

Review Article

Influenza Vaccination during Pregnancy: Mind the Gaps

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Submitted: 04 March 2014

Accepted: 26 June 2014

Published: 30 June 2014

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Abstract

The burden of influenza morbidity in pregnant women has led to the universal recommendation for vaccination of women during any stage of pregnancy. Recent analyses on vaccine effectiveness have suggested that current seasonal influenza vaccines are only moderately protective against influenza infection. While the data may be more encouraging during influenza pandemics, the more we learn about influenza vaccines the more we understand that a one-size-fits-all approach may leave segments of the population uncovered. High quality evidence on vaccine efficacy during pregnancy is lacking due to exclusion of pregnant women from placebo controlled randomized studies, low vaccine coverage, and low case numbers. This review discusses recent observations regarding effectiveness, immunogenicity, and timing of maternal vaccination, and outlines some of the knowledge gaps in understanding influenza vaccination in this population. Well-designed and executed studies combined with a thoughtful discussion on including pregnant women in influenza research are needed to increase our understanding of the maternal immune response to influenza vaccines. As new data emerge to inform our understanding, we must remain open to reinterpreting and recalibrating our assumptions, and be prepared to respond with policies and recommendations based on evidence obtained from rigorous, well-designed studies.

Keywords

- Influenza vaccine
- Pregnancy
- Maternal immunization

ABBREVIATIONS

ACIP: Advisory Committee on Immunizations Practices; CDC: Centers for Disease Control; VE: Vaccine Effectiveness; HAI: Heme Agglutination Inhibition; TIV: Trivalent Influenza Vaccine

INTRODUCTION

Evidence collected over several decades indicates that pregnant women and young infants are at increased risk for complications from influenza; as such, vaccination of pregnant women with inactivated Trivalent Influenza Vaccine (TIV) began in the mid-1960s. Influenza infection in pregnancy is associated with adverse maternal and neonatal outcomes, including preterm labor and delivery, respiratory hospitalization, pneumonia, acute respiratory distress syndrome, overwhelming sepsis, and death [1-12]. Increased influenza-related mortality during pregnancy is associated with pandemics (1918, 1975, 2009) [13-16].

Control of influenza in this population is an important public health concern. Recommendations for universal vaccination of woman at all stages of pregnancy has been the policy of the Advisory Committee on Immunizations Practices (ACIP) of the Centers for Disease Control (CDC) since 2004 [17-20] followed by the World Health Organization in 2005 [21]. The American College of Obstetrics and Gynecology issued new guidelines in September 2010 recommending that all pregnant women at any gestational age be vaccinated against influenza [22].

Finally, the latest WHO Strategic Advisory Group of Experts recommendation, published in 2012, urges countries using or considering introducing seasonal influenza vaccination to include all pregnant women as the highest priority group [23].

There has been increased scrutiny of influenza Vaccine Effectiveness (VE) as well as a developing debate regarding the extent to which vaccination prevents morbidity and mortality across all populations. This rich unfolding debate continues to be informed by new studies implementing ever more sophisticated experimental techniques. Such studies add to our collective understanding of influenza vaccine, but in so doing, expose the gaps in our understanding, and remind us that where influenza is concerned, nothing is ever simple.

GAPS IN UNDERSTANDING

Immunogenicity and vaccine response during pregnancy

It has been a widely held belief that the immune response to influenza vaccine in pregnant women is indistinguishable from that of non-pregnant women, and that gestational age appears to have no effect on antibody response [24-27]. However, findings from three recent studies suggest that we may need to entertain a more nuanced approach to our understanding of the maternal immune response and its relationship to clinical effectiveness - immunogenicity and seroconversion may not tell the entire story.

In a 2011 study, Ohfiji et al. reported a lower seroprotective antibody response to pandemic A (H1N1) vaccine in pregnant women who had received prior seasonal influenza vaccine, and suggested that the potential interference between H1N1 and seasonal vaccination needs additional investigation [28]. Schlaudecker et al. directly compared immunogenicity of inactivated influenza vaccine in pregnant vs. non-pregnant women and found that pregnancy modified antibody responses to the vaccine [29]. They demonstrated a significantly decreased post-immunization Hem Agglutination Inhibition (HAI) geometric mean titer, and a non-significantly decreased geometric mean ratio (fold increase) to influenza A antigens after influenza vaccine, even though overall seroconversion and seroprotection rates were comparable between the two groups of women. In a 2013 blinded randomized control study, Bischoff et al. found that the immune response to an adjuvanted pandemic A (H1N1) vaccine in pregnant women was decreased compared with non-pregnant women [27].

On their own, evidence from these three studies is insufficient to radically change our approach to maternal influenza vaccination. However, these observations do create a ripple in our sea of understanding. Data from these studies can, and should, guide further studies that include analysis and direct comparison of pregnant and non-pregnant women. Such studies are needed to begin filling in the gaps and understand more fully the effects of pregnancy on immunogenicity of influenza vaccine antigens.

Timing- is it really everything (or at least something)?

Two recent studies of vaccine effectiveness during the 2011/12 influenza season suggest that vaccine effectiveness may wane with increasing time since vaccination [30,31]. In both of these studies, vaccination effectiveness waned in people who were vaccinated 93 days - around three months - or more before presentation of symptoms. While these observations are relevant to all populations, understanding timing relative to vaccine effectiveness is essential for women who are exposed to influenza during pregnancy.

These recent observations of waning vaccine effectiveness imply that women vaccinated during the first trimester of pregnancy will become *less* well protected as their pregnancy progresses. It is well documented that serious influenza-related morbidity in healthy pregnant women most often occurs during the second and third trimester of pregnancy. So a reasonable goal is to ensure the highest possible level of protection during the last trimesters. If the studies on waning immunity are correct, this is precisely opposite of what occurs in women who are vaccinated early in pregnancy; protection wanes as risk increases.

To be sure, further virological and epidemiological studies are needed to confirm and fully understand the recent studies. But as our understanding evolves, policy makers may need to revisit and reconsider the recommendation for influenza vaccination of all pregnant women during any stage of pregnancy. Highest risk during second and third trimester combined with observations that vaccine efficacy may wane with time should invite a review of data and recommendations to increase likelihood that the time frame for maximum protection coincides with the time frame of highest risk. Questions regarding optimal time for vaccination, or

whether repeat vaccinations should be encouraged for women vaccinated early in pregnancy need additional exploration [32].

Speaking of timing - maternal vaccination for protection of neonates

An important secondary - or "two-for-one" - benefit of maternal vaccination is the protection from influenza afforded to infants during the first months of life. Cross-placental transfer of immunity occurs when antibodies cross the placenta via active transport, particularly in the final weeks of pregnancy. It is logical to assume that vaccine-induced maternal antibody transmitted to the fetus will provide protection to the infant during the first months of life, and several studies document increased antibody titers in infants of vaccinated mothers [33].

Over the past 8 years, four studies have documented a protective effect of maternal vaccination for protection of influenza illness in infants [33-36]. Three of these studies provide data on the trimester during which vaccination occurred. A combined total of 730 women received influenza vaccines in these three studies. Eighty percent of the vaccinated women were immunized during the third trimester of pregnancy. No women in these studies were vaccinated during their first trimester. Notably, in the only randomized, blinded clinical study to assess infant protection, all of the women were vaccinated in their third trimester of pregnancy [34].

While many studies have documented maternal antibodies in cord blood following vaccination, there are no studies showing that first trimester influenza vaccination confers protection to infants from laboratory-confirmed influenza infection. This lack of evidence along with the previously discussed observations regarding vaccine timing call for a more complete examination of infant protection vis-a-vis the timing of maternal vaccination.

The recommendation to vaccinate all pregnant women regardless of gestational age is motivated in part by operational concerns. Timing of the influenza vaccine campaigns occurs in the fall. Later in the season, access to vaccine may be more difficult for women who will be pregnant during the peak of influenza season [37]. But since pregnancy is a period of regularly scheduled and repeat visits, a more tailored approach to influenza vaccine coverage may be more appropriate. Such an approach may enhance the goal of preventing serious influenza-related illness in pregnant women and their infants.

Current recommendations

The ACIP recommends that all women who are pregnant or who might be pregnant in the upcoming influenza season receive influenza vaccination. The recommendation that all US women during *any* trimester of pregnancy receive influenza vaccine is unique. No other US vaccine carries this recommendation [37]. Curiously, supporting data for this recommendation are limited, particularly for women in the first trimester of pregnancy [37,38].

The ACIP states that published peer reviewed studies are the primary source of data for recommendations. Nonetheless, no published peer review studies documenting protection of women or infants following maternal vaccination in the first trimester of pregnancy are cited in support of the recommendations. The

studies cited in support of influenza vaccine effectiveness in pregnant women include results derived from women vaccinated during the third trimester only [39].

As to recommendations for maternal vaccination to protect neonates, the ACIP states, "Vaccination during pregnancy has been shown to protect infants from influenza" [39]. This statement is indeed accurate. However, of the two papers cited in support of this statement, one is a blinded randomized controlled trial including only women vaccinated in the third trimester; the other is a review paper in which the reviewed studies showing clinical effectiveness included women vaccinated in the second or third trimesters only [34,40]. Again, no peer reviewed studies are cited which document protection of infants following first trimester vaccination of their mothers.

The recommendation for early intervention is based on the desire to protect women during pregnancy. However laudable this goal, there is limited evidence to support efficacy of vaccination during the first trimester for protection of women or neonates.

STARTING TO FILL THE GAPS

Lessons learned from the 2009 H1N1 pandemic

Pregnant women need safe, effective interventions to prevent morbidity and mortality from influenza infection. Experimental data on influenza vaccination of pregnant women is scarce and the quality of the evidence not high overall. The 2009 H1N1 pandemic provided a chance to improve understanding of influenza vaccination during pregnancy. The pandemic afforded a unique opportunity to evaluate the effectiveness of maternal vaccination during an influenza season in which there was a high rate of viral circulation, as well as a close match between the vaccine strain and the circulating viral strain. Pregnant women were prioritized to receive the vaccine and were strongly advised to be vaccinated [41] resulting in higher than usual vaccination rates [42].

Since the 2009 pandemic, a number of studies have examined monovalent pandemic A (H1N1) vaccination of pregnant women. Synthesizing evidence from this new and expanding database should increase our understanding of maternal influenza vaccination. Since 2010, sixteen published studies have examined pandemic H1N1 vaccine in pregnant women. Six studies measured seroconversion and HAI titers [43-48], and eight addressed safety and/or birth outcomes [49-56]. Only two studies examined clinical efficacy of pandemic A (H1N1) vaccine during pregnancy. One study of adjuvanted A (H1N1) vaccine reported 70% effectiveness in pregnant women against the circulating H1N1 infection [16] while another study of non-adjuvanted vaccine reported a 61% effectiveness [57].

Well-designed research studies including pregnant women

Influenza illness during pregnancy is an important public health concern, particularly during pandemic years, and vaccination remains the best tool for prevention of influenza infection; it should be recommended.

The universal recommendation for influenza vaccine in pregnant women is driven by the increased risk for morbidity

and mortality in this population, coupled with an expectation of vaccine safety and effectiveness. A great preponderance of evidence supports safety of seasonal and pandemic influenza vaccination during pregnancy, and emerging data suggest that maternal influenza vaccination is associated with improved pregnancy outcomes such as birth weight and preterm birth [15,57-59].

Data on vaccine effectiveness are more mixed. There is limited evidence that the current seasonal influenza vaccine is more than moderately protective [38]. While the data may be more encouraging during pandemics, the more we learn about influenza vaccines the more we understand that a one-size-fits-all approach may leave segments of the population uncovered. The need to think about influenza vaccines in terms of target populations is very important and deserves serious exploration.

High quality evidence on vaccine efficacy has been lacking due to exclusion of pregnant from placebo controlled randomized studies, low vaccine coverage, and low case number [51]. Immune responses during pregnancy are likely to be different from that of a non-pregnant adult. However, we continue to extrapolate from the non-pregnant adult population [37]. History with such extrapolation - from men to women, or adults to children - has taught us that this practice often is misguided and can lead to suboptimal treatment.

The importance of studying subpopulations that have previously been excluded from research is undeniable. In the 1990s, reports emerged indicating that women were underrepresented in biomedical research, leading to under-investigation of their health concerns. The passage of the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act encouraged the inclusion of children in research, and has shown that many previous assumptions regarding treatment of children were incorrect.

Since the establishment of the Women's Health Initiative and passage of the NIH reauthorization act in 1993, much progress has been made on the inclusion of women in research. Thoughtful discussion regarding inclusion of pregnant women in clinical research lags behind.

The 2009 H1N1 pandemic disproportionately impacted pregnant women, drawing attention to the fact that - although they need medical treatment - pregnant women are a marginalized study population [60]. Perhaps lessons learned from the recent H1N1 pandemic will provide a driving force in changing the culture of conducting studies with pregnant women.

DISCUSSION AND CONCLUSION

Four million women in the US, and 131 million women worldwide, give birth every year [60]. Options for pregnant women should be informed by scientifically rigorous data obtained from well-designed and executed studies that include pregnant women. It is time for a broader discussion of maternal influenza vaccination to provide pregnant women and their health care providers with information to make the best possible evidence-based decisions. Subtle differences in immunogenicity, vaccine timing, or other yet-to-be explored topics have the potential to impact the health of pregnant women as well as their newborns.

As new data emerge to inform our understanding of maternal influenza vaccination, we must remain open to reinterpreting and recalibrating our assumptions, and be prepared to respond with policies and recommendations based on evidence obtained from rigorous, well-designed studies. Anything less leaves pregnant women and newborns underserved and vulnerable to serious and preventable influenza illness. It's time to start filling in the gaps.

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Cite this article

Manske JM, Bye EC (2014) Influenza Vaccination during Pregnancy: Mind the Gaps. *Ann Public Health Res* 1(2): 1007.