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A Pilot Study Showing a Stronger H1N1 Influenza Vaccination Response during Pregnancy in Women Who Subsequently Deliver Preterm

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Abstract

Problem: Preterm birth (PTB), or the delivery of an infant prior to 37 weeks of gestation, is a major health concern. Although a variety of social, environmental, and maternal factors have been implicated in PTB, causes of preterm labor have remained largely unknown. There is evidence of effectiveness and safety of influenza vaccination during pregnancy, however fewer studies have looked at vaccination response as an indicator of an innate host response that may be associated with adverse pregnancy outcomes. We carried out a pilot study to analyze the flu vaccine response during pregnancy of women who later deliver preterm or term.

Method of Study: We performed a secondary analysis of the individual-level data from an influenza vaccination response study (openly available from ImmPort) measured by hemagglutination inhibition assay of 91 pregnant women with term deliveries and 11 women who went on to deliver preterm. Flu vaccination responses for H1N1 and H3N2 influenza strains were compared between term and preterm deliveries.

Results: Women who went on to deliver preterm showed a significantly ($P < 0.001$) greater flu vaccine response for the H1N1 strain than women who delivered at term. The vaccine response for H3N2 was not significantly different between these two groups ($P = 0.97$).

Conclusions: Although the sample size is limited and additional validation is required, our findings suggest an increased activation of the maternal immune system as shown by the stronger vaccination response to H1N1 in women who subsequently delivered preterm, in comparison to women who delivered at term.

Graphical Abstract

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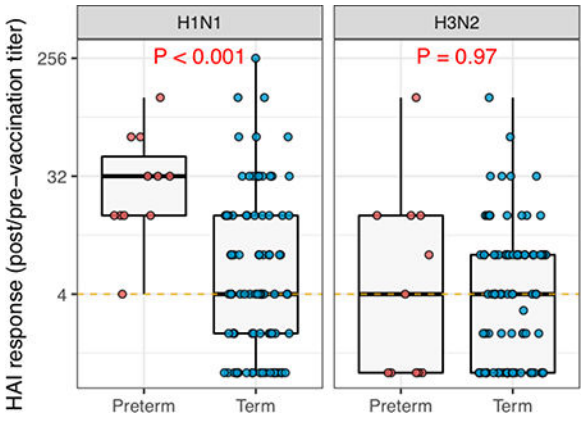

Pilot secondary analysis suggesting that women with a later preterm delivery showed a significantaly greater vaccination response for H1N1 than women whose pregnancy ended with a term delivery. The response to H3N2 was similar between women who went on to deliver term or preterm.

Keywords

Preterm Birth; Flu Vaccination Response; H1N1; ImmPort; Pregnancy Outcomes

Introduction

Approximately 12% of infants born in the United States are born preterm, defined as birth before the 37th week of gestation, and these numbers have been rising in recent decades. Although genetic, environmental, clinical and socioeconomic factors have been implicated in preterm birth (PTB), the basic biology resulting in the onset of labor remains poorly understood. While there are many potential mechanisms which may result in PTB, immunity and inflammation have been shown to play a critical role in adverse pregnancy outcomes including preterm birth[1–7]. Healthy pregnancy involves multiple tolerance mechanisms that prevent the maternal and fetal immune systems from recognizing and rejecting each other[8,9]. Prior to labor, the maternal immune system is thought to modulate inflammatory signaling pathways to avoid rejection of the fetus, whereas in some cases preterm labor is thought to result from a breakdown of this mechanism though a nonspecific innate immune response[10].

Several recent studies and systematic reviews reported an association of influenza vaccination during pregnancy with a decreased risk of PTB[10–14]. For instance, Olsen et al found that among nearly 5000 women who had a live birth, vaccinated women were statistically significantly less likely than unvaccinated women to have an infant born preterm during the period of high influenza virus circulation[12]. A recent study reported that women with 2009 H1N1 influenza during pregnancy were more likely to have adverse birth outcomes, including preterm deliveries, than women without influenza[15]. While most of these studies are epidemiological and are able to quantify the statistical association between vaccination and pregnancy outcomes, they do not consider the magnitude of the influenza vaccine response with respect to outcome. In this present analysis, we focused on the

comparison of the immune responses to influenza vaccination during pregnancy in women who later had a term or preterm birth using an existing pregnancy dataset[16–18] in the ImmPort database[19–21]. Our hypothesis is that a high response could be a marker of predisposition to inflammation leading to PTB.

Methods

ImmPort data repository

The ImmPort data portal (http://www.immport.org) is the archival repository for the National Institute of Allergy and Infectious Diseases (NIAID), hosting immunology focused clinical and molecular datasets created by research consortia[19–21]. With over 300 datasets now publicly accessible, ImmPort is an important source for raw data and protocols from clinical trials, mechanistic studies, and novel methods for cellular and molecular measurements.

Study population

We identified several pregnancy related studies from the ImmPort database. Of these, we selected two studies (ImmPort IDs SDY36 and SDY37 [http://www.immport.org/immport-open/public/study/study/displayStudyDetail/SDY37 and http://www.immport.org/immport-open/public/study/study/displayStudyDetail/SDY36]) that contain women for which flu vaccination response data during and after pregnancy are available. The actual flu vaccination data are stored in SDY37. The original goal of this study was to analyze the immune system during pregnancy and study the response of standard seasonal trivalent inactivated vaccination (TIV) against influenza during and after pregnancy[16–18]. Between October 2006 and January 2010, they enrolled 239 women who received influenza vaccination during their routine clinical care antepartum or postpartum. They aimed to estimate the effects of gestational age and other maternal factors on immunologic responses to influenza vaccination. The authors concluded that adequate immunologic responses to inactivated influenza vaccines were demonstrated during pregnancy and the postpartum period. Even though they noticed some trends, no significant association of gestational age at vaccination or the BMI of the mother with vaccination response were detected. The study did not examine the relationship between vaccination response and pregnancy outcomes. Here we address the question of whether there is a significant difference in the response to vaccination in women who later delivered preterm, in comparison to women who delivered at term. Therefore, we only included women who were vaccinated during pregnancy and had pre- as well as post-vaccination data available for at least one of the two seasonal influenza A strains. As reported in the original work, for the season 2009/2010, women received either the standard seasonal 2009/2010 TIV or the monovalent inactivated vaccine against the circulating pandemic 2009 H1N1, or both of these. In our analysis, we only included responses to the standard seasonal TIV vaccine. A further requirement was that we could identify if the delivery was term or preterm. This decision was in most cases based on the reported gestational age by examination using the Ballard Maturational Assessment (retrieved from the DELIVERY AND NEWBORN RECORD (dnbr_VIP004.txt) from ImmPort) with minor additional information based on the medical notes shared in the ImmPort data set. A delivery was defined as preterm if the gestational age by examination

was less than 37 weeks. The vaccination time point was identified from the SPECIMEN TRACKING (spectk4_VIP004.txt) file from ImmPort as the listed pregnancy week at study day 1.

Hemagglutination inhibition assay and seroconversion rate

The collection of samples and the measurement of flu vaccine response is described in detail in the original paper by Sperling et al[16]. In summary, serum samples were collected pre-vaccination and 4–8 weeks post-vaccination. The response to flu vaccine was measured by standard hemagglutination inhibition assay (HAI). The greatest dilution of the serum that blocked hemagglutination is detected (e.g. 1:160) and the HAI titer is defined as the reciprocal of that value (160 in this example). HAI response is defined as the fold change of post-vaccination HAI titer over pre-vaccination HAI titer. Seroconversion rate was defined as the proportion of subjects with a ≥ 4-fold increase in HAI antibody titer at post-vaccination in comparison to pre-vaccination, or a post-vaccination HAI titer of ≥ 40 if the pre-vaccination titer was < 10.[16]

As reported in Sperling et al[16], the viruses that were used in the HAI assay were either pseudotyped (6:2 recombinants) to match the vaccine strains Wisconsin/67/2005, Brisbane 10/2007, and Brisbane 59/2007, or the wild-type vaccine strains New Caledonia/20/99 and Solomon Islands/03/2006.

Statistical analysis

Continuous variables, like HAI titers or vaccine response values, were compared between the two groups of women who went on to deliver preterm or term using Mann–Whitney U test. Categorical variables were compared using Fisher's exact test. The statistical analysis was carried out in R.

In all presented boxplots (Turkey boxplots) the medians are shown. The 'hinges' represent the first and third quartile. The whiskers are the smallest and largest values after outliers are excluded. Outliers are defined as values greater than the 75th percentile plus 1.5 times the interquartile range (IQR), or less than 25th percentile minus 1.5 times the IQR.

Results

We identified a cohort of 102 pregnant women from the original study of influenza vaccine response[16] with data available in ImmPort, who delivered successfully. One twin-delivery was excluded from our study population. The demographics and vaccination information of the 91 term and 11 preterm deliveries are presented in Table 1. The median age of the women who later delivered preterm was 29 years and of women with a term delivery was 25 years ($P = 0.45$). As expected, babies that were born preterm had a significantly ($P < 0.001$) lower average birth weight (median = 2.4 kg) than those born at term (median = 3.4 kg). First trimester was defined as less than 13 weeks of gestation, second trimester between 13 and less than 28 weeks of gestation, and the third trimester was defined as over 28 weeks of gestation. All but 1 woman who later delivered preterm got vaccinated within the first two trimesters while women with term delivery were vaccinated across all three trimesters (Table 1). The study was performed across the 4 flu seasons from 2006/2007 to 2009/2010.

The original study looked at vaccination responses against the two influenza A strains H1N1 and H3N2. We first studied the pre- and post-vaccination HAI titers between those women who later delivered preterm versus those who delivered at term. Baseline pre-vaccination HAI titers were neither statistically significantly different for H1N1 ($P = 0.08$) nor for H3N2 ($P = 0.88$) (Figure 1A). Also, post-vaccination, neither the titers against H1N1 ($P = 0.05$) nor H3N2 ($P = 0.81$) were significantly different in women who later delivered preterm, compared to those that delivered at term (Figure 1B).

We then calculated the fold change between post-vaccination to pre-vaccination titers, to ascertain the vaccine response (Figure 2). The HAI response for H1N1 was significantly greater in women who later delivered preterm than in those later delivering at term ($P < 0.001$). No such difference was seen for H3N2 ($P = 0.97$). The yellow dotted line in Figure 2 shows the 4-fold threshold defined as seroconversion with a pre-vaccination titer ≥ 40. If the pre-vaccination titer was < 10, seroconversion was defined as a post-vaccination HAI titer of ≥ 40. For H1N1, 10 of the 11 women (90.1%) who later underwent preterm birth showed seroconversion, compared to 57.3% of those who later delivered at term. This result holds true for the different influenza A H1N1 strains used over the 4 vaccination seasons covered in the study (Table 2). Women who went on to deliver preterm showed a seroconversion of 100% for 2 of the 3 different H1N1 strains. For the thirst H1N1 strain (A/New Caledonia/20/99), 2 of the 3 women (67%) vaccination with this strain showed seroconversion. For the participants with later term delivery, the seroconversion rate ranged from 36% to 77% for the 3 H1N1 strains.

We observed a trend towards lower pre-vaccination HAI titers in women with later PTB than those who delivered at term (Figure 1A), which might have played a role in the post-vaccination HAI titer levels and the calculated response to vaccine (Figure S1). To control for this, we repeated the analysis, including only participants with a pre-vaccination titer of ≤ 40. Also, in this subset of participants (n=11 (H1N1 and H3N2) for later PTB, n=77 (H1N1) and n=79 (H3N2) for later term delivery), the women who later delivered preterm showed significantly ($P = 0.002$) greater HAI responses against H1N1 than those who finally delivered at term. No significant difference was detected for H3N2 ($P = 0.87$).

The authors of the original paper reported a trend that seroconversion rates to TIV vaccine strains were lowest in the first trimester and higher in the late third trimester (defined as 34 weeks of gestation and later) even though this difference was found to be not significant [16]. The distribution of vaccination responses across the three trimesters, the vaccine strain and later term or preterm delivery in our subset of women does not obviously reflect this trend (Figure S2). However, the number of vaccinations in the second or third trimester (Table 1) were too few for robust statistical analysis (4 and 3 for women with preterm and term deliveries for the second trimester, and 1 woman with preterm delivery in the third trimester).

Only 1 (9.1%) of the women who later delivered preterm had her pre-vaccination blood draw in the third trimester while it were 44 (48.4%) of the women who went on to deliver at term (Table 1). To get an idea if the trimester in which the women got vaccinated was a confounder in the differential vaccination response between women with later term or

preterm delivery, we compared the vaccine responses in a subset of only the women that got vaccinated during the first 2 trimesters. In this subset of women, the vaccine response against H1N1 was significantly greater in the group of women with later PTB than in the group with later term delivery ($P < 0.001$) as it was detected for the whole study population. The response against H3N2 was also with this adjustment of the sample population not significant ($P = 0.79$). In this subset of women, all 10 who later delivered preterm showed seroconversion for H1N1, compared to 25 of 45 women (55.5%) who later delivered at term. The seroconversion rate for H3N2 was again similar between women who later delivered preterm (60%) or term (55%).

Discussion

Although genetic, environmental, clinical, socioeconomic and maternal factors have been implicated in PTB, causes of preterm birth have remained largely unknown[22,23]. Immunity and inflammation have been shown to play an important role in parturition timing. In this study we investigated immune response to influenza vaccination during pregnancy in women who ended up having a preterm birth in comparison to women with term deliveries. We observed a greater vaccine response against H1N1 in women with subsequent preterm delivery than in women who delivered at term. The response against H3N2 was not significantly different between women with later preterm and term delivery. This result points towards the hypothesis of a more active immune system in women with a later PTB than in women with later term deliveries.

We hypothesize that the H3N2 response was not significantly different because the overall immune response to vaccination and vaccine effectiveness is suggested to be lower against H3N2 than against H1N1[24,25].

The analysis of all women, independent of the time of vaccination during pregnancy, would have provided the largest possible data set for our secondary analysis, but also carries several limitations, including the significant changes that happen in the maternal immune system during the third trimester. In order to address this issue, we performed the analysis limited to those women who got vaccinated within the first two trimesters. In this subset, our findings of a greater vaccine response and seroconversion rate to H1N1 in women who went on to deliver preterm than those who had a term delivery still persist.

There are several further limitations of our study that should be recognized. This was a re-analysis of an existing data set, designed to answer a different question, so the study was not optimized for this analysis. The number of women who later delivered preterm in the study cohort was small; thus the results can only be seen as a suggestion towards a stronger vaccine response to H1N1 vaccination in women who subsequently deliver preterm than at term. Based on these results, we can hypothesize that flu vaccination response to these strains could serve as a possible marker for immune system components and their association with preterm delivery. However, we acknowledge that further studies, designed specifically to follow up on this, are necessary before a stronger conclusion can be drawn. This work also reflects solely associations between vaccine responses in pregnant women and subsequent preterm vs term deliveries – the potential for a causal link needs to be

investigated in follow-up studies. Additional data from other immunological assays which measure information such as inflammatory cytokine concentrations and specific T cell populations should be examined in future studies. Finally, there are numerous other phenotypic confounders that need to be considered including maternal age, preeclampsia, gestational diabetes, chorioamnionitis and others for which the sample size in this secondary analysis was too small.

The development of preeclampsia during pregnancy can sometimes result in clinically induced preterm delivery. The number of preeclampsia cases stratified by final term or preterm delivery is too small in this study to make a final conclusion about association of flu vaccination response and preeclampsia in relation to term or preterm delivery but we observed the HAI response values for H1N1 amongst women with final preterm deliveries ($P = 0.63$) as well as among women who later delivered at term ($P = 0.54$) were not significantly different between those with or without preeclampsia diagnosis. Also for H3N2, neither women who delivered preterm ($P = 0.09$) nor term ($P = 0.12$) show a significant difference in the HAI response based on whether or not they had preeclampsia. Given the small sample size, these results can only be seen as a pilot study and would need to be studied further in a specific larger cohort.

In conclusion, by studying the flu vaccine response in women who were vaccinated during pregnancy, we observed a trend towards a significantly greater response against the H1N1 strain in women whose pregnancy subsequently resulted in a preterm delivery than in women whose pregnancy resulted in a term delivery, which might be explained by an increased activation of the immune system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations:

HAI	Hemagglutination inhibition assay
IQR	Interquartile range
PTB	Preterm birth
TIV	Trivalent inactivated vaccination

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Highlights

- Women who go on to deliver preterm have a greater flu vaccine response for the H1N1 strain than women who delivered at term
- No difference was observed for H3N2
- An increased activation of the maternal immune system might be linked to preterm birth

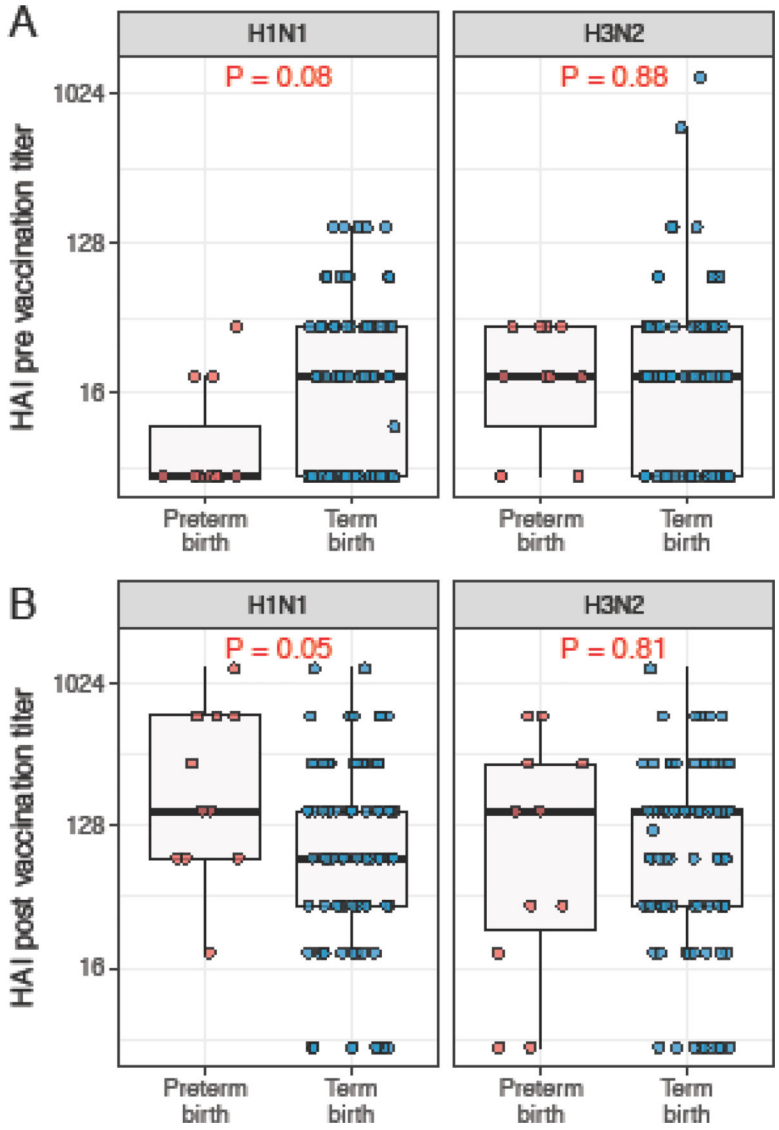

Figure 1: HAI titers stratified by H1N1 and H3N2 for women with later preterm or term delivery.

(A) Shows the pre-vaccination HAI titers, and (B) the post-vaccination HAI titers.

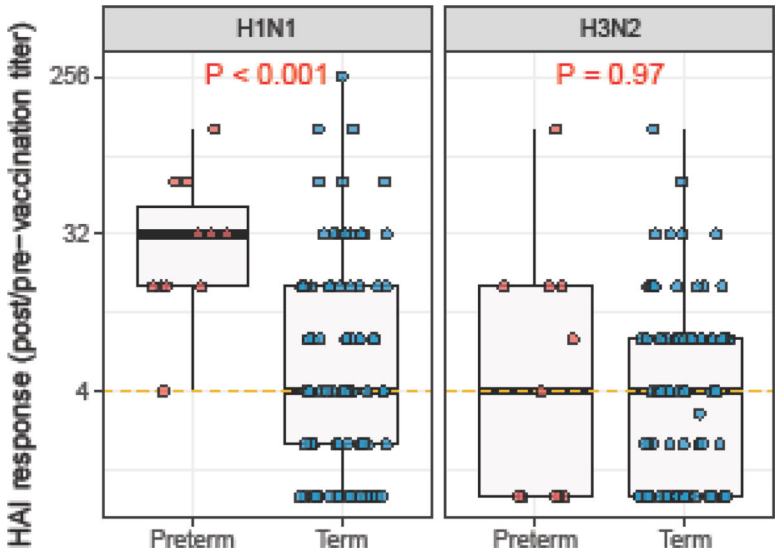

Figure 2: HAI responses against H1N1 and H3N2 strains for women who later delivered preterm or term.

Women with a later preterm delivery showed a significantly greater vaccination response for H1N1 than women whose pregnancy ended with a term delivery. The response to H3N2 is similar between women who went on to deliver term or preterm.

Table 1:

Demographics and vaccination information of the study population.

	Preterm birth	Term birth	*P*-value[‡]
n	11	91[†]	
Age, median (IQR) [years]	29 (9)	25 (10.5)	0.45
BMI (pre pregnancy), median (IQR)	25.4 (8.4) [4 NA]	26.7 (7.1) [39 NA]	0.92
Hispanic or Latino, n (%)	7 (63.6%)	45 (50%) [1 NA]	0.53
Birth weight, median (IQR) [kg]	2.4 (1.2)	3.4 (0.7)	< 0.001
Female baby, n (%)	7 (63.6%)	43 (47.3%)	0.35
Preeclampsia, n (%)	4 (36.4%)	6 (6.6%)	0.01
Prior pregnancy, n (%)	9 (81.8%)	71 (78%)	0.99
Vaccination time point, n (%)			< 0.001
in 1st trimester	6 (54.5%)	44 (48.4%)	
in 2nd trimester	4 (36.4%)	3 (3.3%)	
in 3rd trimester	1 (9.1%)	44 (48.4%)	
Received influenza vaccine in the prior year (self-reported), n (%)	1 (10%) [1 NA]	30 (34.1%) [3 NA]	0.16
Flu season, n (%)			0.27
2006/2007	3 (27.3%)	12 (13.2%)	
2007/2008	4 (36.4%)	21 (23.1%)	
2008/2009	2 (18.2%)	39 (42.9%)	
2009/2010	2 (18.2%)	19 (20.9%)	

[†]Of the women who later delivered at term, for 2 no H1N1 for 1 no H3N2 HAI response data was available

[‡]Mann-Whitney-U test for continuous variables, Fisher's exact test for categorical variables

NA: data not available

Table 2:

Seroconversion rates stratified for women who later delivered term or preterm are shown grouped by the specific influenza virus strain in the administered seasonal trivalent inactivated influenza vaccine.

			Preterm birth		Term birth	
Influenza A strain	**Specific strain**	**Seasons**	**n**	**Seroconversion rate, %**	**n**	**Seroconversion rate, %**
H1N1	A/New Caledonia/20/99	2006–2007	3	67%	11	36%
	A/Solomon Islands/3/2006	2007–2008	4	100	22	77
	A/Brisbane/59/2007	2008–2009 / 2009–2010	4	100	56	54
H3N2	A/Wisconsin/67/2005	2006–2007 / 2007–2008	7	57%	33	55%
	A/Brisbane/10/2007	2008–2009 /2009–2010	4	50	57	61