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Risk of Spontaneous Abortion After Inadvertent Human Papillomavirus Vaccination in Pregnancy

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Abstract

Objective—To evaluate the risk of spontaneous abortion after quadrivalent human papillomavirus (4vHPV) vaccination before and during pregnancy across seven integrated health systems within the Vaccine Safety Datalink.

Methods—Within a retrospective observational cohort, we compared risks for spontaneous abortion after 4vHPV in three exposure windows: distal (16–22 weeks prior to last menstrual period (LMP)), peripregnancy (within 6 weeks prior to LMP) and during pregnancy (LMP through 19 weeks of gestation). Women 12–27 years of age with a pregnancy between 2008 and 2014, with continuous insurance enrollment 8 months prior to and through pregnancy end, and with a

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live birth, stillbirth, or spontaneous abortion were included. Pregnancies were identified through validated algorithms. Spontaneous abortions and stillbirths were verified via chart review, with spontaneous abortions adjudicated by clinical experts. We excluded multiple gestations, spontaneous abortions before 6 weeks of gestation, and women using medications increasing risk for spontaneous abortion. Spontaneous abortion risk after 4vHPV during pregnancy was compared to distal vaccination using time dependent covariate Cox models. Spontaneous abortion risk for peri-pregnancy versus distal vaccination was evaluated with standard Cox models.

Results—We identified 2,800 pregnancies with 4vHPV exposure in specified risk windows: 919 (33%) distal, 986 (35%) peripregnancy and 895 (32%) during pregnancy. Mean age was 22.4 years in distal and peripregnancy groups versus 21.4 years among women vaccinated during pregnancy. Among women with distal 4vHPV exposure, 96 (10.4%) experienced a spontaneous abortion. For peripregnancy and during pregnancy exposures, spontaneous abortions occurred in 110 (11.2%) and 77 (8.6%), respectively. The risk of spontaneous abortion was not increased among women who received 4vHPV during pregnancy (adjusted hazard ratio 1.10 (95% CI: 0.81–1.51)) or peripregnancy 1.07 (0.81–1.41).

Conclusion—Inadvertent 4vHPV exposure during or peripregnancy was not significantly associated with an increased risk for spontaneous abortion.

Introduction

Since 2006 the Advisory Committee on Immunization Practices (ACIP) has recommended the human papillomavirus (HPV) vaccine for routine administration in girls ages 11–12 years, with catch up vaccination for women through age 26.¹ There are currently three HPV vaccine formulations, the bivalent HPV, quadrivalent HPV (4vHPV), and nonavalent, targeting an increasing number of HPV subtypes. In the United States, 4vHPV was the primary vaccine administered until the 2015 licensure of the nonavalent one. Despite suboptimal coverage during adolescence, HPV vaccination has been associated with significant population level decreases in HPV prevalence.^{2–4}

Pregnancy is listed as a precaution for HPV vaccination.^{1,5} As approximately 10% of women 18–26 years of age experience pregnancy each year,⁶ and routine pregnancy testing before vaccination is not advised, inadvertent vaccination during pregnancy does occur. To date, data on HPV vaccine exposures during or around the time of pregnancy have not raised concerns.^{7–11} Using automated data from the Vaccine Safety Datalink, our group previously reported inadvertent 4vHPV vaccination during pregnancy or periconception occurred in 1.5% of pregnancies among women ages 13–27; these exposures were not associated with adverse maternal or infant outcomes including preeclampsia, gestational diabetes, preterm birth, small-for gestational age and birth defects.¹²

Prior studies on HPV vaccination and risks for fetal demise have been limited by small numbers,^{10,13} lack of a comparison group,⁹ or inability to conduct detailed case adjudication.⁷ Goals of the current study were to evaluate risks for spontaneous abortion after 4vHPV vaccination during pregnancy or peri-pregnancy within the Vaccine Safety Datalink.

Materials and Methods

This retrospective, observational cohort study was conducted within the Vaccine Safety Datalink. The Vaccine Safety Datalink is a collaborative effort between the Centers for Disease Control and Prevention's Immunization Safety Office and several large integrated healthcare systems to monitor the safety of vaccines and conduct studies about rare and serious adverse events after immunizations administered within the United States¹⁴

Data for this study came from the seven Vaccine Safety Datalink sites (Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Northwest, Kaiser Permanente Washington, Kaiser Permanente Colorado, Marshfield Clinic, and HealthPartners) with available data files. Adolescent and young women ages 12–27, who had pregnancies ending between January 2008 and November 19, 2014, were identified based on claims, electronic health and birth records using a validated algorithm.¹⁵

Continuous insurance coverage for the period starting 8 months prior to the last menstrual period (LMP) through the end of pregnancy was required. To be included in the final cohort for analysis, at least one dose of 4vHPV had to be administered at a Vaccine Safety Datalink site during a pre-specified risk window: distal (16–22 weeks prior to LMP), peri-pregnancy (the 42 days prior to LMP) and during pregnancy (LMP through 19 weeks of gestation) (Figure 1). Risk windows were chosen based on review of existing literature^{7,10,16} and potential for biologic plausibility, allowing for a washout period between the peri- and during pregnancy risk windows and the distal comparison, the control period. In order to accommodate data availability and to reduce the number of charts for review, eligible dates for HPV administration varied by site. For HealthPartners all 4vHPV doses were administered from January 1, 2008–December 31, 2012, for Kaiser Southern California all 4vHPV doses were administered from January 1, 2012–December 31, 2013, while at the remaining Vaccine Safety Datalink sites, 4vHPV doses were administered from January 1, 2008–December 31, 2013. Vaccines were identified from standardized Vaccine Safety Datalink files and based on claims, electronic health records (EHR) and immunization registry data.

Pregnancy outcomes were initially identified through the previously described and validated pregnancy algorithm.¹⁵ This algorithm assigns gestational age for live births based on birth records. For spontaneous abortions and stillbirths, as there are no birth records, the algorithm assigns a default gestational ages of 10 weeks and 28 weeks, respectively. In a second step, spontaneous abortion and stillbirth outcomes were confirmed through medical chart review and the algorithm-assigned gestational ages were replaced by more accurate values based on the date of LMP and the estimated date of delivery (EDD) obtained from manual chart review. Cases classified through the automated algorithm as “unknown abortion” (UAB) also underwent chart review to identify additional spontaneous abortions. Consistent with prior studies, spontaneous abortions occurring before 6 weeks of gestation were excluded as these are often difficult to confirm and many of these early pregnancy losses are unrecognized.¹⁷ The following pregnancy outcomes were also excluded: therapeutic abortions, ectopic pregnancies, gestational trophoblastic disease, and multiple gestations. In addition, women with pharmacy dispensings or claims for medications increasing risk for spontaneous abortion, starting 6 months prior to pregnancy and through

end of pregnancy were excluded (Table 1). The final cohort consisted of women with spontaneous abortions occurring between 6 and less than 20 weeks of gestation, stillbirths occurring between 20–43 weeks, and live births.

Chart reviews were conducted by trained chart abstractors at all Vaccine Safety Datalink sites with data entered into Research Electronic Data Capture (REDCap).¹⁸ Data collected included LMP, EDD, urine or serum human chorionic gonadotropin levels (HCG), onset of spontaneous abortion symptoms, ultrasound results and pathology results. As described above, all spontaneous abortions, UABs and stillbirths were initially identified using the pregnancy algorithm and assigned a default gestational age at fetal demise; however, more precise classification of 4vHPV into the three exposure windows was determined once more accurate clinical data were available. Based on the adjudication results and verified EDD or LMP dates, eligible pregnancies were selected in each of the three eligible exposure windows. To start, using a wide exposure window, those with one or more doses of 4vHPV administered up to 29 weeks before the algorithm assigned pregnancy start or LMP, through the end of pregnancy underwent chart review. Based on LMP and EDD data entered during chart review, pregnancy start and end dates were adjusted. Spontaneous abortions with 4vHPV exposures in *wide risk windows* (distal 24–14 weeks and peri-pregnancy 56 days to LMP) or for the period starting two weeks before and ending two weeks after the final risk windows underwent adjudication. Following adjudication, spontaneous abortions and stillbirths with 4vHPV exposures in the *final risk windows for analysis*, *distal* (16–22 weeks prior to LMP), *peri-pregnancy* (within 42 days prior to LMP) and *during pregnancy* (LMP through 19 weeks of gestation), were retained (Figure 1). Patients with more than one 4vHPV dose in an eligible exposure window were assigned an exposure window with “during pregnancy” exposures as highest priority and “distal vaccination” as lowest priority.

Spontaneous abortion outcomes were confirmed based on published criteria from the American College of Obstetrics and Gynecology.¹⁹ Gestational age at fetal demise was assigned based on reported symptomatology, LMP and EDD, ultrasound and pathology reports. Urine and serum HCG levels were also used to identify early spontaneous abortions and other pregnancy outcomes. All spontaneous abortions with ultrasound or pathology reports uploaded into REDCap underwent further case adjudication by two obstetrician investigators (HSL and SS) to confirm outcomes and assign gestational age at time of fetal demise.

Covariates, including demographics, pre-pregnancy maternal comorbidities (e.g., diabetes, hypertension, and systemic lupus erythematosus), maternal health care utilization (having one or more ambulatory visit and one or more inpatient visit in the year prior to pregnancy), 4vHPV dose number, and receipt of other vaccines before 20 weeks of gestation, and on the same day as peri- or during pregnancy 4vHPV administrations, were assessed through electronic health record and administrative data. Obesity and smoking were assessed through multiple sources including ICD-9 codes, EHR data (for live births) and chart review (for spontaneous abortions and stillbirths).

We first conducted descriptive analyses for the covariates listed above, comparing frequency distributions by exposure group. Spontaneous abortion risk after 4vHPV during pregnancy,

peri-pregnancy, and peri- or during pregnancy, was compared to distal vaccination, the control period, using time dependent covariate Cox regression models. This approach allowed us to account for both immortal time bias²⁰ and adjust for fixed and time dependent potential confounders. We also compared peri-or during pregnancy 4vHPV exposures when administered concomitantly with other vaccines, to distal vaccination using a time dependent covariate Cox regression model. In addition, we compared spontaneous abortion risk after 4vHPV peri-conception to distal vaccination using standard Cox regression models. Two models for each association were computed, the first one included maternal age as a fixed effect, and full adjusted models included as fixed effects maternal age, neighborhood poverty index based on Census geocode, healthcare utilization in the previous year of pregnancy, smoking, obesity (body mass index ≥ 30 kilogram/meter²), race, ethnicity, 4vHPV dose number (first, second or third), and site.

We also explored whether there was a period around the time of conception where an increased risk was observed. For these exploratory analyses, we limited the cohort to women receiving the 4vHPV from 42 days before LMP to 28 days after LMP and used a generalized additive model to fit a smooth curve. For women with 4vHPV exposure during pregnancy, we explored timing from vaccination to spontaneous abortion, by gestational week at vaccination. In additional exploratory analyses, we evaluated among vaccinations administered at greater than 4 weeks of gestation, whether there was an increased risk within 28 days after 4vHPV, when compared to distal vaccination. In final exploratory analyses we evaluated whether spontaneous abortion risks varied by dose number or with concomitant vaccination.

Our study was powered to detect hazard rate ratios of 1.37 or greater assuming 1000 women with 4vHPV exposure during pregnancy and 1,000 during distal vaccination, with 80% power at 0.05 significance level with a two-sided log rank test. This study was approved by the IRBs of all participating sites with a waiver of informed consent.

Results

Of 208,965 pregnancies in women aged 12–27 years, with continuous insurance enrollment from 8 months prior to pregnancy through pregnancy end, we identified 2,800 eligible pregnancies with 4vHPV exposure in the specified study risk windows; 919 distal (33%), 986 (35%) peri-pregnancy and 895 (32%) during pregnancy. Figure 2 shows the flowchart of inclusions and exclusions. For women vaccinated during pregnancy, the mean gestational age at vaccination was 3.6 weeks (standard deviation (SD) 3.7 weeks). Mean age was 22.4 years in the distal and peri-pregnancy groups versus 21.4 years among women vaccinated during pregnancy. Compared to distal vaccination, women receiving 4vHPV during pregnancy had later entry into prenatal care (14 weeks, SD 6.5 weeks vs 12 weeks, SD 5.1 weeks, $p < .001$) and were more likely to receive other vaccines during pregnancy and prior to 20 weeks of gestation (47% vs 24%). The most common other vaccines administered during pregnancy were influenza, meningococcal and the tetanus, diphtheria and acellular pertussis vaccine. See Table 2 for other baseline comparisons by 4vHPV exposure group.

Of 774 spontaneous abortions initially identified using the pregnancy algorithm with 4vHPV exposure *within 29 weeks of LMP or during pregnancy*, 528 were confirmed via chart review as a possible or probable spontaneous abortion (68% confirmation rate). In addition, 25 of 69 pregnancies with an “unknown abortion outcome” from the automated algorithm were confirmed by chart review as spontaneous abortions and 4 of 26 pregnancies identified with a stillbirth outcome based on the automated algorithm were confirmed by chart review as an spontaneous abortion occurring between 6–19 weeks of gestation. Of the 557 confirmed spontaneous abortions, 283 had a 4vHPV exposure in the final analysis risk windows and were retained in the cohort.

Among 919 women with distal 4vHPV exposure, 10.4% experienced a spontaneous abortion while unadjusted rates were 8.6% for vaccination during pregnancy and 11.2% for peri-pregnancy exposures (Table 3). In age-adjusted analyses, receipt of 4vHPV during or peri-pregnancy was not associated with increased risks for spontaneous abortion (age-adjusted hazard ratios (95% Confidence intervals) 1.04 (0.77–1.41) and 1.07 (0.82–1.41), respectively. In fully adjusted models adjusting for age, poverty level, health utilization before pregnancy, obesity, history of smoking and race, receipt of 4vHPV during or peri-pregnancy, was also not associated with increased risks for spontaneous abortion (fully adjusted hazard ratios 1.10 (0.81–1.51) and 1.07 (0.81–1.41), respectively). Results were similar for a combined exposure window (during or peri-pregnancy) as compared to distal vaccination, age-adjusted hazard ratio 1.13 (0.88–1.44) fully adjusted hazard ratio 1.16 (0.90–1.48).

Concomitant vaccination or receipt of one or more additional vaccines on the same days as 4vHPV peri-pregnancy or during pregnancy did not increase the risk of spontaneous abortion, age-adjusted hazard ratio 1.05 (0.76–1.46), fully adjusted hazard ratio 1.09 (95% CI 0.78–1.54) as compared to distal vaccination. Receipt of a second or third 4vHPV dose peri-pregnancy or during pregnancy, as compared to a first dose, was also not associated with increased spontaneous abortion risk, age-adjusted hazard ratio 1.11 (0.83–1.48), fully adjusted hazard ratio 1.09 (95% CI 0.81–1.46). (Table 4). Exploratory analyses did not show an increased risk for spontaneous abortion cluster based on time from vaccination or gestational age at vaccination. (Figures 3 and 4). As shown in Figure 4, among women with a 4vHPV exposure during pregnancy and spontaneous abortion, the time from vaccination to spontaneous abortion varied by the gestational week at vaccination. Analyses restricted to spontaneous abortions occurring within 28 days of 4vHPV exposure, as compared to distal vaccination, did not demonstrate an increased risk, fully adjusted hazard ratio 0.93 (0.48–1.83).

Discussion

In this observational cohort study, we found no association between 4vHPV exposure during or peri-pregnancy and risk for spontaneous abortion. This study supports current clinical practice, where pregnancy testing is not routinely performed prior to vaccination.

Findings from our study are consistent with data from pre-licensure clinical trials and post-licensure safety assessments.²¹ In the 4vHPV pre-licensure clinical trials, approximately

15% of subjects became pregnant.²² However, only 6% of these pregnancies were within 30 days of vaccination. In this subgroup (n=266), rates for spontaneous abortion were 18.2% in women vaccinated with 4vHPV and 21% in the placebo group. Using data from the 4vHPV manufacturer sponsored pregnancy registry, including 216 exposures within 30 days of LMP and 1060 exposures during first trimester, Goss et al. reported spontaneous abortion rates to be 4.2% and 6.6%, respectively.¹⁶ More recently, Scheller and colleagues used registry data from Denmark including 463 pregnancies with 4vHPV exposures from 7–22 weeks of gestation and reported a hazard ratio of 0.71 (95% CI: 0.45–1.14). Our approach differed as we included vaccinations occurring before 7 weeks of gestation, along with peri-pregnancy exposures, while our outcomes were verifiable spontaneous abortions that occurred at 6 weeks of gestation or later.

Our study, which included 895 women with 4vHPV exposures during pregnancy and 986 peri-pregnancy exposures, adds to the literature regarding risks for spontaneous abortion after inadvertent vaccination. To date, the optimal risk window for evaluating of spontaneous abortion risk after vaccination is not known. The 4vHPV administrations that we captured were inadvertent and generally occurred early in pregnancy. Given that background spontaneous abortion rates peak early, at 6–7 weeks of gestation, and this period overlaps with inadvertent 4vHPV exposures, assessments of risk during pregnancy but within a specified risk window (eg, 28-days) would be prone to bias. Our exploratory evaluation of the time between 4vHPV and spontaneous abortion did not demonstrate a window with a statistically significant increased risk. Rather, any apparent clustering of spontaneous abortion by timing of vaccination was likely due to changes in background spontaneous abortion risk by gestational week.²¹

Some prior studies have suggested risk for spontaneous abortion after maternal vaccination may be increased with repeated antigen exposure. In post-marketing surveillance of bivalent HPV in the United Kingdom, receipt of 2 doses within a 4–5 week period was associated with increased risk (hazard ratio=2.55, 95% CI: 1.09–5.93).¹⁰ Similarly, in a case-control study by Donahue and colleagues, risks for spontaneous abortion were highest in women who received influenza vaccine containing A/H1N1pdm2009 (pH1N1) antigen in both the current and prior influenza seasons.²³ During the time of our study, 4vHPV was administered as a 3-dose vaccine series. We required 8 months of continuous enrollment prior to LMP. We may not have captured earlier vaccinations and thus could not be certain whether the dose identified in the current study was a first, second or third dose. Nevertheless, as compared to a first dose, receipt of a second or third 4vHPV dose peri-pregnancy or during pregnancy was not associated with increased risk for spontaneous abortion.

Additional limitations to this research should be noted. First, women vaccinated during pregnancy were most likely unaware that they were pregnant. Thus, they may have differed from women who were aware that they were pregnant in other ways that could impact spontaneous abortion risk. We were unable to assess use of cigarettes or alcohol during pregnancy in this population. Second, as with any observational study, there was potential for misclassification of exposure status. Uncertainty in LMP dating could impact whether an exposure was assigned as peri-pregnancy, during pregnancy, or distal, versus not eligible for

inclusion. For pregnancies ending in live birth, gestational age at delivery came primarily from birth records. For stillbirths and spontaneous abortions, gestational age was based upon chart review and expert adjudication. However, even with extensive review, in cases of spontaneous abortion, gestational age cannot always be confirmed and in these cases, estimates based on LMP were applied. Furthermore, the risk of spontaneous abortion after peri-pregnancy or during early pregnancy 4vHPV exposure may not be fully captured in our analysis, as spontaneous abortions before 6 weeks of gestation are often not clinically confirmed, and thus, for this study they were excluded.¹⁷ A final limitation that due to our sample size, we were not able to rule out small increases in risk.

In conclusion, inadvertent 4vHPV exposure during or peri-pregnancy was not associated with statistically significant increased risk for spontaneous abortion. In February 2015, the nonavalent HPV vaccination, targeting 5 additional oncogenic HPV strains, was recommended by ACIP to be incorporated as part of existing HPV vaccine recommendations.⁵ Therefore, in future work we will evaluate spontaneous abortion risk after inadvertent exposures with this new vaccine.

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Figure 1. Exposure windows for analysis, for quadrivalent human papillomavirus vaccine (4vHPV), distal, peripregnancy, and during pregnancy. LMP, last menstrual period.

Figure 2.

Flow chart of pregnancies and final cohort across seven Vaccine Safety Datalink sites. *Not mutually exclusive. †Dates for quadrivalent human papillomavirus vaccine (4vHPV) administrations varied by site: HealthPartners 2008–2012, Kaiser Southern California 2012–2013, other Vaccine Safety Datalink sites 2008–2013. ‡Wide risk windows: distal 24–14 weeks and peripregnancy 56 days to last menstrual period (LMP), during pregnancy LMP to 19 weeks of gestation. §Medications excluded if dispensed 6 months prior to last menstrual period through end of pregnancy: prostaglandin analogs, vitamin A analogs, selected immunosuppressants (mycophenolate mofetil, methotrexate, azathioprine, thalidomide), selected anticonvulsants (carbamazepine, phenytoin, phenobarbital, primidone, topiramate, valproic acid), amiodarone, warfarin, and lithium. ¶4vHPV exposure windows for analysis: distal 22–16 weeks before last menstrual period, peripregnancy 42 days before LMP until LMP, during pregnancy LMP to 19 weeks of gestation.

Figure 3.

Smoothing spline model component for spontaneous abortion by gestational week for peripregnancy and early during pregnancy of quadrivalent human papillomavirus vaccine (4vHPV) exposure. Analysis of deviance for spline of gestational week at 4vHPV $\chi^2=5.13$, degrees of freedom=2, $P=.08$. The y-axis represents gestational week when 4vHPV administered. Last menstrual period is 0 weeks of gestation.

Figure 4.

Kernel density plot of weeks from quadrivalent human papillomavirus vaccine (4vHPV) to spontaneous abortion according to gestational week at 4vHPV exposure, among women with exposures during pregnancy. Timing from 4vHPV to spontaneous abortion varies by gestational week of vaccination, likely due to two factors. First spontaneous abortions at <6 weeks of gestation were not included. Thus, for vaccination at 0–2 weeks of gestation, 4 weeks of gestation was the earliest interval that a spontaneous abortion could occur. Secondly, background risk for spontaneous abortion is highest at 6–7 weeks of gestation and decreases each week thereafter.

Table 1

List of medications associated with increased risk for spontaneous abortion, directly or through teratogenic effects.

Drug Class	Drug Name
Prostaglandin Analog	Mifepristone
Prostaglandin Analog	Carboprost
Prostaglandin Analog	Sulprostone
Prostaglandin Analog	Gemeprost
Prostaglandin Analog	Misoprostol
Immunosuppressant	Methotrexate
Vitamin A Analog	Isotretinoin
Vitamin A Analog	Bexarotene
Vitamin A analog	Acitretin
Immunosuppressant	Mycophenolate Mofetil
Immunosuppressant	Azathioprine
Immunosuppressant	Thalidomide
Anticoagulant	Warfarin
Mood Stabilizer	Lithium
Antiarrhythmic	Amiodarone
Antiarrhythmic	Dronedarone
Anticonvulsant	Carbamazepine
Anticonvulsant	Fosphenytoin
Anticonvulsant	Mephobarbital
Anticonvulsant	Phenobarbital
Anticonvulsant	Phenytoin (phenytoin sodium)
Anticonvulsant	Primidone
Anticonvulsant	Topiramate
Anticonvulsant	Valproic Acid and derivatives (valproate sodium, divalproex)

Table 2

Baseline characteristics of cohort, by quadrivalent human papillomavirus vaccine final analysis exposure groups¹.

	Quadrivalent HPV Vaccination in distal period (Control)	Quadrivalent HPV peri-pregnancy	Quadrivalent HPV during pregnancy
	N=919	N=986	N=895
Maternal age mean $\pm$ SD in years	22.4 $\pm$ 3.4	22.4 $\pm$ 3.4	21.4 $\pm$ 3.6
Maternal age group			
12–14 years	3 (<1%)	4 (<1%)	14 (2%)
15–19 years	239 (26%)	229 (23%)	304 (34%)
20–24 years	358 (39%)	417 (42%)	354 (39%)
25–27 years	319 (35%)	336 (34%)	223 (25%)
Maternal race and ethnicity			
Asian	59 (6%)	50 (5%)	42 (5%)
African American, non-Hispanic	118 (13%)	150 (15%)	154 (17%)
Hispanic	454 (49%)	529 (54%)	434 (48%)
White, non-Hispanic	255 (28%)	222 (22%)	223 (25%)
Other or not available	33 (4%)	25 (4%)	42 (5%)
Prenatal Care	864 (94%)	925 (94%)	841 (94%)
Gestational week at first prenatal visit $\pm$ SD	12 $\pm$ 5.1	12 $\pm$ 5.0	14 $\pm$ 6.5
Quadrivalent HPV dose			
First	450 (49%)	490 (50%)	433 (48%)
Second	308 (33%)	308 (31%)	312 (35%)
Third	161 (18%)	188 (19%)	150 (17%)
Receipt of other vaccines during pregnancy ²	224 (24%)	209 (21%)	422 (47%)
Receipt of concomitant vaccines peri- and during pregnancy	--	293 (30%)	326 (36%)
History of ever Smoking ³	244 (27%)	233 (24%)	224 (25%)
Obesity ⁴	269 (29%)	306 (31%)	231 (26%)
Pre-pregnancy Diabetes	4 (<1%)	4 (<1%)	7 (1%)
Pre-pregnancy Hypertension	13 (2%)	16 (2%)	13 (2%)
Systemic Lupus Erythematosus	0 (0%)	1 (<1%)	1 (<1%)
Poverty ⁵ mean $\pm$ SD	23 $\pm$ 15	24 $\pm$ 15	24 $\pm$ 15

¹ Quadrivalent HPV final analysis exposure windows: *Distal* 22 to 16 weeks before last menstrual period (LMP),

Peri-pregnancy 42 days before LMP until LMP, *During Pregnancy* LMP to 19 weeks of gestation;

²Other vaccines were administered prior to 20 weeks of gestation and include: meningococcal, influenza, and acellular pertussis;

³Smoking assessed through electronic health record and chart review

⁴Obesity assessed through pre-pregnancy weight, diagnosis codes and chart review

⁵Percent in census tract at <150% federal poverty level

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Table 3

Risks for spontaneous abortion by quadrivalent human papillomavirus vaccine final analysis exposure groups.¹

Quadrivalent HPV final analysis exposure group	Spontaneous Abortion N (%)	Age adjusted Hazard Ratios ² 95%CI	Fully Adjusted Hazard Ratios ³ 95% CI
Distal (control)	96 (10.4)	ref	ref
Peri-pregnancy	110 (11.2)	1.07 (0.82–1.41)	1.07 (0.81–1.41)
During Pregnancy	77 (8.6)	1.04 (0.77–1.41)	1.10 (0.81–1.51)
Peri-pregnancy or during pregnancy	187 (9.9)	1.13(0.88–1.44)	1.16 (0.90–1.48)

¹Quadrivalent HPV final analysis exposure windows: *Distal* 22 to 16 weeks before last menstrual period (LMP),

Peri-pregnancy 42 days before LMP until LMP, *During Pregnancy* LMP to 19 weeks of gestation;

²Using quadrivalent HPV as a time dependent exposure in a Cox regression model, adjusted by age as age groups;

³Using quadrivalent HPV as a time dependent exposure in a Cox regression model, adjusted by age as age groups, poverty level, health utilization before pregnancy, obesity before pregnancy, history of smoking, race, quadrivalent HPV dose number, and site;

Table 4

Risks for spontaneous abortion with receipt of quadrivalent human papillomavirus vaccine: exploratory analyses by exposure group, concomitant vaccination and dose number

Quadrivalent HPV exploratory analyses, contrasts ¹	Number of pregnancies	Spontaneous Abortion N (%)	Age adjusted Hazard Ratios ² 95%CI	Fully Adjusted Hazard Ratios ³ 95% CI
Quadrivalent HPV peri-pregnancy or during pregnancy with <u>concomitant vaccination</u> ⁴ <i>versus</i> Quadrivalent HPV peri-pregnancy or during pregnancy <u>alone</u>	619 1262	56 (9.0) 131 (10.4)	0.91 (0.66–1.24)	0.92(0.67–1.28)
Quadrivalent HPV peri-pregnancy or during pregnancy <u>with concomitant vaccination</u> <i>versus</i> quadrivalent HPV distal	619 919	56 (9.0) 131 (10.4)	1.05 (0.76–1.46)	1.09(0.78–1.54)
Quadrivalent HPV peri-pregnancy or during pregnancy <u>with second or third dose</u> <i>versus</i> quadrivalent HPV peri-pregnancy or during pregnancy with <u>first dose</u>	958 923	98 (10.2) 89 (9.6)	1.11 (.83–1.48)	1.09(0.81–1.46)
4vHPVQuadrivalent HPV peri-pregnancy or during pregnancy with second or third dose <i>versus</i> 4vHPVquadrivalent HPV distal	958 919	98 (10.2) 96 (10.4)	1.18 (0.89–1.57)	1.20(0.91–1.59)

¹Timing of 4vHPV for contrasts: *Distal* 22 to 16 weeks before last menstrual period (LMP), *Peri-pregnancy* 42 days before LMP until LMP, *During Pregnancy* LMP to 19 weeks of gestation;

²Using quadrivalent HPV as a time dependent exposure in a Cox regression model, adjusted by age as age groups,

³Using quadrivalent HPV as a time dependent exposure in a Cox regression model, adjusted by age as age groups, poverty level, health utilization before pregnancy, obesity before pregnancy, history of smoking, race, quadrivalent HPV dose number, and site;

⁴Concomitant vaccines, administered the same day as 4vHPV for peri- and during pregnancy