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RETRACTED ARTICLE: [A lowered probability of pregnancy in females in the USA aged 25–29 who received a human papillomavirus vaccine injection]

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ABSTRACT

Birth rates in the United States have recently fallen. Birth rates per 1000 females aged 25–29 fell from 118 in 2007 to 105 in 2015. One factor may involve the vaccination against the human papillomavirus (HPV). Shortly after the vaccine was licensed, several reports of recipients experiencing primary ovarian failure emerged. This study analyzed information gathered in National Health and Nutrition Examination Survey, which represented 8 million 25-to-29-year-old women residing in the United States between 2007 and 2014. Approximately 60% of women who did not receive the HPV vaccine had been pregnant at least once, whereas only 35% of women who were exposed to the vaccine had conceived. For married women, 75% who did not receive the shot were found to conceive, while only 50% who received the vaccine had ever been pregnant. Using logistic regression to analyze the data, the probability of having been pregnant was estimated for females who received an HPV vaccine compared with females who did not receive the shot. Results suggest that females who received the HPV shot were less likely to have ever been pregnant than women in the same age group who did not receive the shot. If 100% of females in this study had received the HPV vaccine, data suggest the number of women having ever conceived would have fallen by 2 million. Further study into the influence of HPV vaccine on fertility is thus warranted.

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Introduction

The birth rates in the United States for women under the age of 30 are at record lows (Martin, Hamilton, and Osterman 2017). Birth rates per 1000 females aged 25–29 fell 11.5% from 118.1 in 2007 to 104.5 in 2015. The recent decline follows a steady increase of 8.5% between 1995 and 2006 (from 108.8 to 118). The basis for the recent decrease remains unknown. Factors contributing to the reduction might be associated with more effective and better use of contraceptives (Sundaram et al. 2017) as well as the recession of 2008 (Schneider 2015).

Perhaps exposure to one or more environmental toxins might be influencing the birth rates. Domingo (1994) reported the adverse effects of metals such as mercury and lead that are common in the human environment as well as metals used in pharmacological products such as aluminum (Al) on fetal development and teratogenicity in mammals. Bhatt (2000) surveyed the literature on environmental endocrine disrupters such as dioxins and polychlorinated biphenyls and found these chemicals were shown to be associated with infertility, menstrual irregularities, and spontaneous abortions. Garry et al. (2002) reported an increased frequency of miscarriages and spontaneous abortions in women exposed to pesticides. Marwa et al. (2017) found that introducing Al to ovarian cells of rats triggered intracellular damage primarily by altering the cellular mitochondria. It is of interest that Veras et al. (2010) demonstrated that exposure to ambient air pollutants was associated with decreased female and male fertility.

In 2006, the U.S. Food and Drug Administration (2006) licensed the first of two vaccines to protect women against the human papillomavirus (HPV). Both HPV vaccines (Gardasil and Cevarix) address HPV 16 and 18, two strains of HPV that produce approximately 70% of cervical cancer cases. Further, Gardasil

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protected against genital warts by interfering with HPV 6 and 11 (Markowitz et al. 2014). The vaccine is recommended for females (and since 2011 for males) aged 11–26.

Reports of young women experiencing primary or premature ovarian failure (POF) after receiving the vaccine were noted (Colafrancesco et al. 2013; Little and Ward 2012, 2014). POF—defined as the onset of menopause before the age of 40—is sometimes referred to as premature ovarian insufficiency and thought to be extremely rare. Symptoms include menstrual disturbances such as primary or secondary amenorrhea as well as hot flashes and mood swings. The estimated incidence for females under the age of 30 is 1 in 1000, rising to 1 in 100 for females under the age of 40 (Rafique, Sterling, and Nelson 2012). However, the use of the birth control pill might mask the existence of POF and thereby understate the incidence of the disorder. Islam and Cartwright (2011) noted that of the 4968 females in a UK birth cohort that had been born in 1958, the number of women who experienced POF was 370 (7.4%). Underlying conditions such as radiation and chemotherapy might give rise to the malady, but 80–90% of POF cases have no apparent cause. POF may be an autoimmune disorder and between 10% and 30% of women with POF also have other autoimmune disorders (Maclaran and Panay 2015).

Both licensed HPV vaccines contain aluminum (Al), which has been associated with autoimmune disorders (Colafrancesco et al. 2013). No apparent epidemiological study on the influence of Al on fertility exists (Krewski et al. 2007), but Karakis et al. (2014) found an association between prenatal exposure to Al and neonatal morbidity. Evidence also suggests a link between Al exposure and POF (Pellegrino et al. 2014).

Geier and Geier (2017) examined the Vaccine Adverse Events Reporting System (VAERS) database to determine whether uptake of the HPV vaccine affected the number of reports of autoimmune reactions. VAERS is a passive system where vaccine administrators or recipients report adverse effects after receiving a vaccine. Between 2006 and 2014, HPV vaccine recipients or their health care providers noted 48 cases of ovarian damage associated with autoimmune reactions. In addition to the Geier and Geier findings, the VAERS database between 2006 and 2017 indicated other symptoms that affect the ability to bear children: spontaneous abortion (214 cases), amenorrhea (130 cases), and irregular menstruation (123 cases).

Methods

This study examined the decline in birth rates amongst women at the peak of their childbearing years in the United States since 2007. Data on live births per 1000 females aged 25–29 originated from the Centers for Disease Control and Prevention (CDC) WONDER database "Births" section: https://wonder.cdc.gov/natality.html. The database reports the numbers starting in 1995. The number of births is divided by the number of females in the age group using data from WONDER database "Population" section: https://wonder.cdc.gov/bridged-race-population.html. Figure 1 illustrates

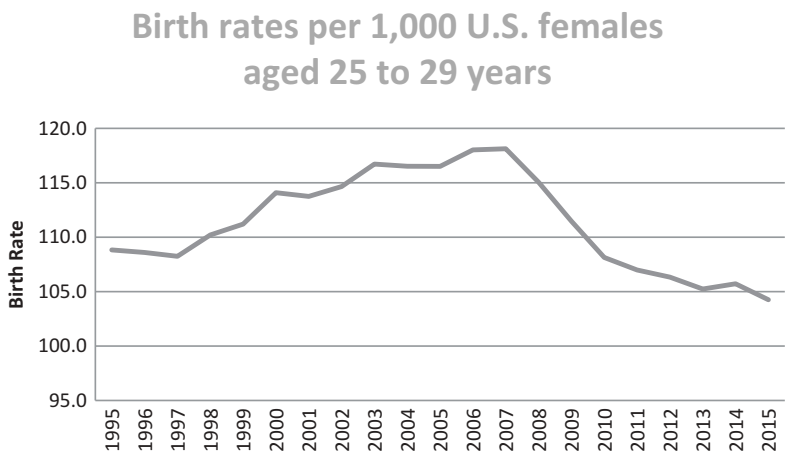

Figure 1. Birth rates per 1000 females in the United States aged 25–29 from 1995 to 2015.

national numbers from 1995 to 2015. The chart reveals the steady increase in birth rates through the mid-2000s, followed by a recent sharp decline that is the subject of this analysis.

To determine whether the change in birth rates over time is statistically significant, regression analysis was performed. Birth rates per 1000 females in the United States aged 25–29 over time (BR(t)) were regressed on a constant (C) that equals 1 as well as two indicators of time: TREND indicates the overall time trend and equals 1 if the observa-tion occurred in the year 1995, 2 in the year 1996,. . ., 21 in the year 2015 and Post-2006_DUMMY is a dummy variable that equals 1 if year of analysis is 2007–2015 and 0 if year of analysis is 1995–2006. Table 1 shows the results of the regression: BR(t) = $C + C \times$ Post 2006_DUMMY + TREND + TREND × Post 2006_DUMMY. The coefficient on the TREND variable (1.0) is positive and statistically signifi-cant, suggesting that over time, the birth rate rose an average 1 per year. However, a change seemed to occur beginning in 2007. The coefficient on the TREND × Post 2006_DUMMY variable (−2.6) is negative and statistically significant, sug-gesting that birth rates fell an average of 1.6 per year (= 1.0 − 2.6) between 2007 and 2015.

To analyze possible influences associated with these changes in birth rates, this study examined responses to the National Health and Nutrition Examination Survey (NHANES). The survey collects data on health status of individuals in the United States along with demographic and socioeconomic information. The National Center for Health Statistic (NCHS) at the CDC administered the survey and selected a representative sample of the US population based upon complex sampling procedure (for details, see https://www.cdc.gov/nchs/nhanes/participant.htm). Data are provided in 2-year cycles.

Starting in 1999, the NHANES asked females aged 12 and up "RHQ131: Has the survey participant ever been pregnant? Please include (current pregnancy,) live births, miscarriages, stillbirths, tubal pregnancies and abortions." Responses could be (1) yes, (2) no, (7) refused, (9) don't know, or (.) missing. Starting in 2007, the NHANES asked the question to females aged 9 and above, "IMQ040: Has the survey participant ever received one or more doses of the HPV vaccine?" Response choices were the same as for the pregnancy question. In 2015, the NCHS moved these questions to the National Health Interview Survey, an annual survey that is not directly compatible with NHANES. The years of study are therefore 2007—when NHANES first asked about HPV vaccine uptake—to 2014, the final year NHANES included the questions concerning pregnancy and HPV shots.

To analyze the data, the SURVEY FREQ and SURVEY LOGISTIC procedures from SAS Version 9.4 were used. The SURVEY FREQ procedure provided analysis of the relationship between exposure to the HPV vaccine and prevalence of having been pregnant. The SURVEY LOGISTIC procedure performed a multiple logistic regression on the data and determined whether the odds of having been pregnant (the response variable) were influenced by explanatory variables such as receiving the HPV shot. Following the NHANES tutorial at https://www.cdc.gov/nchs/tutorials/NHANES/NHANESAnalyses/LogisticRegression/Task2b_SAS92.htm, the vari-able SDMVSTRA was included to control for stra-tification when estimating the variance. To control for the clustering effect of observations, the vari-able SDMVPSU was used to identify the primary sampling unit. Since the response to the questionnaire varied among different groups, NHANES oversamples some groups of people. A weighting variable was included in the analysis to seek to

Table 1. Results from regressing birth rates per 1000 females in the United States aged 25–29 between 1995 and 2015 on a constant and time indicators: BR(t) = constant + constant × post-2006_DUMMY +TREND + TREND × post-2006_DUMMY, where constant = 1; post-2006_DUMMY = 1 if year of analysis was 2007–2015 and 0 if year of analysis was 1995–2006; and TREND = 1 if the observation was in the year 1995, 2 in the year 1996,..., 21 in the year 2015.

Variables	
Constant	106.91 (0.0000)
Constant × post-2006_DUMMY	29.31 (0.0000)
TREND	0.95 (0.0000)
TREND × post-2006_DUMMY *N*	−2.55 (0.0000)
Adj R^2	21 .8947

ensure that the sample reflects the US population. Since this study examined 8 years of data, the given weight in each 2-year database (WTINT2YR) was divided by 4.

The study compared women who received the HPV shot with those who did not. Matching the average age of the women in the vaccinated group with the average age of the women in the unvaccinated group is extremely important. Since the vaccine is relatively new and uptake is steadily increasing over time (Stokley et al. 2014), most of the women who have had the shot are relatively young. If the mean age at the time of the interview is significantly higher for the group of women who did not receive the HPV shot than the vaccinated group, the analysis would be comparing older women who were not exposed to the HPV vaccine with younger, vaccinated women. The older women would have a higher probability of being pregnant, precisely because they were older. The younger, vaccinated women would be less likely to ever have been pregnant, perhaps because of the vaccine, but also perhaps because of age.

Table 2 presents descriptive statistics of the data in this analysis according to vaccine status. The SURVEYMEANS procedure in SAS 9.4 was employed to determine the statistics. The dataset was restricted to observations that provided information for all response and explanatory variables. That is, observations that did not provide information on all the variables were dropped from any of the analysis. Table 2 reports that the mean age of the group of vaccinated as well as the unvaccinated women at the time of the interview was 27. The result of a *t*-test suggests that the difference between the two groups was statistically not significant.

Besides receiving the HPV shot, the analysis included other explanatory variables that might affect whether a female had ever been pregnant.

Table 2. Demographic and socioeconomic characteristics, NHANES 2007–2014, females aged 25–29.

	Total sample			Married, currently or formerly			Never married		
	HPV shot	No HPV shot	Difference	HPV shot	No HPV shot	Difference	HPV shot	No HPV shot	Difference
	n = 118	*n* = 582	(*p* Value)	*n* = 32	*n* = 272	(*p* Value)	*n* = 86	*n* = 310	(*p* Value)
Variable									
Age at interview									
Mean	27.006	26.996	.010	27.449	27.195	.253	26.806	26.781	.025
se of mean	.123	.079	(.947)	.268	.106	(.386)	.138	.110	(.886)
Ratio of family income to poverty									
Mean	3.173	2.739	.434	3.343	2.885	.458	3.096	2.581	**.514**
se of mean	.202	.093	(.053)	.355	.119	(.230)	.216	.136	(.047)
College graduate[a]									
Mean (%)	50.1%	34.3%	**15.8%**	51.2%	32.3%	18.9%	49.6%	36.5%	13.1%
se of mean	.062	.032	(.025)	.101	.034	(.086)	.071	.042	(.115)
Race/Ethnicity: NH White[a]									
Mean (%)	62.5%	64.0%	−1.5%	68.4%	69.6%	−1.2%	59.8%	58.1%	1.8%
se of mean	.051	.030	(.795)	.090	.035	(.905)	.061	.033	(.799)
Race/Ethnicity: Hispanic[a]									
Mean (%)	13.4%	17.2%	−3.8%	11.4%	18.1%	−6.7%	14.3%	16.2%	−1.9%
se of mean	.031	.018	(.297)	.046	.026	(.217)	.040	.016	(.659)
Race/Ethnicity: NH Black[a]									
Mean (%)	13.8%	10.8%	3.0%	14.0%	4.5%	9.4%	13.8%	17.7%	−3.9%
se of mean	.033	.014	(.400)	.051	.008	(.078)	.036	.024	(.370)
Race/Ethnicity: Other[a]									
Mean (%)	10.3%	7.9%	2.4%	6.2%	7.8%	−1.6%	12.1%	8.1%	4.0%
se of mean	.025	.012	(.400)	.046	.017	(.749)	.027	.013	(.184)
Height									
Mean	27.006	26.996	.010	27.449	27.195	.254	26.806	26.781	.025
se of mean	.123	.079	(.947)	.268	.106	(.385)	.138	.110	(.886)

[a]Variable is a dummy variable, where 1 indicates the attribute and 0 otherwise. The mean of this variable is the percentage of the sample that possesses the particular attribute.
Statistically significant results in **bold**.
se of mean: Standard error of mean.
Statistical significance determined by $\frac{(\text{mean}_1 - \text{mean}_2)}{\left(\text{sqrt}\left(se\text{ of mean}_1^2 + se\text{ of mean}_2^2\right)\right)}$.
NH: Non-Hispanic

These variables were age at the time of the interview (RIDAGEYR), ratio of family income to poverty (INDFMPIR), and educational level (DMDEDUC2). Race and ethnicity (RIDRETH1) were added as random controls. Observations where the response was "refused," "don't know," or "missing" were dropped from the analysis. The raw values of RIDAGEYR and INDFMPIR were used. The educational variable, DMDEDUC2, was recoded into a dummy variable that was 1 if the woman was a graduate of a 4-year college (DMDECUC2 = 5) and 0 if not (DMDECUC2 = 1, 2, 3, or 4). RIDRETH1 was recoded into four racial/ethnic groups—Hispanic, non-Hispanic black, non-Hispanic white, and other. The study included only females (RIAGENDR = 2), and subsets of the sample were analyzed according to the marital status (DMDMARTL) of the participant. If a female was married, widowed, divorced, or separated (responses 1, 2, 3, or 4), she was considered for this analysis to be "married, currently or formerly." Women who chose response 5 were considered to be "never married." The dichotomy is important, because most never-married women are probably seeking to avoid pregnancy, while married women probably want to have a child or children at some point.

Table 2 demonstrates that the group of vaccinated women was similar to those females who did not receive the HPV injection, with two exceptions. The differences in the means of most of the explanatory variables were not statistically significant. For the entire sample, there was no marked difference in age, ratio of family income to poverty, or ethnic/racial composition between the two groups (column 3). College attainment was higher for women who received the shot, but only for the entire sample. There was no marked difference in college attainment for the subsets of married women (column 6) and unmarried women (column 9). The ratio of family income to poverty was higher for never-married women who received the shot (3.1) than did not receive the shot (2.6). These differences are addressed in robustness checks of the model.

The sample included 700 females aged 25–29 between the years 2007 and 2014. Recall that NHANES selects survey participants strategically such that the survey reflects the US population. The sample of 700 females represented 7944,091 females. The subset of ever-married women included 304 survey participants who represented 3842,661 women; the subset of 396 never-married women represented 4091,429 women.

Results

Table 3 presents chi-square analysis and prevalence ratios of pregnancy of women who received at least one HPV shot compared with women who did not receive the HPV vaccine. Using the PROC SURVEYFREQ program in SAS 9.4, data demonstrate chi-square statistics for the 2 × 2 tables that report pregnancy prevalence according to vaccine status. Results for the entire sample as well as the subsets of ever-married women and never-married women were significant suggesting that the prevalence of having been pregnant was not independent of exposure to the HPV vaccine.

Using formulas from Medicalbiostatistics.Com (n.d.), calculations of prevalence ratios were made. Table 3 reports that for the entire sample, the difference in prevalence rate of having been pregnant between women who received the HPV shot (35.3%) and those who did not receive the vaccine (61.1%) was −25.8%. At the level of vaccine uptake reflected in this sample (16.7%), the lowered prevalence rate resulted in 341,654 (= −0.258 × the weighted frequency of 1325,396 women who received the shot) fewer women having been pregnant. If 100% of the females in this study had received the HPV shot, the number of women who would ever have been pregnant might have fallen by 2 million (= −0.258 × the weighted frequency of all 7934,091 women in the study).

For married women, the difference in prevalence of pregnancy between exposure to the HPV vaccine (50.1%) and unexposed group (76.9%) was −26.2%. If all the married women had received the HPV shot, the number of those women who had ever been pregnant would have diminished by 1 million (= −0.262 × 3842,662).

To analyze the dataset further, logistic regressions were utilized to determine the influence of the HPV vaccine on the probability of having been pregnant. Results are presented in Table 4. Results without covariates are shown in the first

Table 3. Prevalence ratios of ever having been pregnant for women who received an HPV shot versus women who did not.

	Total sample			Ever-married women			Never-married women		
	Ever pregnant			*Ever pregnant*			*Ever pregnant*		
HPV shot exposure	Yes	No	Total	Yes	No	Total	Yes	No	Total
Received HPV shot									
Frequency Weighted	52	66	118	21	11	32	31	55	86
frequency	467,579	857,817	1325,396	208,754	203,111	411,865	258,826	654,706	913,532
Percentage	5.9	10.8	16.7	5.4	5.3	10.7	6.3	16	22.3
Did not receive shot									
Frequency Weighted	387	195	582	221	51	272	166	144	310
frequency	4035,001	2573,694	6608,695	2637,592	793,205	3430,797	1397,409	1780,489	3177,898
Percentage	50.9	32.4	83.3	68.6	20.6	89.3	34.2	43.5	77.7
Total									
Frequency Weighted	439	261	700	242	62	304	197	199	396
frequency	4502,580	3431,511	7934,091	2846,346	996,316	3842,662	1656,235	2435,195	4091,430
Percentage	56.8	43.2	100.0	74.1	25.9	100.0	40.5	59.5	100.0
Rao-Scott Chi-square	**18.9012**			**6.3895**			**6.2913**		
$p >$ Chi-square	<0.0001			0.0115			0.0121		
Prevalence rate of ever being pregnant									
Received HPV shot	0.3528			0.5069			0.2833		
Did not receive HPV shot	0.6106			0.7688			0.4397		
Relative prevalence rate of ever being pregnant	0.5778			0.6593			0.6443		
Attributable prevalence rate of ever being pregnant	−0.2578			−0.2619			−0.1564		
Population attributable prevalence:									
At levels of vaccine uptake in sample	−341,654			−107,88			−142,879		
If 25% of population vaccinated	−511,303			7			−159,978		
If 50% of population vaccinated	−1022,605			−251,64			−319,956		
If 100% of population vaccinated	−2045,211			4			−639,912		
				−503,28					
				9					
				−1006,5					
				78					

Statistically significant results in **bold.**

row and suggest women who received at least one HPV shot were less likely to have ever been pregnant. For the entire sample, the odds ratio (OR) for women who received the shot to have ever been pregnant compared with those who did not receive the shot was .35 (CI = .211, .573). The middle three columns provide the results from the same analysis using the subset of 25-to-29-year-old females who were ever married that is women who were at the time of the interview currently married, widowed, divorced, or separated. The OR for married females aged 25–29 who received at least one HPV shot to ever have been pregnant compared with married females who did not receive the shot was .31 (95% confidence interval [CI] = .114, .84). The OR for never-married women (the last three columns) was .5 (CI = .296, .86).

Including covariates produced similar findings, with one exception. While results for the entire sample and for married women remained significant, findings for never-married women between receiving the HPV shot and having been pregnant were no longer significant.

Results for the other explanatory variables in the covariate analysis were expected. The older a female was at the time of the interview (age), the more likely she was ever to have been pregnant. Concerning income, Huber, Bookstein, and Fieder (2010) found that the higher a husband's income, the higher the number of children a woman has, but the higher her own income, the lower the number of offspring and increased probability of childlessness. Since the income variable used in this study measured relative household poverty, the higher the ratio, the more likely a woman was to be working. Therefore, the finding that the higher the ratio, the less likely a woman had ever been pregnant is consistent with previous observations. Huber, Bookstein, and Fieder (2010) also found that more highly educated females were less likely to have children, which this study also demonstrated. A woman who earned a 4-year college degree was less likely to

Table 4. Logistic regression on births of females aged 25–29 in the United States, NHANES 2007–2014.

	Full sample			Married, currently or formerly			Never married		
	OR	*p* Value	95% CI	OR	*p* Value	95% CI	OR	*p* Value	95% CI
Models without covariates									
Received HPV shot vs. did not receive HPV shot	**.348**	<.0001	{.211, .573}	**.309**	.022	{.114, .84}	**.504**	.013	{.296, .859}
Percent concordant	22.3			16.2			22.1		
Percent discordant	8.8			7.1			9.6		
Percent tied	68.9			76.7			68.3		
Models with covariates									
Received HPV shot vs. did not receive HPV shot	**.368**	.001	{.205, .661}	**.311**	.019	{.118, .821}	.610	.139	{.316, 1.18}
Age at interview (years)	**1.300**	.002	{1.103, 1.532}	**1.246**	.039	{1.012, 1.534}	1.133	.180	{.942, 1.363}
Ratio of family income to poverty	**.718**	<.0001	{.635, .812}	**.566**	.000	{.429, .748}	**.689**	<.0001	{.582, .816}
Hispanic vs. NH white	1.008	.977	{.590, 1.722}	.784	.576	{.329, 1.868}	1.303	.397	{.700, 2.427}
NH black vs. NH white	**1.961**	.018	{1.129, 3.408}	2.740	.259	{.466, 16.095}	**4.186**	<.0001	{2.270, 7.717}
Other race/ethnicity vs. NH white	1.252	.505	{.641, 2.443}	1.107	.862	{.327, 3.747}	**1.785**	.080	{.931, 3.424}
College graduate vs. not college graduate	**.240**	<.0001	{.149, .384}	**.430**	.030	{.201, .917}	**.120**	<.0001	{.056, .259}
Percent concordant	79.4			79.5			83.3		
Percent discordant	20.3			20.1			16.6		
Percent tied	.3			.4			.1		
Ever pregnant—No. of sample (= population represented)	439	(= 4502,580.2)		242	(= 2846,345.5)		197	(= 1656,234.7)	
Never pregnant—No. of sample (= population represented)	261	(= 3431,511.5)		62	(= 996,316.0)		199	(= 2435,195.5)	

Response variable: Ever pregnant.
Table reports odds ratios (OR), Scatterthwaite adjusted *F p* values, and 95% confidence intervals (CI). NH: Non-Hispanic. Statistically significant results in **bold**.

have ever been pregnant than one with less than a 4-year college education, regardless of marital status.

An indication of the strength of a logistic model is its ability to predict the response variable using the concordance of the model. The first step to determine concordance is to pair each event with each nonevent. In this study, the event is ever having been pregnant and the nonevent is never having been pregnant. As illustrated in column 1 of Table 4, the number of women who were ever pregnant was 439, and the number of those who were never pregnant was 261. Therefore, this dataset produced 114,579 (= 439 × 261) pairs. The model produces a probability for each element of the pair. If the predicted probability of the event is higher than the predicted probability of the nonevent—e.g., 0.9 for the event and 0.5 for the nonevent—the pair is said to be concordant. If the predicted probability is lower for the event than the nonevent (e.g., 0.7, 0.8), the pair is discordant. If the predicted probabilities for each element of the pair is the same (e.g., 0.6, 0.6), the pair is tied. The number of concordant (or discordant or tied) pairs is divided by the total number of pairs. The higher the % of concordant pairs, the stronger is the model.

As row 2 in Table 4 reports, the % of concordant pairs in the models using only the HPV vaccine as an explanatory variables were low, ranging from 16.2% to 22.3%. The % of concordant pairs for the models with more explanatory variables were higher, ranging from 79.4% to 83.3% (see row 12 in Table 4), suggesting these are relatively strong models.

To test whether these results were related to the number of HPV vaccine doses a woman received, the variable that indicated whether a woman received at least one shot was replaced with three variables to indicate the number of shots she received. If the participant received the HPV vaccine, NHANES included a follow-up question: "IMQ045: How many doses has the survey participant received?" Table 5 notes that the likelihood of pregnancy diminishes as the number of shots a woman receives increases. For the entire sample, the OR for women who received one shot was .41 (CI = .195, .862), while the OR for women who received three shots was .31 (CI = .147, .667) compared with those who did not receive the vaccine.

Table 5. Logistic regression on births of females aged 25–29 in the United States, NHANES 2007–2014, by number of HPV shots.

	Full sample			Married, currently or formerly			Never married		
	OR	*p* Value	95% CI	OR	*p* Value	95% CI	OR	*p* Value	95% CI
Model with covariates									
HPV vaccine—1 shot vs. 0 shots	**.410**	.020	{.195, .862}	.197	.070	{.034, 1.146}	.784	.513	{.373, 1.648}
HPV vaccine—2 shots vs. 0 shots	.344	.187	{.070, 1.699}	.467	.305	{.107, 2.039}	.551	.544	{.078, 3.895}
HPV vaccine—3 shots vs. 0 shots	**.313**	.003	{.147, .667}	.288	.051	{.082, 1.005}	.472	.106	{.189, 1.178}
Age at interview (years)	**1.303**	.002	{1.104, 1.536}	1.239	.040	{1.011, 1.518}	1.140	.168	{.944, 1.377}
Ratio of family income to poverty	**.722**	<.0001	{.640, .816}	**.570**	.000	{.430, .757}	**.701**	<.0001	{.594, .827}
Hispanic vs. NH white	1.019	.944	{.595, 1.746}	.802	.614	{.335, 1.922}	1.320	.384	{.700, 2.491}
NH black vs. NH white	**1.946**	.023	{1.101, 3.441}	2.824	.246	{.477, 16.708}	**4.068**	<.0001	{2.115, 7.824}
Other race/ethnicity vs. NH white	1.156	.679	{.576, 2.318}	.956	.943	{.266, 3.428}	1.747	.112	{.874, 3.492}
College graduate vs. not college graduate	**.247**	<.0001	{.154, .397}	**.434**	.040	{.196, .961}	**.124**	<.0001	{.057, .268}
Percent concordant	78.7			79.8			83.4		
Percent discordant	21.0			19.7			16.5		
Percent tied	.2			.5			.2		
Ever pregnant—No. of sample (= population represented)	433	(= 4439,674.1)		240	(= 2824,969.7)		193	(= 1614,704.5)	
Never pregnant—No. of sample (= population represented)	260	(= 3428,408.4)		62	(= 996,316.0)		198	(= 2432,092.4)	

Response variable: Ever pregnant.
Table reports odds ratios (OR), Scatterthwaite adjusted *F p* values, and 95% confidence intervals (CI). NH: Non-Hispanic. Statistically significant results in **bold**.

To test whether the model was appropriate for estimating the relationship between the response and explanatory variables, a control response variable was used. In this analysis, the response variable of having ever been pregnant was replaced with a dummy variable for height that is 1 if the person was above the average height (BMXHT) of the women in the sample (163.6 cm) and 0 if the person was below the sample's average height. Table 6 shows that the model predicted no marked relationship between height and pregnancy for the entire sample. Findings for the subsets of ever-married and never-married—not reported here, but available upon request from the author—were similar to the observations for the entire sample. These results suggest that the model was appropriate.

Additional robustness tests were performed when the socioeconomic characteristics differed between the group of women who received the HPV vaccine and those that did not. Recall from Table 2 that a greater % of women who received the HPV shot were college-educated than those who did not receive the shot. Table 7 reports that when the total sample was divided according to college attainment, the relationship between receiving the HPV shot and lowered pregnancy holds for both subsets of women. In the models with covariates, the OR of having been pregnant for college graduates who received the shot versus those who did not was .46 (CI = .240, .928); the OR for non-college graduates who received the shot versus those who did not was .33 (CI = .177, .611).

Table 2 also demonstrates that women who were never married and received the HPV shot tended to be wealthier than never-married women who did not receive the injection. Table 8 reports the findings when the never-married women were divided according to those who were above the average ratio of family income to poverty (INDFMPIR ≥ 2.696) and those who were below that average. Recall from Table 4 that for the model with covariates, never-married women demonstrated no marked relationship between receiving the HPV shot and having been pregnant. However, as Table 8 reveals, this finding holds only for never-married women below the mean ratio of family income to poverty. The OR of having been pregnant for women whose ratio of family income was above the average ratio and received the HPV vaccine versus those who did not receive the shot was .41 (CI = .194, .957).

Limitations

One common misperception regarding regression analysis is that it may be used to determine causality. Regressions demonstrate associations, not

Table 6. Logistic regression on births of females aged 25–29 in the United States, NHANES 2007–2014.

	Full sample		
	OR	*p* value	95% CI
Model without covariates			
Received HPV shot vs. did not receive HPV shot	.997	.989	{.618, 1.606}
Percent concordant	[a]		
Percent discordant	[a]		
Percent tied	[a]		
Model with covariates			
Received HPV shot vs. did not receive HPV shot	.965	.888	{.584, 1.596}
Age at interview (years)	1.066	.389	{.920, 1.236}
Ratio of family income to poverty	1.059	.425	{.918, 1.223}
Hispanic vs. NH white	**.198**	<.0001	{.124, .318}
NH black vs. NH white	1.004	.986	{.661, 1.525}
Other race/ethnicity vs. NH white	**.291**	<.0001	{.150, .564}
College graduate vs. not college graduate	.857	.571	{.498, 1.474}
Percent concordant	69.1		
Percent discordant	30.1		
Percent tied	.8		
Above average height—No. of sample (= population represented)	322	(= 4180,297.4)	
Below average height—No. of sample (= population represented)	375	(= 3724,247.1)	

Response variable: Above average height (BMXHT greater than or equal to 163.6 cm = 1; BMXHT less than 163.6 = 0).

[a]SAS 9.4 output reports "Measures of association between the observed and predicted values were not calculated because the predicted probabilities are indistinguishable when they are classified into intervals of length 0.002."

NH: Non-Hispanic. Statistically significant results in **bold**.
Table reports odds ratios (OR), Scatterthwaite adjusted *F p* values, and 95% confidence intervals (CI).

causations. Although the analysis presented here shows a relationship between vaccine injection and lowered probability of ever being pregnant for females aged 25–29, the conclusion that vaccines were the basis for reduced probability cannot be made. A second limitation of this analysis is that general probabilities do not imply individual results. That is, even if the probability of becoming pregnant decreased for the group of females who received the HPV vaccine relative to those who did not receive the shot, the findings do not imply that any given female who receives the shot might encounter difficulty conceiving a child. However, this investigation indicates that more analysis into the HPV shot and fertility is warranted.

Another limitation is determining the mechanism by which the HPV vaccine might affect fertility. As discussed in the introduction, Al in the vaccine might interfere with ovarian function and thereby reduce the ability to conceive. However, other factors may be involved that have not been identified. Lee (2012) found residual recombinant HPV DNA in vaccine samples from nine countries. It is possible that the DNA fragments negatively affected reproductive organs.

Discussion

Data demonstrated that women aged 25–29 who received the HPV injection were less likely to have ever been pregnant than those who did not receive the shot. The 16.7% uptake in the HPV vaccine for the sample was associated with 341,654 fewer women ever having conceived. The OR of having been pregnant for married women who received at least one HPV shot compared with married females who did not receive the shot was .31 (CI = .118, .821). The vaccine uptake for married women was 10.7% and associated with 107,887 fewer women ever having been pregnant. If all married women in the sample had been vaccinated with the HPV shot, data suggest that the number of married women having conceived may have fallen by 1 million.

For never-married women, the results in the model with covariates were not significant. The lack of a relationship between having been pregnant and receiving the HPV shot for the never-married women may be attributed to these females actively avoiding pregnancy. Using birth control would mask any negative effect of the HPV vaccine on fertility. The influence of HPV injection in fertility is probably more fully reflected in the group of married women who are more likely seeking to conceive than never-married women.

Results presented here differ from the findings of McInterney et al (2017), who examined exclusively women trying to conceive. Evaluating data from the Pregnancy Study Online (PRESTO), Mcinerney et al. (2017) found that vaccination against HPV did not markedly affect fecundability. The PRESTO database includes females aged 21–45 who volunteered to be participants in studies that investigated health and nutrition influences on the ability to become pregnant. However, the study on the influence of HPV vaccine uptake

Table 7. Logistic regression on births of females aged 25–29 in the United States, NHANES 2007–2014.

	Total sample					
	College graduate			Not a college graduate		
	OR	*p* Value	95% CI	OR	*p* Value	95% CI
Models without covariates						
Received HPV shot vs. did not receive HPV shot	**.443**	.019	{.226,.866}	**.358**	.004	{.182,.704}
Percent concordant	25.4			17.7		
Percent discordant	9.0			9.4		
Percent tied	65.5			73.0		
Models with covariates						
Received HPV shot vs. did not receive HPV shot	**.456**	.031	{.240, .928}	**.329**	.001	{.177, .611}
Age at interview (years)	**1.294**	.022	{1.041, 1.608}	**1.284**	.005	{1.082, 1.523}
Ratio of family income to poverty	**.877**	.048	{.770, .999}	**.633**	<.0001	{.534, .751}
Hispanic vs. NH white	.813	.650	{.324, 2.040}	1.013	.968	{.537, 1.909}
NH black vs. NH white	**2.671**	.024	{1.114, 4.217}	1.851	.111	{.865, 3.959}
Other race/ethnicity vs. NH white	1.541	.166	{.834, 2.849}	1.118	.846	{.356, 3.509}
Percent concordant	66.0			67.5		
Percent discordant	33.1			32.1		
Percent tied	.9			.4		
Ever pregnant—No. of sample (= population represented)	63	(= 868,341.2)		376	(= 3634,239.0)	
Never pregnant—No. of sample (= population represented)	151	(= 2061,544.0)		110	(= 1369,967.5)	

Response variable: Ever pregnant.

Statistically significant results in **bold**.
Table reports odds ratios (OR), Scatterthwaite adjusted *F p* values, and 95% confidence intervals (CI). NH: Non-Hispanic.

Table 8. Logistic regression on births of females aged 25–29 in the United States, NHANES 2007–2014.

	Never married					
	Below the average income			Above the average income		
	OR	*p* Value	95% CI	OR	*p* Value	95% CI
Models without covariates						
Received HPV shot vs. did not receive HPV shot	.672	.182	{.371,1.215}	**.409**	.026	{.189, .889}
Percent concordant	19.4			26.6		
Percent discordant	12.2			10.5		
Percent tied	68.4			62.8		
Models with covariates						
Received HPV shot vs. did not receive HPV shot	.826	.524	{.454, 1.505}	**.431**	.040	{.194, .957}
Age at interview (years)	**1.219**	.030	{1.020, 1.458}	1.059	.616	{.838, 1.339}
Hispanic vs. NH white	.871	.741	{.377, 2.013}	2.360	.051	{.996, 5.595}
NH black vs. NH white	**2.405**	.031	{1.086, 5.328}	**7.044**	<.0001	{2.652, 18.710}
Other race/ethnicity vs. NH white	1.316	.365	{.718, 2.413}	**2.433**	.010	{1.264, 4.683}
College graduate vs. not college graduate	**.037**	<.0001	{.014, .101}	**.234**	.001	{.105, .523}
Percent concordant	74.8			79.2		
Percent discordant	22.9			19.4		
Percent tied	2.3			1.4		
Ever pregnant—No. of sample (= population represented)	158	(= 1238.863.1)		39	(= 417,371.5)	
Never pregnant—No. of sample (= population represented)	91	(= 843,380.1)		108	(= 1591,815.4)	

Response variable: Ever pregnant.

Statistically significant results in **bold.**
Table reports odds ratios (OR), Scatterthwaite adjusted *F p* values, and 95% confidence intervals (CI). NH: Non-Hispanic.

Never-married women were divided according to whether they were above the average ratio of family income to poverty (INDFMPIR ≥ 2.696) or below the average.

might be comparing older, unvaccinated women with younger, vaccinated women. In one test, unvaccinated women whose mean age was 30.9 were compared with women who received the HPV vaccine before the age of 18. The average age of the latter group was 25.9. Biologically, younger women should be able to conceive more easily than the older ones (Bewley, Davies, and Braude 2005), but Mcinerney et al. (2017) noted that the fecundability rate was the same for both groups. A different result might emerge if investigators had restricted their analysis to participants aged 29 or below, as this study does. In addition, Mcinerney et al. (2017) failed to report the number

of vaccine doses the participant received. As our study shows, the larger the number of doses, the less likely a woman has ever been pregnant.

Perhaps aggregate birth rates are down due to increased rates of abortion. However, Jatlaoui et al. (2017) reported that for females aged 15–44, the absolute number of abortions, number of abortions per 1000, and number of abortions per 1000 live births all steadily declined between 2006 and 2014. Important for the current study, the possible influence of abortions was incorporated into the NHANES survey: Question RHQ131 asked females whether they had ever been pregnant and to "please include (current pregnancy,) live births, miscarriages, stillbirths, tubal pregnancies and abortions."

Perhaps enhanced use of contraception contributed to the falling US birth rates. However, Kavanaugh and Jerman (2018) found that the overall utilization of contraception by females aged 15–44 remained at approximately 60% between 2008 and 2014.

Although contraception rates have remained constant, perhaps birth rates were decreased, because birth control improved. Sundaram et al. (2017) confirm that overall contraceptive failure rates (CFR) declined between surveys taken in 2002 and 2006–2010 from 12% to 10%. This decline is particularly interesting, because CFR of most birth control methods were essentially unchanged between 1995 and 2002. Although overall failure rates fell from 14.9% in 1995 to 12.4% in 2002, that reduction was solely the result of the decline in failure rate of one birth control method, namely withdrawal, from 28% to 18%. The failure rates of all other methods remained steady during that time period.

While couples may be using birth control more effectively, the finding that the failure rates of several methods of birth control fell between 2002 and 2010 is also consistent with females being less fertile. If a sexually active female using a particular method of birth control does not conceive, the individual might credit her birth control with preventing pregnancy when in fact she is less able to become pregnant. This possibility needs to be explored, especially in light of the fact that the lowered birth rate occurred only after the widespread administration of the HPV vaccine.

Perhaps the recession that began in 2008 affected fertility negatively. Using data through 2012, Schneider (2015) noted that fertility fell during the Great Recession that (according to the National Bureau of Economic Research) lasted from 2008 to 2010. Schneider (2015) demonstrated the effect to be least among older women (aged 35–44) and concluded that the influence of recession on fertility was temporary. If the effect was temporary, the birth rate should climb substantially after the recession as the couples who postponed having children joined the younger couples who wanted to start families. Figure 2 illustrates

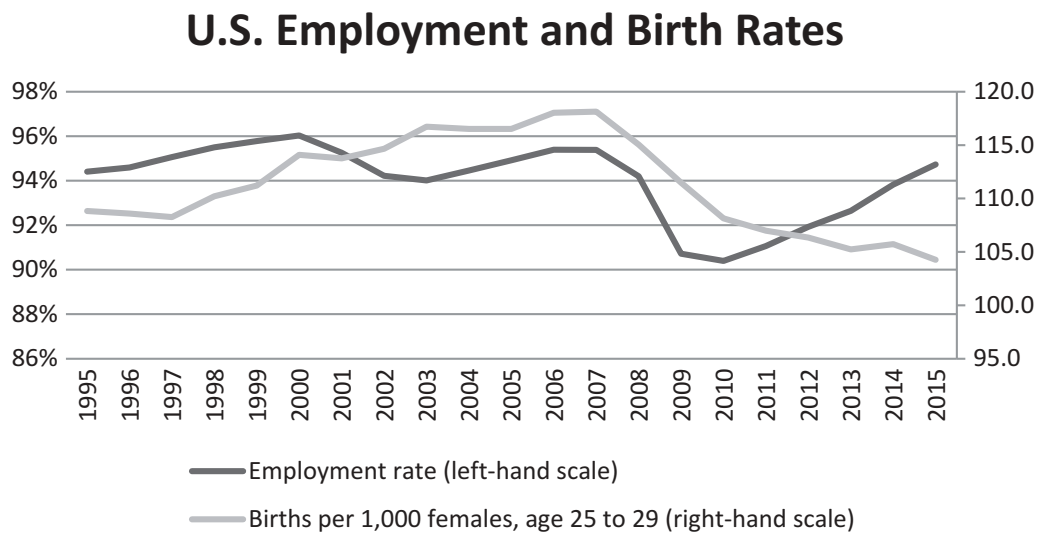

Figure 2. US employment rate and birth rates, 1995–2015.

that the US employment rates and birth rates tended to move together from 1995 to 2009. However, as employment rates recovered starting in 2010, birth rates continued a slow decline. The Pearson statistic, which measures correlation, was not significant from 1995 to 2015, indicating a lack of relationship between employment and birth rates.

Data suggest that at least part of the reason for the recent decline in US birth rates amongst females aged 25–29 may be associated with increasing injection of the HPV vaccine. Questions then arise regarding why the possible link was not found during the safety studies prior to licensing of the vaccine. Flaws in the pre-licensing investigations may have contributed to the lack of findings regarding any effect of the vaccine on reproductive ability of the recipients.

Little and Ward (2014) analyzed the safety studies of the HPV vaccine. In one safety study, over 50% of the girls enrolled were aged 9–12 years, too young to make observations of changes in menses. In another study, older girls were required to use contraception, again making effects of the vaccine on fertility difficult to gauge. Follow-up investigations tended to include only adverse events that occurred within 2 weeks of the administration of the vaccine. Although serious adverse events (SAE) were followed for up to 3 years after the vaccine, SAE did not include menstrual abnormalities. Little and Ward (2014) concluded that safety studies of HPV vaccine did not adequately address the question of ovarian health.

A further possible flaw in the safety investigations involves the placebo. The control groups in some of the clinical trials for HPV vaccines received solutions containing Al (Tomljenovic and Shaw 2013; Tomljenovic, Spinosa, and Shaw 2013) instead of the standard saline solution. The Al itself may produce side effects (Exley 2011) including damage to ovaries (Colafrancesco et al. 2013; Fu et al. 2014). Finding no marked differences in ovarian function between subjects who received the vaccine and those who received the Al-containing placebo might fail to determine adverse events attributed to Al. The vaccine may negatively affect ovarian function, perhaps through Al in the vaccine (Colafrancesco et al. 2013).

Future directions for research

Long-term studies of girls and women who receive the HPV vaccine are warranted. Specifically, investigations need to be undertaken into whether vaccine recipients experience any changes in their menses and ability to conceive. Care needs to be taken so that females taking the birth control pill (or any other intervention that interferes with menstrual cycles) are not included or at least examined separately. Such interventions mask the existence of POF.

Conclusions

Birth rates in the United States have recently fallen (Martin, Hamilton, and Osterman 2017). Data suggest that the HPV vaccine is associated with a lowered probability of having been pregnant. Several case studies link the HPV shot to POF suggesting one mechanism through which the vaccine affected fertility might involve ovarian damage. Other mechanisms through which the HPV shot might influence the probability of conceiving also exist.

This study analyzed survey data that represented nearly 8 million women aged 25–29 living in the United States between 2007 and 2014. Approximately 60% of women who did not receive the HPV vaccine had been pregnant at least once, whereas only 35% of women who were exposed to the vaccine had ever conceived. For married women, 75% of the group not exposed to the HPV vaccine conceived, while only 50% of the exposed group had been pregnant at least once. Results suggest if 100% of the females in this study had received the HPV shot, the number of women who had ever been pregnant would have fallen by 2 million. Logistic regression analysis revealed that females who received at least one HPV shot were less likely to have ever been pregnant than females who received no shots. The model controlled for age, relative wealth, college education, ethnicity, and race of the participant. Although safety studies of the HPV vaccine found no significant link to lowered fertility, the design of the investigations may have missed side effects. The results of this analysis suggest that more study into the influence of the HPV vaccine on fertility is warranted.

Conflict of Interest

The author filed a claim under the Vaccine Injury Compensation Program on behalf of her daughter. The Special Master dismissed the claim due to untimely filing. The claim did not include the HPV vaccine.

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