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Review

Optimizing benefits of influenza virus vaccination during pregnancy: Potential behavioral risk factors and interventions

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ABSTRACT

Pregnant women and infants are at high risk for complications, hospitalization, and death due to influenza. It is well-established that influenza vaccination during pregnancy reduces rates and severity of illness in women overall. Maternal vaccination also confers antibody protection to infants via both transplacental transfer and breast milk. However, as in the general population, a relatively high proportion of pregnant women and their infants do not achieve protective antibody levels against influenza virus following maternal vaccination. Behavioral factors, particularly maternal weight and stress exposure, may affect initial maternal antibody responses, maintenance of antibody levels over time (i.e., across pregnancy), as well as the efficiency of transplacental antibody transfer to the fetus. Conversely, behavioral interventions including acute exercise and stress reduction can enhance immune protection following vaccination. Such behavioral interventions are particularly appealing in pregnancy because they are safe and non-invasive. The identification of individual risk factors for poor responses to vaccines and the application of appropriate interventions represent important steps towards personalized health care.

1. Introduction

1.1. Influenza virus vaccination recommendations for pregnant women

Pregnant women are at high risk for complications, hospitalization, and death due to influenza [1–5]. It is now established that influenza virus vaccination during pregnancy reduces risk of influenza in women and provides antibody protection to infants via both transplacental transfer and breast milk [6]. Studies show no adverse effects of vaccination for risk of preterm labor, C-section, or fetal malformation [7–10]. Serious problems from influenza vaccine, such as severe allergic reaction, are rare. Primary risks are mild and include soreness where the shot was given, aches, fever, and fatigue. Thus, vaccination is recommended by the Centers for Disease Control (CDC) and American College of Obstetricians and Gynecologists (ACOG) to all women without contraindications who are pregnant or will be pregnant during flu season [11,12]. The US Department of Health and Human Services *Healthy People 2020* goal is to achieve 80% influenza vaccination coverage among pregnant women.

Pregnant women have historically received trivalent inactivated influenza vaccine (IIV3), which targets the A/H1N1, A/H3N2, and B strains expected to be predominant in the approaching season. However as of the 2013-2014 flu season, quadrivalent inactivated influenza vaccine (IIV4) is available which includes a second B strain. Inactivated influenza vaccine is now available in intradermal as well as intramuscular forms.

Although benefits for pregnant women and infants are well-documented, influenza vaccines are only 50–70% effective in preventing clinically proven influenza [13,14]. There is great variability in the degree to which individual women mount an adequate antibody response, maintain antibody levels over time (i.e., over the course of pregnancy), and transfer antibody to the fetus/infant. Thus, a next logical step in this clinical effort is to identify factors which may hinder and optimize the effectiveness of vaccination across women and infants. This paper reviews knowledge to-date

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with a focus on behavioral risk factors for poor immune protection following vaccination and behavioral interventions which may promote optimal responses.

1.2. Responses to influenza virus vaccination in pregnant women

Influenza virus vaccine is effective in pregnant women and benefits for their infants. In 2008, the first landmark randomized clinical trial of IIV3 in pregnancy showed a 29–36% reduction in all febrile respiratory illness in women and their infants up to 6 month of age and 63% reduction in clinically proven influenza in the infants during the same time period [14]. Protection from influenza during pregnancy may provide unique health benefits during the perinatal period. Among infants born during influenza season, maternal vaccination has been associated with reduced risk of preterm delivery, small-for-gestational age at birth, and fetal death [15,16]. Further, maternal influenza infection has been linked to increased risk of schizophrenia in adult offspring [17–19], a risk that vaccination could mitigate.

In addition, infants from 0 to 6 months of age have among the highest rates of influenza-associated complications with >1000 hospitalizations per 100,000 infants [20]. Influenza virus vaccine is not approved for infants <6 months. However, maternal vaccination in pregnancy is an effective strategy for protecting infants prior to 6 months. Prospective studies of laboratory-confirmed influenza, including the trial cited above, show that maternal vaccination significantly reduces risk of influenza infection in infants and reduces flu severity in infants who do become infected [14,21–26].

Although beneficial, the protection afforded by flu vaccines is far from 100%. For flu vaccines, it is generally accepted that anti-influenza antibody titers are a good marker of clinical efficacy [27]. Serological studies show that pregnant women in any trimester mount antibody responses to flu vaccines similar to nonpregnant adults [26,28–31]. A protective response is commonly considered to be a 4-fold increase in antibody levels to a specific strain or a titer $\geq$40 in adults, with peak titers achieved at 2–4 weeks after vaccination. The level of IgG antibody to the viral hemagglutinin correlates directly with resistance to influenza infection [27,32,33]. Thus, the ability of women to mount and sustain an adequate antibody response is key to clinical protection.

As in adults, antibody levels predict flu risk in infants. For example, among 573 infants of women vaccinated during pregnancy, risk of flu was directly correlated with cord blood antibody levels for all eight viral antigens assessed across three influenza seasons [23]. As expected, cord blood antibody levels were associated with the magnitude of maternal antibody response [23]. However, despite active transplacental transfer of IgG, an adequate maternal response does not guarantee sufficient antibody in the newborn [31]. Protection in infants depends on both adequate maternal response and sufficient antibody transfer. Notably, recent evidence indicates that in children a titer of 1:110 is required to achieve 50% clinical protection against infection, while the conventional adult cut-off of 1:40 is associated with only 22% protection in children [35]. Thus, it is of clinical value to identify factors which promote sufficient transplacental antibody transfer to the fetus/infant.

Importantly, vaccination during pregnancy can also confer benefits via breastfeeding. In a study of 340 pregnant Bangladeshi women who received either IIV3 or pneumococcal polysaccharide vaccine (control group) during the third trimester of pregnancy, influenza-specific IgG A antibody levels in breast milk were significantly higher for at least 6 months postpartum in women who had received influenza vaccine [34]. Moreover, greater exclusivity of breastfeeding in the first 6 months of life was associated with fewer respiratory illnesses in the infants of the influenza-vaccinated mothers, but not the infants of mothers who received the pneumococcal vaccine.

2. Potential behavioral risk factors for poor antibody responses to vaccination

There are limited data on factors which may negatively affect flu vaccine immunogenicity in pregnant women. Given the recommendation for universal vaccination in pregnancy and ongoing public health efforts to increase vaccination uptake in this population, such research is highly justified. Detailed below, research in non-pregnant populations suggests that two factors that may be of particular importance are weight and psychosocial stress. However, the extent to which these findings translate to pregnancy is not known. Given the considerable neuroendocrine and immune changes observed, effects of stress and obesity on immune parameters may differ in pregnancy versus non-pregnancy. Moreover, in pregnancy, not only the initial antibody response, but also antibody maintenance over time and antibody transfer to the neonate are of particular importance. Thus replication and extension of findings in non-pregnant adults to the context of pregnancy is needed.

2.1. Maternal body mass index: Obesity and underweight

In the U.S., 34.0% of women 20–39 years are clinically obese (BMI $\geq$ 30) [36]. Obesity predicts greater risk of secondary infections among hospitalized patients and respiratory-tract infections in community-dwelling adults [37,38]. Following the 2009 H1N1 pandemic, the CDC for the first time cited obesity as an independent risk factor for influenza severity, hospitalization, and mortality [39–41]. For example, in California, one half of adult hospitalizations for influenza were among obese patients, 2.2 times the prevalence of obesity in the state indicating that the obese were over-represented among those with influenza-related complications [41].

Animal studies support the CDC recognition of obesity as a risk factor for influenza-related complications. Obese mice infected with seasonal flu virus had 6-fold higher mortality rates [42]. In addition, as compared to lean mice, obese mice exposed to a weak strain of influenza showed poorer memory T-cell responses upon secondary exposure to a stronger strain [43,44]. This model parallels memory T-cell responses in the context of vaccination. In addition, in a mouse model, genetically and diet-induced obese mice infected with influenza virus showed greater lung pathology associated with impaired wound repair, suggesting a mechanism by which obesity may result in greater influenza-related complications [45].

Notably, clinical trials of vaccine efficacy often fail to report information on demographics and health behaviors which may affect vaccine immunogenicity. In an analysis of 83 vaccine trials, *none* reported information about obesity [46]. One study in non-pregnant adults reported that obese and non-obese adults exhibited similar peak antibody responses at one month post-vaccination, but obese adults showed steeper drops in antibody levels over the subsequent 11 months, indicating poorer maintenance of protective antibody levels over time [47]. Data also show that, compared to healthy weight controls, peripheral blood mononuclear cells (PBMCs) from overweight and obese adults showed deficiencies in activation and function when stimulated ex vivo with live influenza A virus [48]. These effects have not been replicated in pregnancy. In addition, potential effects of maternal obesity on transplacental anti-influenza antibody transfer are unknown.

Underweight is also a risk factor for poor antibody responses to vaccination. Due to the risks of flu in older adults, studies have

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