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Review

Safety of immunization during pregnancy: A review of the evidence of selected inactivated and live attenuated vaccines

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ABSTRACT

Vaccine-preventable infectious diseases are responsible for significant maternal, neonatal, and young infant morbidity and mortality. While there is emerging scientific evidence, as well as theoretical considerations, indicating that certain vaccines are safe for pregnant women and fetuses, policy formulation is challenging because of perceived potential risks to the fetus.

This report presents an overview of available evidence on pregnant women vaccination safety monitoring in pregnant women, from both published literature and ongoing surveillance programs. Safety data were reviewed for vaccines against diseases which increase morbidity in pregnant women, their fetus or infant as well as vaccines which are used in mass vaccination campaigns against diseases. They include inactivated seasonal and pandemic influenza, mono- and combined meningococcal polysaccharide and conjugated vaccines, tetanus toxoid and acellular pertussis combination vaccines, as well as monovalent or combined rubella, oral poliomyelitis virus and yellow fever vaccines. No evidence of adverse pregnancy outcomes has been identified from immunization of pregnant women with these vaccines.

1. Introduction

Immunological and physiological changes during pregnancy may alter the susceptibility of mothers and fetuses to certain infectious diseases [1] and increase the risk of more serious outcomes. Neonates and premature infants are particularly vulnerable to infections due to their immature immune system. As a result of current epidemiology and a lack of exposure to certain pathogens, pregnant women and their fetus/infant may also be at higher risk for acquiring and developing severe infections.

Immunization of pregnant women can protect them directly against vaccine-preventable infections. It can also protect the fetus and infant via specific antibodies transferred from the mother during the pregnancy. Despite recognized benefits of vaccinations in pregnant women, theoretical safety concerns may result in vaccination being withheld from pregnant women. This report presents an overview of the relevant literature on the safety of vaccination of pregnant women for selected vaccines.

2. Methods

The literature review was based on Medline/PubMed searches not restricted to English language. Publications from 1946 to May 2013 using the search term "Vaccine/pregnant women" were retrieved and supplemented by expert author collections and reports of regulatory authorities. All types of studies – from randomized controlled trials (RCTs) through to case series and signal detection reports as well as review articles – were considered. The

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literature search identified a total of 989 articles. The expert panel consisting of members of the GACVS (Global Advisory Committee on Vaccine Safety of the WHO) considered 112 articles as relevant for the purpose of this analysis. Additionally, the Medicines and Healthcare products Regulatory Agency (MHRA) was contacted concerning the ongoing maternal immunization program in the United Kingdom with tetanus, reduced diphtheria, acellular pertussis, and inactivated poliomyelitis vaccine.

To assess the quality of evidence the following criteria were applied:

Level 1: Evidence from at least one well-designed randomized clinical trial in addition to well-designed and adequately powered observational studies.

Level 2: Evidence from more than one well-designed and adequately powered observational study.

Level 3: Evidence from one large well-designed observational study and/or several small observational studies.

Level 4: Evidence from expert opinion based on clinical experiences and passive surveillance data.

The group focused on currently available vaccines, with priority given to vaccines which are recommended by WHO for maternal immunization or which are used or have been used in mass vaccination campaigns that include pregnant women or in which pregnant women may be inadvertently vaccinated. Currently, WHO has identified pregnancy as a specific indication for immunization for influenza and tetanus [2,3].

The authors assessed (a) the demonstrated or potential benefit of vaccination during pregnancy (including evidence of disease morbidity in pregnant women and fetuses/infants, and of the effectiveness of the vaccine in pregnant women); and (b) evidence of safety of vaccination or lack of evidence of different adverse pregnancy outcomes. The body of evidence for each individual vaccine was reviewed by two authors of the panel. Following this, the document was further edited and approved in consensus by the expert group. The review is based on expert group's discussion and consensus.

3. Results

3.1. Inactivated vaccines

3.1.1. Inactivated influenza vaccines

3.1.1.1. Non-adjuvanted inactivated trivalent seasonal and monovalent pandemic influenza vaccines. Several publications have summarized the evidence of the risks of serious maternal influenza disease, particularly in the second and third trimester, and the safety and effectiveness of maternal immunization with inactivated influenza vaccines [4–7]. Seasonal influenza disease is more severe in pregnant women with an underlying medical condition [8]. The increased severity of disease in pregnant women infected with the 2009 pandemic influenza strain has been widely documented, with rates of serious adverse outcomes similar to, or higher than, those of any other risk group studied [6,9].

Increased fetal risks associated with maternal influenza infection have also been documented following well-described pandemics [4,10–16]. Specific effects of maternal influenza disease include fetal death due to maternal morbidity or premature onset of labor [17–19], as well as decreased birth weight and an increased proportion of infants born small for gestational age [13–15,20].

Adequate immunological responses to inactivated influenza vaccines during pregnancy and the efficient transplacental transfer of antibodies have been demonstrated in several studies. One randomized controlled trial (RCT) and several non-randomized studies have also shown the effectiveness of seasonal inactivated influenza vaccination in preventing morbidity in pregnant women and laboratory-confirmed infection and hospitalization in their infants [4,21–23]. For example Zaman et al. [21] found a significant reduction of laboratory-confirmed influenza among infants of mothers who received influenza vaccine than infants in the control group with a vaccine effectiveness of 63% (95% CI 5 to 85) and a reduction in the rate of febrile illness among the mothers of 36% (95% CI, 4 to 57). In a retrospective cohort study in the US infants of vaccinated mothers were 45–48% less likely to have influenza hospitalizations than infants of unvaccinated mothers [24]. Study data also suggest that the prevention of infection with seasonal influenza in pregnant women by immunization can positively influence fetal growth and prematurity during the period of increased circulating influenza virus in the community [20,25].

Immunogenicity studies of one 2009 pandemic influenza vaccine demonstrated that a single dose of vaccine elicited satisfactory antibody titers associated with transplacental transfer of antibodies as indirect evidence of protection against illness in mothers and their infants [26].

Prospective trials, retrospective database assessments, post-marketing passive reporting systems, and pregnancy registries have the potential to collect substantial data on the safety of non-adjuvanted inactivated influenza vaccines administered to pregnant women. For instance, from 1990 to 2009 it is estimated that 11.8 million pregnant women received this vaccine in the USA. Yet, the Vaccine Adverse Event Reporting System (VAERS) database received only 20 notifications of serious adverse events (AE) and 128 reports of non-serious AEs following administration of trivalent influenza vaccine (TIV) during that period. The most frequent reported adverse events were spontaneous abortion ($n = 17$) and stillbirth ($n = 6$). The overall reporting rate was 12.5 per 1 million pregnant women vaccinated and for spontaneous abortion 1.9 cases per 1 million vaccinations in pregnant women. The low reporting rate did not raise any signal [27]. Multiple studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies [4,28–34]. For example, an early study by Heinonen [28], which evaluated children born to nearly 2300 women who had received influenza vaccine during pregnancy, documented only one malignancy during the first year of life; this is comparable to expected background rates [34]. A review by Tamma et al. [32] included ten observational studies and two RCTs that reported diverse safety outcomes for the mother and fetus such as maternal death, spontaneous abortions, stillbirths, preterm birth, postpartum hemorrhage, low birth weight and congenital abnormalities. Among over 4400 pregnant women given inactivated influenza vaccine, no harmful effects were identified. Ten studies in this review addressed fetal health, and identified no increase in adverse birth outcomes or congenital anomalies over reported background rates. A more recent review [34] of the effects of maternal influenza immunization on the fetus confirmed no increase in adverse pregnancy outcomes or congenital anomalies.

During the 2009–2010 influenza A (H1N1) vaccination period, no safety concerns related to serious adverse reactions, complications on delivery and abnormal fetal outcomes were identified in pregnant women or in their infants, either in clinical trials or in monitoring systems [26,27,34–38] after maternal vaccination with different sub-virion or split-virion non-adjuvanted inactivated influenza A (H1N1) vaccines, even when two doses of vaccine were given [39]. Reports to VAERS also showed no increase in spontaneous abortions or stillbirths (the most commonly reported outcomes) over expected levels following administration of H1N1 influenza vaccines [27,34].

3.1.1.2. Adjuvanted inactivated monovalent pandemic influenza vaccines. Newer influenza vaccine formulations containing oil-in-water adjuvants have been approved for seasonal and pandemic

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