these organizations have acknowledged the distinctive medical as well as sociological and ethical issues that need to be addressed by having pregnant women and their fetuses involved in the design of experimental protocols [13]. The words of Anne Lyerly, MD, MA, Professor of Social Medicine and the Associate Director of the University of North Carolina Center for Bioethics, must be remembered when making decisions for pregnant women, "People tend to think first about the ethical problems of including pregnant women in research". "In this case, the gravest ethical problem would be if we failed to include them, since it is pregnant women—and their babies—who will face the most serious consequences of infection" [39]. It is hoped that those regulators, physicians, ethicists, pharmaceutical representatives, and researchers who create vaccine policy decisions reach the consensus that pregnant women have the right to choose for themselves whether they wish to receive potentially life-saving immunizations for the protection not only of themselves but also their unborn infants.

Conclusions

The historical concerns regarding exposing pregnant women and fetuses to the risk of medications has resulted in their being excluded from the design and testing phases of vaccine development. The policies by institutional review boards and research agencies that automatically deny pregnant women the opportunities to participate in vaccine clinical trials has left an important gap in knowledge of the effects of vaccines to both mothers and their fetuses during pregnancy. In particular, the fear that a live virus vaccine may result in fetal infection has prevented pregnant women from receiving potentially life-saving vaccines during outbreaks and humanitarian crises, an approach which has come at great cost for both mothers and their children. Although this policy of protectionism may be done with the best intentions, it has unfairly deprived pregnant women of their rights to judge for themselves and their fetus the risks of vaccination versus acquiring infection—surely this is the right of the mother. When it comes to such emerging and epidemic viral diseases as Zika, Ebola and Lassa fever, an excess of precaution can be dangerous. The public health and medical establishments must move forward with the responsible and informed inclusion of pregnant women in the design, clinical trials, and implementation of vaccine programs both now and in the future. When vaccinating a pregnant woman, multiple lives are at stake, not just one.

Compliance with Ethical Standards

Conflict of Interest David A. Schwartz declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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