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The Effect of Vaccination against Human Papillomavirus on Fecundability

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Abstract

Background—The human papillomavirus (HPV) vaccine was developed to prevent infection with strains of HPV that cause cervical cancer. While HPV infection has been associated with reduced semen quality and lower pregnancy rates in some, no studies have examined the relationship between HPV vaccination and fecundability. We hypothesize that HPV prevention via vaccination will protect fecundity.

Methods—We analyzed data from Pregnancy Study Online (PRESTO), a preconception cohort of North American pregnancy planners. Between 2013 and 2017, we followed 3,483 female pregnancy planners and 1,022 of their male partners for 12 months or until reported pregnancy, whichever came first. At baseline, participants reported whether they had been vaccinated against HPV and their age at vaccination. We estimated fecundability ratios (FR) and 95% confidence intervals (CI) using proportional probabilities models adjusted for sociodemographics, smoking, and abnormal Pap test before HPV vaccination (females only).

Results—HPV vaccination was more prevalent among females (33.9%) than males (5.2%). There was little overall association between female vaccination (FR=0.98, 95% CI: 0.90, 1.08) or male vaccination (FR=1.07, 95% CI: 0.79, 1.46) and fecundability. Among females with a history of sexually transmitted infections or pelvic inflammatory disease (*i.e.*, a group at high risk of exposure to HPV infection), those vaccinated against HPV had higher fecundability than those not vaccinated (FR=1.35, 95% CI: 0.99, 1.86).

Conclusion—Although HPV vaccination had little effect on fecundability overall, HPV vaccination was positively associated with fecundability among women with a history of sexually transmitted infections.

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Introduction

Human papillomavirus (HPV) is a cause of cancers of the cervix,[1] vagina, penis, rectum, and oral cavity.[2] HPV infection is extremely common; 45.2% of men and 39.9% of women in the United States (U.S.) had evidence of current infection in 2014.[3] Effective in immunizing against HPV strains linked to genital warts, cervical dysplasia, and carcinoma, HPV vaccines (Gardasil, Cervarix) became available in the U.S. and Canada in 2006.[4] While rodent studies have indicated no effect of HPV vaccination on fertility,[5–7] no studies have examined this relationship in humans.

Detectable HPV infection among males has been associated with reduced sperm motility, increased antisperm antibodies,[8] and lower pregnancy rates[9] in studies of infertile couples; another study found no effect on semen quality.[10] Among females undergoing intrauterine insemination, 1.9% with detectable HPV infection conceived compared with 11.4% without the virus.[11] Surgical treatment for HPV-associated cervical dysplasia may also influence fertility. One registry-based case-control study found increased pregnancy rates among women who underwent cervical surgery compared with untreated women,[12] while another smaller case-control study found that women who underwent cone biopsy, loop electrosurgical excision, cryosurgery, or laser vaporization had twice the odds of infertility compared with untreated women.[13]

Despite the potential harms of HPV infection and the lack of evidence that HPV vaccination impairs fertility, public concern about adverse effects of HPV vaccination on fertility is a reason for low uptake among pre-adolescents internationally.[14, 15] We examined the association between HPV vaccination and fecundability among couples trying to conceive. We hypothesized that HPV prevention via vaccination will protect fecundity.

Methods

Study population

Pregnancy Study Online (PRESTO) is an ongoing prospective cohort study of pregnancy planners in the U.S. and Canada.[16] Participants were enrolled between June 2013 and May 2017, and were recruited primarily through advertisements on social media. Eligible women were aged 21–45 years, not using contraception or fertility treatments, in a stable relationship with a male partner, and not currently pregnant. Female participants completed a baseline questionnaire and bimonthly follow-up questionnaires for 12 months or until reported pregnancy. Over 80% of participants completed at least one follow-up questionnaire. Women were given the option to invite their male partners to complete a baseline questionnaire. Eligible men were aged ≥21 years. Boston Medical Center's institutional review board approved the study protocol.

Assessment of HPV vaccination and covariates

At baseline, participants provided detailed data on lifestyle and behavioral factors, socioeconomic status, medical and reproductive history, and medication use, including whether they had been vaccinated against HPV and at what age.

Assessment of time-to-pregnancy (TTP)

At baseline, female participants reported their typical menstrual cycle length, date of last menstrual period (LMP), and number of menstrual cycles they had been trying to conceive. On each follow-up questionnaire, females reported their LMP date and pregnancy status. TTP, in cycles, was calculated as: cycles trying to conceive at study entry + ((LMP date from most recent follow-up questionnaire - date of baseline questionnaire)/cycle length) + 1. Couples contributed cycles from study entry until conception, fertility treatment initiation, loss to follow-up, or 12 cycles, whichever occurred first.

Exclusions

Of the 5,020 women enrolled, we excluded 881 women who had been trying to conceive for >6 cycles at enrollment (28.5% vaccinated), 161 women with implausible LMP data, and 495 women with no follow-up. The final analytic sample included 3,483 women and 1,022 men (51% of those invited).

Data analysis

We evaluated the association between HPV vaccination (ever vs. never) and age at vaccination (<18 and ≥18 years) and fecundability, separately for men and women. We calculated crude fecundability (total number of pregnancies/total number of cycles) and used proportional probabilities regression models to estimate fecundability ratios (FR) and 95% confidence intervals (CI). The FR represents the average per-cycle probability of conception comparing vaccinated with unvaccinated participants. Selection of potential confounders was guided by the literature and the drawing of a causal directed acyclic graph. We controlled for age (<25, 25–29, 30–34, ≥35 years), non-Hispanic white (yes versus no), smoking (current, past, never), education (≤12, 13–15, 16, ≥17 years), annual household income (≤49,000, 50,000–99,000, 100,000–149,000, ≥150,000 USD), and region of residence (U.S. Midwest, Northeast, South, West; Canada). Models for females were additionally adjusted for parental education (≤12, 13–15, 16, ≥17 years) and abnormal Pap test before vaccination; secondary analyses further controlled for irregular menses (yes versus no) and recent hormonal contraceptive use (yes versus no), which may act as intermediates.[17] In an effort to identify subgroups for whom HPV vaccination might provide greater protection against subfertility, female analyses were stratified by history of sexually transmitted infections (STI) or pelvic inflammatory disease (PID), and lifetime number of sexual partners. Small numbers of vaccinated males precluded such stratification.

Data on vaccination (ever vs. never) and age at vaccination were missing for 0.2% and 0.7% of females and 0.7% and 1.7% of males, respectively. Missing covariate data ranged from 0.0% (age, race, and region) to 6.3% (age at abnormal Pap test). We used PROC MI to impute missing exposure and covariate data, and PROC MIANALYZE to combine coefficient and standard error estimates across five imputed datasets.[18]

Results

Table 1 shows baseline characteristics of the 3,483 women and 1,022 men in this analysis. HPV vaccination was more common among women (33.9%) than men (5.2%). Of those

vaccinated, 22.3% of women and 22.6% of men were vaccinated before age 18. Mean age at vaccination was 21 years for women (IQR: 18–24 years) and 22 years for men (IQR: 18–26 years). Median time since vaccination was 8 years for women (IQR: 6–9 years) and 6 years for men (IQR: 2–10 years). Among women, vaccination was positively associated with income, education, and residence in the Northeast U.S., and inversely associated with age, smoking, parity, irregular menses, and history of miscarriage or infertility. Women vaccinated before age 18 were less likely to have genital warts or an abnormal Pap test. Male vaccination was positively associated with younger age, smoking, and physical activity. Men vaccinated before age 18 were more likely to live in the Midwest U.S. and have a higher number of sexual partners; those vaccinated at age ≥18 had lower income, and a lower probability of doing something to improve chances of conception (Table 1). Vaccination status did not differ substantially between individuals who completed the study (33.8% of females, 5.0% of males) and those lost to follow-up (34.8% of females, 7.8% of males).

Overall, there was little association between female HPV vaccination (FR=0.98, 95% CI: 0.90, 1.08) or male HPV vaccination (FR=1.07, 95% CI: 0.79, 1.46) and fecundability. Results did not differ appreciably by age at vaccination (Table 2). Results were similar after excluding females with an abnormal Pap test before vaccination and after adjusting for irregular menses and recent hormonal contraceptive use (data not shown).

Results were consistent across subgroups of women with ≤4 or ≥10 sexual partners. Among women with a history of STI/PID, vaccination was positively associated with fecundability (FR=1.35, 95% CI: 0.99, 1.86; further restriction by abnormal Pap test: FR=1.38, 95% CI: 1.00, 1.90). The association was driven by lower fecundability among unvaccinated women with a history of STI/PID (0.11); fecundability among vaccinated women with a history of STI/PID (0.14) was similar to that among unvaccinated women without a history of STI/PID (0.14).

Comment

We found little association overall between vaccination and fecundability, but HPV vaccination was associated with increased fecundability among the subset of women with a history of STI/PID. It is possible that women who engage in risky unprotected sex are more likely to be exposed to HPV and to experience benefits from vaccination. Indeed, our data indicated that unvaccinated women with a history of STI/PID had appreciably lower fecundability; those vaccinated with a history of STI/PID had similar fecundability to unvaccinated women without a history of STI/PID. These findings agree with the animal literature demonstrating no adverse effects of HPV vaccination on rat fecundability[5–7] and with the human literature finding adverse effects of HPV infection on fertility.[8, 9, 11]

Study limitations include our reliance on self-reported data, potential residual confounding by factors such as childhood socioeconomic status and sexual risk, 51% male participation, and small numbers of vaccinated males and participants vaccinated at early ages. Vaccination prevalence was low because many participants were adults when vaccination became available. Because age is related to both vaccination and fecundity, and vaccination recall accuracy may decrease with increasing age, differential exposure misclassification

may have biased FRs in an unpredictable direction. Some women were vaccinated after having abnormal Pap tests. Because an abnormal Pap test is a marker of active or previous HPV infection, vaccination may not prevent the adverse effects of HPV in this subgroup. Nevertheless, analyses in which we accounted for abnormal Pap test before vaccination (via model adjustment or restriction) were similar to the main results.

Overall, we found little association between HPV vaccination and fecundability, except for a modest positive association among vaccinated women with a history of STI/PID. These findings should reassure individuals hesitant about vaccination due to fertility concerns. Future research could examine medical record documented vaccination in a cohort of men and women vaccinated at younger ages.

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Table 1

Baseline characteristics of cohort by age at HPV vaccination, PRESTO, 2013–2017.

	Females (N=3,483)			Males (N=1,022)		
Characteristic[a]	**Unvaccinated**	**Vaccinated age <18 years**	**Vaccinated age ≥18 years**	**Unvaccinated**	**Vaccinated age <18 years**	**Vaccinated age ≥18 years**
Number of participants N (%)	2,303 (66.1)	263 (7.6)	917 (26.3)	969 (94.8)	12 (1.2)	41 (4.0)
Age (years, mean)	30.9	25.9	29.3	31.8	28.0	29.4
Partner's age (years, mean)	31.9	31.4	31.5	29.9	30.1	30.2
Non-Hispanic white (%)	85.6	87.7	86.3	87.4	97.5	83.8
Household income <$50,000 (%)	18.0	13.7	12.4	15.5	10.3	16.9
Less than a college degree (%)	22.1	15.9	13.6	26.3	34.4	26.1
Geographic region (%)						
Midwest	16.6	27.8	14.1	17.4	23.8	18.8
Northeast	26.4	31.5	40.3	33.0	33.2	25.9
South	23.5	16.3	20.6	21.1	16.0	21.6
West	13.7	10.6	16.6	15.7	16.8	27.3
Canada	19.8	13.8	8.4	12.6	10.3	6.4
Physical activity (MET-hrs/wk, mean)	34.7	35.5	38.6	33.2	37.2	37.2
Body mass index (kg/m^2, mean)	26.7	27.1	25.9	27.6	28.0	26.1
Multivitamin use (%)	82.7	81.8	85.1	35.2	39.7	31.3
Ever smoker (%)	25.3	21.0	19.7	25.8	26.3	29.5
Alcohol intake (drinks/week, mean)	3.3	5.0	3.7	6.4	5.0	4.3
Parous (%)	30.9	25.4	19.2	--	--	--
Irregular menses (%)	16.7	16.1	12.1	--	--	--
Doing something to improve chances of conception (%)	74.7	73.8	73.9	76.7	81.5	60.4
Intercourse frequency <1 time/week (%)	20.7	10.6	20.2	24.8	16.0	32.9
Hormonal last method of contraception (%)	36.0	44.7	43.7	36.1	18.5	25.7
History of spontaneous abortion (%)	23.3	14.6	17.5	--	--	--
History of infertility (%)	6.8	5.2	3.5	6.9	1.3	3.8
History of sexually transmitted infection (STI)						
Chlamydia (%)	5.9	5.8	5.2	2.5	0.0	5.4

Characteristic[a]	Females (N=3,483)			Males (N=1,022)		
	Unvaccinated	Vaccinated age <18 years	Vaccinated age ≥18 years	Unvaccinated	Vaccinated age <18 years	Vaccinated age ≥18 years
Genital warts (%)	3.6	0.9	3.1	1.6	0.0	0.0
Herpes (%)	3.6	1.5	4.1	1.6	0.0	0.0
Pelvic inflammatory disease (PID)	0.8	0.4	0.7	--	--	--
Abnormal Pap smear (%)	34.3	29.3	39.9	--	--	--
Number of sexual partners (mean)	7.3	7.6	7.4	6.0	7.9	7.2

[a]All characteristics, except for age, are age-standardized to the female and male cohorts at baseline.

Table 2

HPV vaccination and fecundability among pregnancy planners.

Exposure	No. of Cycles	No. of Pregs	Crude Fecundability	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]
Females					
Unvaccinated	10,332	1,402	0.14	1.00 (Reference)	1.00 (Reference)
Vaccinated	4,936	751	0.15	1.08 (1.00–1.17)	0.98 (0.90–1.08)
Vaccinated < Age 18	1,094	154	0.14	1.03 (0.88–1.20)	1.00 (0.85–1.17)
Vaccinated ≥ Age 18	3,842	597	0.16	1.09 (1.00–1.19)	0.98 (0.89–1.08)
Males					
Unvaccinated	4,177	634	0.15	1.00 (Reference)	1.00 (Reference)
Vaccinated	211	36	0.17	1.03 (0.76–1.39)	1.07 (0.79–1.46)
Vaccinated < Age 18	48	8	0.17	0.95 (0.50–1.80)	1.10 (0.56–2.19)
Vaccinated ≥ Age 18	163	28	0.17	1.06 (0.75–1.48)	1.06 (0.75–1.50)

FR=fecundability ratio

[a]Male and female models are adjusted for age at baseline, education, income, geographic region of residence, race/ethnicity, history of smoking. Models for females are additionally adjusted for abnormal Pap test before age at vaccination and parent's education.

Table 3

HPV vaccination and fecundability stratified by number of sexual partners and history of STI/PID

Exposure	No. of Cycles	No. of Pregs	Crude Fecundability	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]	No. of Cycles	No. of Pregs	Crude Fecundability	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]
	≤4 Sexual Partners					≥10 Sexual Partners				
Females										
Unvaccinated	4,186	604	0.14	1.00 (Reference)	1.00 (Reference)	2,958	388	0.13	1.00 (Reference)	1.00 (Reference)
Vaccinated	2,145	321	0.15	1.06 (0.92–1.22)	1.00 (0.85–1.17)	1,304	210	0.16	1.08 (0.90–1.30)	0.99 (0.79–1.24)
	No History of STI/PID					History of STI/PID				
Females										
Unvaccinated	8,896	1,241	0.14	1.00 (Reference)	1.00 (Reference)	1,436	161	0.11	1.00 Reference)	1.00 (Reference)
Vaccinated	4,335	664	0.15	1.05 (0.97–1.15)	0.95 (0.87–1.05)	601	87	0.14	1.27 (1.00–1.61)	1.35 (0.99–1.86)
	No History of STI/PID and No Abnormal Pap Test before Vaccination					History of STI/PID and No Abnormal Pap Test before Vaccination				
Females										
Unvaccinated	8,896	1,241	0.14	1.00 (Reference)	1.00 (Reference)	1,436	161	0.11	1.00 (Reference)	1.00 (Reference)
Vaccinated	3,611	547	0.15	1.03 (0.94–1.13)	0.96 (0.87–1.05)	361	56	0.16	1.41 (1.07–1.85)	1.38 (1.00–1.90)

FR=fecundability ratio

[a]Models are adjusted for age at baseline, education, income, geographic region of residence, race/ethnicity, history of smoking. Models for females are additionally adjusted for abnormal Pap test and parent's education.