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Vaccine. Author manuscript; available in PMC 2020 May 28.

Published in final edited form as:

Vaccine. 2020 May 19; 38(24): 4038–4043. doi:10.1016/j.vaccine.2020.03.035.

No Association between HPV Vaccination and Infertility in U.S. Females 18–33 Years Old

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Abstract

Background—Human papillomavirus (HPV) vaccines have been recommended as primary prevention of HPV-related cancers for over 10 years in the United States, and evidence reveals decreased incidence of HPV infections following vaccination. However, concerns have been raised that HPV vaccines could decrease fertility. This study examined the relationship between HPV immunization and self-reported infertility in a nationally representative sample.

Methods—Data from the 2013–2016 National Health and Nutrition Examination Survey were analyzed to asses likelihood of self-reported infertility among women aged 20 to 33, who were young enough to have been offered HPV vaccines and old enough to have been queried about infertility (n=1,114). Two logistic regression models, stratified by marital history, examined potential associations between HPV vaccination and infertility. Model 1 assessed the likelihood of infertility among women who had never been pregnant or whose pregnancies occurred prior to HPV vaccination. Model 2 accounted for the possibility of latent and/or non-permanent post-vaccine infertility by including all women 20–33 years old who reported any 12-month period of infertility.

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Author contributions

This study design was by Drs. Schmuhl, Zhang, LoConte, and Conway and Ms. Mooney. The conduct of the research was by Drs. Schmuhl and Zhang and Ms. Mooney, with analysis by Drs. LoConte, Conway and Cooney. The first draft of the article was by Dr. Schmuhl and Ms. Mooney with revisions by all other co-authors. All authors approved of the submitted version of the article.

[*]Nicholas Schmuhl and Katherine Mooney contributed equally to this article as co-first authors.

Conflicts of interest

Dr. Conway has been engaged as a consultant or participated in advisory boards with: Sanofi Pasteur, GSK, Pfizer, and Merck Vaccines and has served as a principal investigator for a Sanofi Pasteur project.

No other authors have any potential conflicts of interest to disclose.

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Results—8.1% reported any infertility. Women who had ever been married and had received an HPV vaccine were **less** likely to report infertility (OR 0.04, 95% CI 0.01–0.57) in model 1. No other associations between HPV and infertility were found.

Conclusion—There was no evidence of increased infertility among women who received the HPV vaccine. These results provide further evidence of HPV vaccine safety and should give providers confidence in recommending HPV vaccination. Further research should explore protective effects of HPV vaccines on female and male fertility.

Keywords

vaccines; human papillomavirus; fertility; reproductive health; cancer; vaccine beliefs

Introduction

Human papillomavirus (HPV) is a virus that causes a very common sexually transmitted infection [1] and is linked to cervical, vulvar, vaginal, anal, and oropharyngeal cancers in females and oropharyngeal, anal, and penile cancers in males [2]. The HPV vaccine has been recommended for adolescents and young adults as primary prevention for HPV-related cancers for over 10 years [3], and a recent Cochrane review of 26 randomized controlled trials (RCTs) found that the vaccine is both effective and safe [4]. While HPV vaccination rates are improving, they still lag behind other recommended adolescent vaccines in the United States [5]. HPV vaccine rates fall victim to some of the same barriers that adversely impact uptake of other vaccines – including access disparities, inadequate healthcare provider recommendations, and poor vaccine knowledge and attitudes [6]. Other barriers appear unique to the HPV vaccine, which prevents cancer-causing sexually transmitted infections. Notably, a number of studies have revealed parental [7,8] and physician [9,10] anxieties about associations between the HPV vaccine and sexual behavior, which are not supported by evidence [11].

Recently, a small number of case reports [12–14] and anecdotes in the popular press [15,16] have given rise to concerns among some that the HPV vaccine causes lowered fertility by inducing primary ovarian insufficiency (POI). These concerns were refuted by a recent population-based cohort study of nearly 200,000 women that found no association between the HPV vaccine and POI [17]. However, POI is not the only condition implicated in female infertility. Furthermore, no research has suggested a biologically plausible mechanism by which HPV vaccines could cause POI or any other condition related to infertility. On the contrary, HPV vaccines have been found to protect against infections that adversely affect reproductive function. [18] Thus, the purpose of this study was to explore potential associations between HPV vaccination and infertility. We selected the National Health and Nutrition Examination Survey (NHANES [19]) as the data source for this inquiry, since it provides nationally representative data inclusive of individuals' immunization and reproductive health histories. If females vaccinated against HPV reported higher rates of infertility than those not vaccinated, more specific investigation of links between the HPV vaccine and conditions that cause infertility would be warranted.

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Methods

NHANES has collected data to assess the health and nutritional status of adults and children in the U.S. intermittently since 1959, and continuously since 1999. The cross-sectional survey utilizes a representative sample of about 5,000 people living in various counties across the country. NHANES has inquired about reproductive health and outcomes, including pregnancy, since its inception. In 2007–2008, NHANES first included questions about the HPV vaccine, and continues to do so. In 2013, the program began to include questions about difficulty or inability to become pregnant. In order to investigate potential associations between HPV vaccination and infertility, we analyzed data from two survey periods of the NHANES study: 2013–2014 (the first period that inquired about infertility) and 2015–2016 (the most recently available period). We confined our sample to women between 20 and 33 years old (N=1114) for two reasons: 1) NHANES did not query women younger than 20 if they had ever been pregnant; and 2) women older than 33 years old at the time of the 2013–2014 period would not have received the HPV vaccine, which was introduced in 2006. According to University of Wisconsin-Madison policies, this study did not require prior Institutional Review Board approval because the data set was de-identified and publicly available without restriction via the Centers for Disease Control and Prevention website.

Outcome of interest: infertility

Difficulty or inability to become pregnant can be attributed to various factors, including age and disease. Infertility is defined as a failure to become pregnant after 12 months of regular and unprotected sexual intercourse [20]. Primary infertility occurs when a woman meets the definition of infertility and has never been pregnant. Secondary infertility occurs when a woman has been pregnant in the past, but is later unable to become pregnant [21].

NHANES specifically asked female participants whether they were “pregnant **now**?” and whether they had “**ever** been pregnant?” with the specification that ever being pregnant included a current pregnancy, live births, miscarriages, stillbirths, tubal pregnancies, and abortions. While a history of pregnancy suggests fertility, those who have never been pregnant are not necessarily infertile. Therefore, we used the following question, introduced in the 2013–2014 period of NHANES data collection, as a closer proxy for infertility:

> [Has participant] ever attempted to become pregnant over a period of at least a year without becoming pregnant? (yes/no)

The purpose of this study was to assess whether receipt of the HPV vaccine is associated with self-reported infertility. While the HPV vaccine is recommended during an age-range that ideally predates sexual activity and when most women or girls are not attempting to become pregnant, we accounted for both early pregnancy and late-adopters of the vaccine. In our first analysis, we assessed the likelihood of reporting a 12-month period of infertility among women 20–33 years old who have never been pregnant (primary infertility), as well as women whose only pregnancies occurred prior to the age at which they received a first dose of the HPV vaccine (post-vaccine infertility).

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Similarly, if the HPV vaccine were related to infertility, it could be hypothesized that the effect would be permanent, as would certainly be the case if the etiology of infertility were POI; however, the effect might also be shorter-term. The effect of the vaccine on fertility could also be either immediate or delayed. To account for the possibility of latent and/or non-permanent, post-vaccine infertility, we performed a second analysis of all women 20–33 years old who reported any 12-month period of infertility, whether or not they had become pregnant at another time (i.e. primary or secondary infertility).

Hypothesized predictor of infertility: any doses of HPV vaccine

As the main predictor variable, we used responses to the question,

> [Has participant] **ever** received one or more doses of the HPV vaccine?

This question has been asked of female NHANES participants between the ages of 9 and 59 since 2007.

NHANES also queries those who report having received the HPV vaccine regarding the age at which they received the first dose. Using these additional data, we created a composite variable with four categories: No vaccine; first dose before 18 years of age; first dose at 18 or older; and unknown age at receipt of first dose. This composite predictor variable accounted for the possibility of latency in any potential relationship between HPV vaccine and infertility.

Other factors

During the two periods analyzed for this study, NHANES tracked several other health factors relevant to fertility, including body mass index (BMI), ever using birth control pills, and history of several sexually transmitted infections (STI). For the following analyses, we created a binary variable gauging whether an individual had any history of STI, based on self-report or laboratory results included in NHANES, as demonstrated by Anyalechi and colleagues[22]. Other covariates were health insurance status, routine access to healthcare, and socio-demographics, including age, race/ethnicity, marriage, education, and income. In addition to controlling for the aforementioned factors, we excluded women who reported having had their uterus or both ovaries removed, as both procedures result in a loss of fertility.

While recurrent miscarriage is a distinct condition from infertility, it can be related to some of the same underlying factors, and thus may be an important variable in the relationship between HPV vaccine and infertility. Unfortunately, NHANES did not ask explicitly about miscarriages; however, we attempted to account for miscarriage by controlling for history of live birth alongside history of pregnancy in our analysis of women who report any infertility. In multivariable models, any prior pregnancy and history of live birth were co-linear so only pregnancy history was retained in the final model.

Statistical analysis

We calculated descriptive statistics (i.e. percentages, means, and standard deviations) for self-reported infertility, the receipt of HPV vaccination, and other factors. Survey weights

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provided by NHANES were used to account for the complex sampling design and response rates and to generate estimates at the population level. Multivariable logistic regression analyses were performed to examine the association between self-reported infertility and HPV vaccination status. Analyses were stratified by marital status based on the assumption that women who have never been married may be less likely to have attempted to become pregnant. All the regression models were adjusted for sociodemographic characteristics and other health- and healthcare-related factors. Due to multicollinearity between the history of prior pregnancy and live birth (see Table 1), the variable of the history of live birth was excluded from the regression models. All analyses were conducted with the software STATA/SE 14.2 (StataCorp LP, College Station, TX).

Results

Overall, 8.1% of our sample reported having ever experienced a 12-month period of infertility. The rate of primary infertility (i.e. among women who had never been pregnant) was 3.7%, and the rate of secondary infertility (i.e. among women who had been pregnant in the past) was 12.0%. In general, females who reported infertility during the past 12 months differed from their counterparts in several ways. Those with a history of infertility were slightly older (27.8 years vs. 25.3 years; $p<0.001$), more likely to be obese (57.4% vs. 32.3%; $p<0.001$) and more likely to have ever been married (78.3% vs. 55.1%; $p<0.001$). They also had a lower income-to-poverty ratio (2.1 vs. 2.5; $p=0.034$) and were less likely to have health insurance (65.1% vs. 81.0%, $p=0.001$). Women who reported infertility had a higher rate of history of past pregnancy (78.7% vs. 50.9%, $p<0.001$) and livebirth (78.7% vs. 50.8%, $p<0.001$). Compared to those with no history of infertility, those who reported any period of infertility were no more or less likely to have received an HPV vaccine at any age. See table 1.

Primary and Post-vaccine infertility

Our first analysis included women with primary or post-vaccine infertility, defined as women who had never been pregnant, or who had not been pregnant since receiving the HPV vaccine, and reported a year of attempting pregnancy without success. Multivariable models indicated no association between HPV vaccination and infertility among women in this population, regardless of age at first receipt of the vaccine or marital history. BMI was the most significant predictor of infertility in our model, with obese women in the overall population more than five times more likely to report infertility (OR 5.25, 95% CI 1.52–18.1) compared to women with underweight or normal BMI. Race also played a role, as Black women were nearly five times more likely to report infertility (OR 4.74, 95% CI 1.20–18.8) than White women in the overall population. Women covered by health insurance were less likely than their counterparts to report infertility, both in the overall population (OR 0.21, 95% CI 0.07–0.62) and among married women (OR 0.05, CI 0.01–0.42). Health insurance coverage was not a significant predictor among never married women. Age, education, income/poverty ratio, ever use of birth control pills, history of STI, and routine access to health care were not associated with the likelihood of reporting primary or post-vaccine infertility. See table 2.

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Any infertility

When including all women between the ages of 20 and 33 in these two periods of the NHANES sample, we did not find a significant relationship between HPV vaccination and infertility, regardless of age at first receipt of the vaccine or marital history. In this sample, women who had ever been married were more than twice as likely to report any 12-month period of infertility as those who had not been married (OR 2.25, 95% CI 1.29–3.92). After stratification by marital status, we found that among never married women, those with higher incomes were less likely to report infertility (OR 0.64, 95% CI 0.44–0.94). No other variables were associated with infertility in this subgroup. Married women with BMIs categorized as obese were more than twice as likely to have experienced infertility (OR 2.39, 95% CI 1.23–4.66), a pattern which persisted in the overall sample (OR 2.08, 95% CI 1.21–3.56). Among married women, those covered by health insurance were less likely to report infertility (OR 0.34, 95% CI 0.18–0.66), and this pattern persisted in the overall sample (OR 0.50, 95% CI 0.30–0.83). Age, race, ever use of birth control pills, education, history of STI, pregnancy history, and routine access to health care were not associated with likelihood of reporting any period of infertility. See table 3.

Discussion and conclusions

In both analyses, the first focusing on women with possible primary or post-vaccine infertility and the second attempting to take into account latent and/or non-permanent post-vaccine infertility and controlling for history of pregnancy, we observed no association between HPV vaccination and self-reported infertility. Importantly, the analyses were conducted with a proxy for infertility that is nearly identical to how infertility is defined in clinical practice and controlled for important covariates like ever using birth control. Obtaining null results using an outcome variable that broadly defines infertility dispels concerns about association between HPV vaccination and infertility due to POI or any other condition. This lack of association may help allay public concerns about vaccine safety and bolster HPV vaccination rates. In combination with a lack of evidence showing any causal link between HPV vaccines and infertility, these results should help providers feel confident in making strong recommendations for HPV vaccination for adolescent girls and boys, in line with Advisory Committee on Immunization Practice guidelines [23].

The statistically significant relationships between infertility and other variables in our analyses were largely expected. For example, the relationship between obesity and infertility, which was seen in both analyses, is well supported by prior data [24]. It should also be no surprise that women who have ever been married were more likely to report infertility (Table 3) as this population is presumably more likely to be trying to have children. Interestingly, increased odds of reporting infertility among Black women was seen in the first analysis (women who had never been pregnant, post-HPV vaccination), but not the larger second analysis of women who had ever experienced a 12-month period of fertility. Previous research has observed, but not explained, increased odds of infertility among Black women when controlling for common risk factors [25]. It is difficult to interpret findings that women with insurance coverage were less likely to report infertility than those without insurance in

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both samples analyzed (Tables 2 and 3), because NHANES did not query women about attempts to conceive, or lack thereof.

There are several limitations that should be considered when interpreting the results of this study. First, the sample size was limited because survey questions about infertility and HPV immunization only coincided for two periods of the NHANES study (2013–2014 and 2015–2016). Similarly, the upper age limit for inclusion in this study was 33 years, because women older than 33 during the 2013–2014 NHANES survey would not have been eligible for the HPV vaccine when it was introduced in 2006. If possible, future research should include older women to explore the possibility that some instances of infertility go unnoticed until a later age.

Second, all variables were self-reported, including HPV vaccination status and inability to become pregnant when desired. It is possible that questions of vaccination status in particular could be subject to recall bias since the many vaccinations given throughout childhood and adolescents are easily confused. However, previous research using self-reported receipt of =/> 1 dose of HPV vaccine (NHANES question IMQ060) have compared respondents' answers to medical records and have documented 86%−87% sensitivity, 83%−87% specificity, and 70%−73% agreement [26,27].

Among women without a history of infertility, the NHANES data did not allow us to distinguish those who had been successful in their attempts to become pregnant from those who had never tried to conceive. Another limitation was the inability to easily control for miscarriage, an important covariate that could be associated with infertility. Because miscarriage was not explicitly measured by NHANES, we were limited to a proxy constructed by comparing self-reported pregnancies and live births.

While only one subgroup in these analyses showed a significantly lower rate of infertility among those who had been vaccinated against HPV, ongoing research seeks to understand whether HPV vaccines are actually protective of fertility. A recent systematic review of more than 100 peer-reviewed articles published between 1994 and 2014 found that HPV *infections* were related to decreased reproductive function in both males and females. The studies reviewed focused largely on the association of HPV infection with semen parameters, failed *in vitro* fertilization, and poor pregnancy outcomes (e.g., miscarriage) [18]. Given that the 9-valent HPV vaccine is 96% effective at preventing HPV infections and related conditions [3], it is reasonable to believe that those who are vaccinated will have fewer fertility problems. Moreover, cancers and pre-cancers caused by HPV infection also restrict fertility. For example, cervical cancer workup and treatment (e.g. cervical conization) can result in cervical insufficiency, miscarriages, and preterm birth. Further research is needed to quantify the benefits of HPV vaccination to both female and male fertility. In the meantime, healthcare providers and patients can be reassured that there is no association between HPV vaccination and infertility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Funding source

This work was supported by University of Wisconsin Carbone Cancer Center Support Grant NCI P30 CA014520.

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Table 1.

Descriptive statistics of females aged 20–33: National Health and Nutrition Examination Survey, 2013–2016 (N=1114)

	No self-reported infertility (N=1018)	Self-reported infertility (N=96)	P-value*
Overall, %	91.9	8.1	
Personal characteristics			
Age, mean (SD)	25.3 (4.4)	27.8 (4.0)	**<0.001**
Race, %			0.284
NH white	57.8	56.0	
NH black	13.1	16.7	
Hispanic	17.9	20.9	
Other	11.2	6.4	
College education, %	32.6	21.8	0.079
Ever married, %	55.1	78.3	**<0.001**
Ratio of family income to poverty, %	2.5 (1.6)	2.1 (1.4)	**0.034**
Health related factors			
HPV vaccination and age of first dose, %			0.06
No vaccine	63.8	79.6	
Before 18	16.0	8.3	
18 or older	16.5	8.9	
Age unknown	3.7	3.2	
BMI category, %			**<0.001**
Underweight or normal	41.9	28.6	
Overweight	25.8	14.0	
Obese	32.3	57.4	
Had ever taken birth control pills, %	70.3	63.2	0.196
Had any sexually transmitted infections, %	18.2	17.3	0.840
History of pregnancy, %	50.9	78.7	**<0.001**
History of live birth, %	50.8	78.7	**<0.001**
Healthcare related factors			
Covered by health insurance, %	81.0	65.1	**0.001**
Had a routine place to go for healthcare, %	78.4	82.3	0.422

*P-values are based on t-test for continuous variables and chi-square test for categorical variables.

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Table 2.

Predictors of primary and post-vaccine infertility[1] among females aged 20–33, National Health and Nutrition Examination Survey, 2013–2016

	Overall (N=505)		**Ever married (N=184)**		**Never married (N=321)**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
HPV vaccination and age of first dose						
No vaccine	Ref		Ref		Ref	
Before 18	1.04	0.22–4.97	--*		1.51	0.26–8.78
18 or older	0.42	0.11–1.54	0.07	0.01–1.09	0.83	0.16–4.35
Age unknown	--*		--*		--*	
Age	1.13	0.98–1.30	0.96	0.73–1.09	1.06	0.88–1.28
Race						
NH white	Ref		Ref		Ref	
NH black	**4.74**	**1.20–18.8**	--*	--	5.11	0.90–28.8
Hispanic	1.22	0.32–4.70	2.29	0.34–15.6	0.43	0.03–6.03
Other	--*	--	--*	--	--*	--
College education	0.12	0.01–1.05	0.48	0.03–7.13	--*	--
Ever married	2.61	0.89–7.71	NA		NA	
Ratio of family income to poverty	0.79	0.51–1.21	0.90	0.41–1.96	0.68	0.37–1.24
BMI category						
Underweight or normal	Ref		--*	--	Ref	
Overweight	0.98	0.19–4.97			0.70	0.11–4.64
Obese	**5.25**	**1.52–18.1**			2.25	0.48–10.5
Had ever taken birth control pills	0.70	0.26–1.94	0.29	0.04–2.15	0.56	0.13–2.36
Had any sexually transmitted infections	1.73	0.44–6.86	--*	--	3.57	0.69–18.3
Covered by health insurance	**0.21**	**0.07–0.62**	**0.05**	**0.01–0.42**	0.53	0.11–2.48
Had a routine place to go for healthcare	0.84	0.28–2.55	0.60	0.06–5.89	0.82	0.17–3.85

[1] Primary infertility refers to infertility reported by women who have never been pregnant, and post-vaccine infertility refers to infertility reported by those whose only pregnancies occurred prior to the age at which they received a first dose of the HPV vaccine.

* Variables were dropped due to perfect prediction.

Bold values represent statistical significance at the 0.05 level.

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Table 3.

Predictors of any infertility among females aged 20–33, National Health and Nutrition Examination Survey, 2013–2016

	Overall (N=1114)		Ever married (N=608)		Never married (N=506)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
HPV vaccination and age of first dose						
No vaccine	Ref		Ref		Ref	
Before 18	0.77	0.32–1.87	0.67	0.18–2.45	0.96	0.27–3.43
18 or older	0.69	0.69–1.47	0.43	0.15–1.29	1.08	0.36–3.26
Age unknown	0.44	0.10–1.95	0.74	0.16–3.54	--*	
Age	1.04	0.97–1.11	1.04	0.96–1.13	0.99	0.88–1.11
Race						
NH white	Ref		Ref		Ref	
NH black	1.32	0.71–2.47	0.92	0.37–2.26	1.77	0.63–4.94
Hispanic	0.76	0.41–1.40	0.86	0.43–1.74	0.48	0.11–2.12
Other	0.55	0.24–1.27	0.62	0.25–1.53	--*	--
College education	0.78	0.40–1.53	1.16	0.53–2.53	--*	--
Ever married	**2.25**	**1.29–3.92**	NA		NA	
Ratio of family income to poverty	0.94	0.79–1.13	1.06	0.85–1.32	**0.64**	**0.44–0.94**
BMI category						
Underweight or normal	Ref		Ref		Ref	
Overweight	0.69	0.34–1.39	0.54	0.22–1.30	1.08	0.33–3.54
Obese	**2.08**	**1.21–3.56**	**2.39**	**1.23–4.66**	1.98	0.75–5.24
Had ever taken birth control pills	0.86	0.53–1.41	0.80	0.43–1.47	0.95	0.38–2.33
Had any sexually transmitted infections	1.26	0.68–2.34	0.99	0.41–2.37	1.77	0.68–4.63
History of pregnancy	1.29	0.73–2.28	1.43	0.70–2.93	1.10	0.40–3.02
Covered by health insurance	**0.50**	**0.30–0.83**	**0.34**	**0.18–0.66**	0.99	0.38–2.58
Had a routine place to go for healthcare	1.59	0.86–2.93	1.91	0.89–4.08	0.88	0.30–2.63

*Variables were dropped due to perfect prediction.

Bold values represent statistical significance at the 0.05 level.