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Risk of spontaneous abortion and other pregnancy outcomes in 15–25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom

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ABSTRACT

Background: We assessed the risk of spontaneous abortion (SA) after inadvertent exposure to HPV-16/18-vaccine during pregnancy using an observational cohort design.
Methods: The study population included women aged 15–25 years registered with the Clinical Practice Research Datalink General Practice OnLine Database in the United Kingdom (UK), who received at least one HPV-16/18-vaccine dose between 1st September 2008 and 30th June 2011. Exposed women had the first day of gestation between 30 days before and 45 days (90 days for the extended exposure period) after any HPV-16/18-vaccine dose. Non-exposed women had the first day of gestation 120 days–18 months after the last dose. SA defined as foetal loss between weeks 1 and 23 of gestation (UK definition).
Results: The frequency of SA was 11.6% (among 207 exposed) and 9.0% (632 non-exposed), women: hazard ratio (HR) adjusted for age at first day of gestation 1.30 (95% confidence interval: 0.79–2.12). Sensitivity analysis per number of doses administered (−30 to +45-day risk period) showed a HR for SA of 1.11 (0.64–1.91) for 18/178 women with one dose during the risk period versus 2.55 (1.09–5.93) in 6/29 women with two doses within a 4–5 weeks period. The proportion of pre-term/full-term/postterm deliveries, small/large for gestational age infants, and birth defects was not significantly different between exposed and non-exposed women. Results were consistent using a (United States) SA definition of foetal loss between weeks 1–19 and/or the extended risk period.
Conclusion: There was no evidence of an increased risk of SA and other adverse pregnancy outcomes in young women inadvertently HPV-16/18-vaccinated around gestation. Nevertheless, women who are pregnant or trying to become pregnant are advised to postpone vaccination until completion of pregnancy.

1. Introduction

Cervarix™ (Human papillomavirus [HPV]-16/18-vaccine, GSK Vaccines) contains HPV-16 and HPV-18 virus-like particles formulated with the proprietary Adjuvant System, AS04. HPV-16/18-vaccine is indicated for girls and women from 9 years of age onwards, for the prevention of persistent infection, pre-cancerous lesions, and cervical and other genital cancers caused by oncogenic HPV.

Unintended exposure to HPV-16/18-vaccine prior to the onset of pregnancy or during pregnancy is possible in the population recommended for vaccination, and unplanned pregnancies and their outcomes were closely monitored in clinical trials. A pooled analysis of pre-licensure clinical trial data suggested a numerical imbalance in spontaneous abortion (SA) among young women 15–25 years of age when the first day of the last menstrual period

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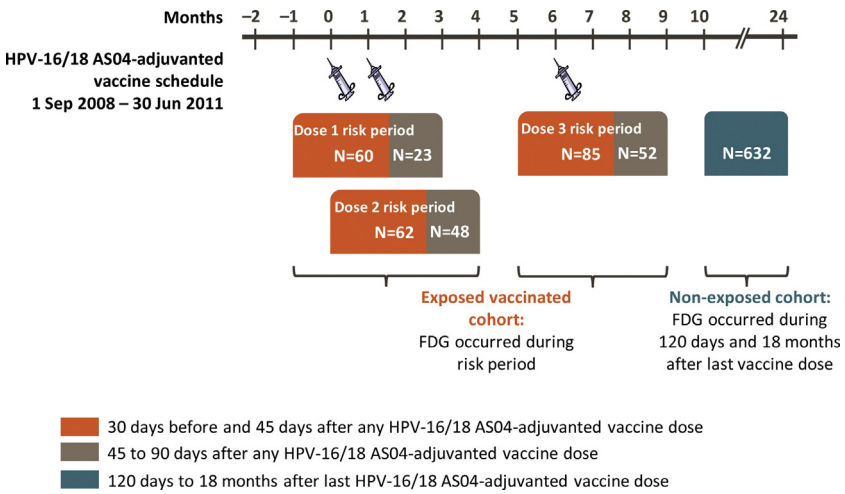

Fig. 1. Number of subjects identified as exposed or non-exposed according to time of the first day of gestation in relation to HPV-16/18 vaccination. FDG = first day of gestation.

(LMP) occurred between 30 days before and 45 days after (−30 to +45) any dose of HPV-16/18-vaccine (11.0%) versus controls who received hepatitis A vaccine (5.8%) [1]. The Center for Biologics Evaluation and Research in the United States (US) requested that GSK conduct a post-licensure analytic epidemiological study to investigate these findings further [2].

An independent analysis of two studies of HPV-16/18-vaccine concluded that an increased SA risk among pregnancies conceived within 3 months of vaccination could not be completely ruled out [3]. Post-licensure surveillance data indicate that pregnancy outcomes including SA in pregnant women who were inadvertently vaccinated with HPV-16/18-vaccine were in line with published literature in unvaccinated populations [4].

After a feasibility assessment (see web material), we assessed the risk of SA within a cohort of vaccinated women and compare pregnancies exposed around gestation to a non-exposed cohort of pregnancies using the Clinical Practice Research Datalink General Practice OnLine Database (CRPD GOLD) in the United Kingdom (UK). The HPV immunisation programme between the 2008 and 2010 school years, achieved a HPV-16/18-vaccine coverage of 89.0%, 87.6% and 83.8% for the first, second and third doses, respectively, by 2010/11 [5,6].

2. Methods

2.1. Data source, population and setting

CPRD GOLD is one of the largest anonymised primary care database, and captures longitudinal medical records including demographic and lifestyle parameters, clinical events, referrals to specialists and immunisation records from around 600 general practices [7]. Complementary information can be obtained through the free text data practice management system from CPRD GOLD [7]. Additionally, a mother–baby link allows linkage of medical records of women to those of offspring [8].

The study population included women aged 15–25 years registered in CPRD GOLD and with the first day of gestation available from the database between 1st September 2008 and 30th June 2011. Eligible women were to have received at least one dose of HPV-16/18-vaccine during the same period (see web material for CPRD GOLD HPV vaccination codes). Vaccinated women who received an unspecified HPV vaccine or *Gardasil*® (Merck & Co.) were excluded. Women in the non-exposed cohort who had a previous pregnancy included in the exposed cohort were also excluded. If multiple pregnancy episodes occurred during the study period, only the first pregnancy in the database was considered for the analysis.

The study protocol was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency database research [9]. No patient informed consent was needed because patient information in CPRD GOLD is fully anonymised. The study is registered at www.clinicaltrials.gov NCT01905462, EU PAS Register Number ENCEPP/SDPP/3310.

2.2. Study cohorts

Exposed and non-exposed cohorts were defined according to the first day of gestation, defined as the first day of LMP, or as the estimated date of delivery minus 280 days (equal to the median gestational age of 40 weeks), or as adjusted according to ultrasound dating, and exposure to HPV-16/18-vaccine as recorded in CPRD GOLD. Exposed women were those with first day of gestation between −30 and +45 days after any HPV-16/18-vaccine dose (an extended risk period −30 to +90 days after any HPV-16/18-vaccine dose was also considered) (Fig. 1). Non-exposed women were protocol-defined as having first day of gestation between 120 days to 18 months after the last HPV-16/18-vaccine dose, and had no further HPV-16/18-vaccine dose before the outcome (Fig. 1).

The analysis of SA excluded women who were not pregnant, or for whom the first day of gestation was outside the study period or not confirmed after medical record review. The analysis of other pregnancy outcomes, neonatal outcomes, and birth defects excluded women for whom the first day of gestation was not compatible with the confirmed outcome, or women whose pregnancy outcome was unknown.

2.3. Outcome definition

The primary study outcome was the occurrence of SA during weeks 1–23 of gestation (UK definition). Secondary outcomes included the occurrence of SA during weeks 1–19 of gestation (US definition) and the occurrence of other pregnancy outcomes: induced/therapeutic and other abortions, stillbirth (defined as intra-uterine death of foetus after 23 weeks gestation in the UK or after 19 weeks gestation in the US), birth defects, small (defined as ≤10th percentile for sex and age on birth weight or length) or large (≥90th percentile of normal weight or length) for gestational

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age at birth [10], pre/post-term delivery and infant death before age 12 weeks.

2.4. Data collection and case ascertainment

The final study database consisted of data extracted from CPRD GOLD (Supplementary Fig. 1). Pregnancy outcomes were identified using pre-defined algorithms (Supplementary Tables 1 and 2). Information extracted included demographic characteristics, obstetric history, lifestyle during pregnancy (smoking, alcohol consumption), medical conditions, vaccination records, and drug use during gestation. Specific de-identified free text associated with pregnancy endpoints, estimated date of delivery, ultrasound scan tests and birth details was requested for pregnancy endpoint confirmation. All subject profiles were reviewed by Pallas, Health Research and Consultancy B.V., the Netherlands.

A safety physician within GSK reviewed all pregnancy outcomes other than live, full-term deliveries of normal weight-for-gestation babies. Final case ascertainment was adjudicated by two independent external experts specialised in teratology who remained blinded with respect to the exposure status of the cases throughout the ascertainment process. Final ascertainment of cases of SA with a doubtful outcome, and all cases of therapeutic/other abortion, stillbirth, infant death and birth defect were reviewed by both experts. All other SA cases were reviewed by one expert, while the other expert reviewed a random sample of 10% of SA cases as a quality check (all decisions were in agreement with the classification made by Pallas). One expert reviewed all cases of unrealistically long pregnancy (more than 43 weeks gestation).

2.5. Statistical analysis

All statistical comparisons were made between the exposed and non-exposed cohorts. Demographic and baseline characteristics were compared using Fisher's exact test, Wilcoxon test or Cochran–Mantel–Haenszel test.

A Cox proportional hazards model that included the exposure status as a binary independent variable and the age at first day of gestation as a continuous covariate was used to estimate hazard ratios (HR) for SA. The dependent variable was the time between the first day of gestation and the event, or censoring (week 23 of gestation, date of induced/therapeutic abortion, date of maternal death, date of last available pregnancy data whichever occurred first). The aHR was derived as the exponential of the coefficient associated with the exposure status and its 95% Wald confidence interval (95% CI) was estimated.

A planned sensitivity analysis used a Cox proportional hazards model, which in addition to age at first day of gestation, included the following covariates when they occurred in ≥5% of subjects: smoking, alcohol consumption, gestation start during the H1N1 pandemic season, general practice region, diabetes and high blood pressure during pregnancy, number of previous pregnancies, vaccination with another vaccine from −90 to +90 days gestation, and use of contra-indicated drugs during the first trimester of gestation. Another planned exploratory sensitivity analysis used Cox proportional hazards models to assess the risk of SA according to the number of doses received during the risk period (1 dose-, 2 dose-exposed subcohorts) compared to the non-exposed cohort. Additional (post hoc) analyses assessed the number of doses and time of vaccination (before or after first day of gestation); the dose received (1st, 2nd, or 3rd dose) in the pre-defined risk period; and excluding subjects receiving the third dose during the risk period.

We used criteria posed by the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS, see supplement) to interpret the results [11].

Logistic regression models were used to compare other pregnancy outcomes with occurrence of the outcome as a binary dependent variable, the exposure status as a binary independent variable and the age at first day of gestation as a continuous covariate. The odds ratio and its 95% CI were derived. It should be noted that these adverse events were secondary endpoints and the study was not powered to detect pre-defined risks for these endpoints. There was no previous safety signal for any other adverse pregnancy outcome.

2.6. Sample size

Based on a feasibility assessment which estimated the number of potential eligible subjects and assuming a proportion of SA of 11.5% of pregnancies and that 20% of subjects would have incomplete 23-week gestation data, the study had 98% power to detect a relative risk (HR) of 2.0 of SA between the exposed and non-exposed cohorts subjects if the first day of gestation was −30 to +45 days after any dose of HPV-16/18-vaccine (two-sided log-rank test with type I error rate of 5%). The HR detectable with 80% power was 1.69.

3. Results

Of 161,849 HPV-vaccinated women in CPRD GOLD, 1046 (0.6%) met the inclusion criteria (see web material). Of these, 839 (962 for the extended risk period) were included in the primary analysis of SA: 207 (330) in the −30 to +45(+90) day exposed, and 632 in the non-exposed cohorts (Supplementary Fig. 1). The non-exposed cohort was approximately 6 months older than the exposed cohort ($p < 0.0001$), around 3 months younger at first vaccination dose ($p = 0.03$), had fewer pregnancy onsets during the H1N1 pandemic season (14.4% versus 36.2%, $p < 0.001$) and had fewer exposures to other vaccines within 3 months before first day of gestation (1.6% versus 4.8%, $p = 0.01$) (Table 1). The cohorts were similar in terms of general practice region, history of previous pregnancies and/or SA. Information about lifestyle and medical history, when available, indicated no differences between the cohorts (Table 1).

3.1. Pregnancy outcomes

3.1.1. Spontaneous abortion

Among 839 women in the primary analysis (Fig. 1), pregnancy outcome information was available in 87.0% ($n = 730$). SA occurred in 9.7% ($n = 81$): 11.6% ($n = 24$) in the exposed cohort and 9.0% ($n = 57$) in the non-exposed cohort. The mean gestational age at the time of SA was 78.4 days (range 48–142 days) in the exposed cohort and 73.7 days (range 34–134 days) in the non-exposed cohort.

The overall age-adjusted HR for SA in weeks 1–23 gestation in women with first day of gestation between −30 and +45 days after any HPV-16/18-vaccine dose was (1.30; 95% CI 0.79–2.12; $p = 0.30$) (Table 2, Fig. 2).

The HR adjusted for other covariates was similar to the main model (1.34, 95% CI: 0.81–2.24; $p = 0.25$). The model by number of doses received during the risk period showed that for subjects who received only 1 dose within the −45 to +30-day risk period ($n = 18/178$), there was no increase in SA risk (aHR 1.11, 95% CI 0.64–1.91; $p = 0.71$). For women who received two doses of HPV-16/18-vaccine within the −45 to +30-day risk period ($n = 6/29$), the aHR was 2.55 (95% CI: 1.09–5.93, $p = 0.03$) (Table 2).

The findings for the extended −30 to +90-day risk period were consistent with the main analysis (Supplementary Table 3). The findings for the analysis defining SA as occurring between weeks 1 and 19 gestation were also consistent with the main analysis for both risk periods (Supplementary Table 4).

Additional analyses were conducted in order to explore the observed increased risk of SA in women who had received two

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Table 1
Demographic characteristics of the exposed and non-exposed cohorts defined according to the first day of gestation (cohort for the analysis of spontaneous abortion, −30 to +45 day and −30 to +90 day risk periods).

Characteristic		Non-exposed, $N = 632$ n (%)	Exposed (−30 to +45 days), $N = 207$ n (%)	p-value	Exposed (−30 to +90 days), $N = 330$ n (%)	p-value
Age in years at first day of gestation	Mean (SD)	18.5 (1.18)	17.9 (1.13)	<0.0001	18.0 (1.18))	<0.0001
	Range	15.2–23.9	15.1–23.3	–	15.0–23.3	–
	9–15 year group	17 (2.7)	8 (3.9)	<0.0001	13 (3.9)	<0.0001
	16–18 year group	386 (61.1)	174 (84.1)	–	262 (79.4)	
	19–25 year group	229 (36.2)	25 (12.1)	–	55 (16.7)	
Age in years at first HPV-16/18 dose	Mean (SD)	17.30 (1.14)	17.54 (1.10)	0.027	17.6 (1.12)	<0.0001
	Range	14.23–23.47	14.58–23.23	–	14.3–23.2	
Region of residence	North England	137 (21.7)	37 (17.9)	0.71	56 (17.0)	0.35
	Midlands	96 (15.2)	33 (15.9)	–	57 (17.3)	
	South England	259 (41.0)	90 (43.5)	–	139 (42.1)	
	Ireland Scotland Wales	140 (22.2)	47 (22.7)	–	78 (23.6)	
Marital status	Single	105 (94.6)	37 (100)	0.01	55 (94.8)	0.02
	Married–Engaged-Co-habiting	6 (5.4)	0 (0.0)	–	3 (5.2)	
	Missing	521	170	–	272	
Number of previous pregnancies	0	164 (84.1)	78 (91.8)	0.33	116 (89.2)	0.46
	1	22 (11.3)	5 (5.9)	–	10 (7.7)	
	2	7 (3.6)	1 (1.2)	–	2 (1.5)	
	3+	2 (1.0)	1 (1.2)	–	2 (1.5)	
	Missing	437	122	–	200	
Number of previous abortions/stillbirths	0	181 (85.0)	84 (92.3)	0.15	127 (90.1)	0.27
	1	27 (12.7)	6 (6.6)	–	11 (7.8)	
	2	3 (1.4)	0 (0.0)	–	2 (1.4)	
	3+	2 (0.9)	1 (1.1)	–	1 (0.7)	
	Missing	419	116	–	189	
Smoking status during pregnancy	Smoker	45 (11.2)	20 (14.0)	0.37	31 (14.3)	0.30
	Missing	229	64	–	113	
Alcohol consumption during pregnancy	Yes	47 (29.0)	21 (32.3)	0.63	32 (30.5)	0.89
	Missing	470	142	–	225	
Diabetes during pregnancy	Yes/probable[a]	8 (15.4)	2 (10.0)	0.72	5 (17.2)	1.0
	Missing	580	187	–	301	
High blood pressure during pregnancy	Yes	37 (8.0)	15 (9.3)	0.62	21 (8.3)	0.89
	Missing	170	46	–	78	
First day of gestation during H1N1 pandemic	Before	3 (0.5)	50 (24.2)	<0.0001	65 (19.7)	<0.0001
	During	91 (14.4)	75 (36.2)		132 (40.0)	
	After	538 (85.1)	82 (39.6)		133 (40.3)	
Number of HPV-16/18-vaccine doses	1	83 (13.1)	32 (15.5)	0.14	49 (14.8)	0.07
	2	130 (20.6)	50 (24.2)	–	86 (26.1)	
	3	417 (66.0)	125 (60.4)	–	194 (58.8)	
	4	2 (0.3)	0 (0.0)	–	1 (0.3)	
Exposure to other vaccines	<3 mo before first day of gestation	10 (1.6)	10 (4.8)	0.015	24 (7.3)	<0.0001
Exposure to contraindicated drugs	Yes	215 (34.0)	74 (35.7)	0.67	119 (36.1)	0.57

N = number of subjects. p-value: Fisher exact test or Wilcoxon test, p-value for previous pregnancies, previous abortions and number of HPV vaccine doses are computed by Cochran–Mantel–Haenszel. n/% = number/percentage of subjects in a given category (unless otherwise specified). SD = Standard deviation.

[a] Diabetes in the Exposed and non-exposed −30 to +45 cohort: yes = 7 cases and probable = 3 cases. Diabetes in the exposed and non-exposed −30 to +90 cohort: yes = 10 cases and probable = 3 cases

doses of HPV-16/18 vaccine during the risk period. In women who received one HPV-16/18-vaccine dose during the −30 to +45-day risk period ($n = 178$), the Cox hazards proportional model did not show evidence of increased SA risk, regardless of dose number (first, second or third) or timing (before or after the first day of gestation) (Table 2 and Fig. 2).

For women who received two doses during the risk period ($n = 29$), the numbers were too small to explore different timings of exposure; for most women in whom one dose was administered before and one dose after the first day of gestation ($n = 23$ aHR 2.80, 95% CI: 1.11, 7.06; $p = 0.03$).

Considering the extended −30 to +90-day risk period, the highest frequency of SAs occurred when the time-interval between doses was 4–5 weeks (10/39, 26%) compared to an interval of longer than 5 weeks (1/20, 5%). The gestational age at SA was similar among the different cohorts and in subjects exposed to one or two doses within either risk period (data not shown).

Applying VAMPSS criteria, based on the HR and on the confidence intervals, the proposed interpretation of our study results are: "no evidence of risk" for the −30 to +45-day risk period and "evidence of relative safety" for the −30 to +90 risk period (for both the 1–23 and 1–19-week SA definitions) (Fig. 2). The difference between the two risk periods is mainly due to the width of the CI related to the number of subjects (207 versus 330) than a difference in the HR estimates (1.3/1.2). The results in a few women who received two doses during the risk period would be classified as showing "a positive association" whereas the results showed "evidence of relative safety" for one dose exposure (and similar results for the extended period).

3.1.2. Other pregnancy outcomes

There were seven stillbirths (0.8%), 1.4% ($n = 3$ at mean gestational age 185.7 days, range 162–204) in the exposed and 0.6% ($n = 4$, mean gestational age 180.3-days, range 162–190) in the non-exposed cohort. The proportion of pre-term, full-term and post-term deliveries appeared to be similar amongst the exposed and non-exposed cohorts (Table 3).

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Table 2
Cox proportion hazard analysis of SA during the first 23 weeks of gestation – age adjusted, and for other covariates (cohort for the analysis of spontaneous abortion, −30 to +45 day risk period).

Category	*N*	*n* (%)	Adjusted HR (95% CI)	*p*-value
Primary analysis (age adjusted)				
Total	839	81 (9.7)	–	–
Exposed	207	24 (11.6)	1.30 (0.79; 2.12)	0.30
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	1.00 (0.82; 1.20)	0.96
Sensitivity analyses (adjusted for age and number of doses within the risk period)				
1 dose	178	18 (10.1)	1.11 (0.64; 1.91)	0.71
2 doses	29	6 (20.7)	2.55 (1.09; 5.93)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.82; 1.19)	0.91
Sensitivity analyses (adjusted for age and covariates)				
Exposed	207	24 (11.6)	1.34 (0.81; 2.24)	0.25
Non-exposed	632	57 (9.0)	1.00	–
Alcohol consumption during pregnancy	68	10 (14.7)	1.79 (0.78; 4.09)	0.17
Smoking during pregnancy	65	4 (6.2)	0.55 (0.20; 1.53)	0.25
High blood pressure during pregnancy	52	3 (5.8)	0.56 (0.18; 1.81)	0.33
Vaccination 3 months before or after first day of gestation	67	6 (9.0)	0.84 (0.36; 1.95)	0.69
Exposure to H1N1 pandemic	166	15 (9.0)	0.88 (0.49; 1.58)	0.67
Contraindicated drugs during pregnancy	289	29 (10.0)	1.06 (0.61; 1.84)	0.85
Region				
Midlands	129	13 (10.1)	0.83 (0.41; 1.70)	0.62
South England	349	32 (9.2)	0.83 (0.47; 1.46)	0.52
Ireland–Scotland–Wales	187	16 (8.6)	0.74 (0.38; 1.43)	0.37
North England	174	20 (11.5)	1.000	
Age at first day of gestation (continuous)	–	–	0.98 (0.81; 1.19)	0.86
Post hoc analyses (adjusted for age and covariates)				
1 or 2 dose exposure according to first day of gestation				
1 dose before	102	10 (9.8)	1.09; (0.55; 2.15)	0.82
1 dose after	76	8 (10.5)	1.15; (0.54; 2.44)	0.71
2 doses before	6	1 (16.7)	1.78; (0.25; 12.87)	0.57
1 dose before and 1 after	23	5 (21.7)	2.80; (1.11; 7.06)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.82; 1.20)	0.95
Dose number (one dose)				
1st dose	52	5 (9.6)	1.10 (0.44; 2.80)	0.84
2nd dose	41	4 (9.8)	1.10 (0.39; 3.08)	0.86
3rd dose	85	9 (10.6)	1.14 (0.56; 2.32)	0.71
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	1.00 (0.82; 1.23)	0.97
Excluding women who received dose 3 only in the risk period				
1 dose	93	9 (9.7)	1.08 (0.52; 2.23)	0.83
2 doses	29	6 (20.7)	2.54 (1.09; 5.92)	0.03
Non-exposed	632	57 (9.0)	1.00	–
Age at first day of gestation (continuous)	–	–	0.99 (0.81; 1.20)	0.90

N = number of subjects in a given category. *n*/% = number of SAs. HR = hazard ratio with Wald 95% CI.

Table 3
Pregnancy outcomes in the exposed and non-exposed cohorts (cohort for the analysis of spontaneous abortion, −30 to +45 day and −30 to +90 day risk periods).

Outcome category	Exposed (−0 to +45), *N* = 207 *n* (%)	Exposed (−30 to +90), *N* = 330 *n* (%)	Non-exposed, *N* = 632 *n* (%)
Known confirmed outcome	182 (87.9)	227 (83.9)	548 (86.7)
Spontaneous abortion	24 (11.6)	34 (10.3)	57 (9.0)
Induced abortion	21 (10.1)	33 (10.0)	66 (10.4)
Therapeutic abortion	0 (0.0)	1 (0.3)	1 (0.2)
Other abortion	0 (0.0)	0 (0.0)	2 (0.3)
Stillbirth	3 (1.4)	3 (0.9)	4 (0.6)
Live births[a]	134 (73.6)	206 (74.4)	418 (76.3)
Pre-term delivery	6 (2.9)	16 (4.8)	27 (4.3)
Full-term delivery	109 (52.7)	167 (50.6)	349 (55.2)
Post-term delivery	19 (9.2)	23 (7.0)	42 (6.6)
At least one small for gestation	8 (6.0)	14 (6.8)	27 (6.5)
At least one large for gestation	1 (0.7)	4 (1.9)	14 (3.3)
Normal baby	64 (47.8)	88 (42.7)	186 (44.5)
Unknown for small/large for gestation	61 (45.5)	100 (48.5)	191 (45.7)
Unknown outcome	25 (12.1)	53 (16.1)	84 (13.3)

N = number of mothers. *n*/% = number/percentage of subjects in a given category. −30 to +45 day risk period.

[a] A total of five twin pregnancies resulted in three (full-term live births, one pre-term delivery and one stillbirth and one live pre-term birth from the same pregnancy). −30 to +90 day risk period: seven twin pregnancies among them one stillbirth and one pre-term live birth from the same pregnancy, four full-term pregnancies and two pre-terms pregnancies.

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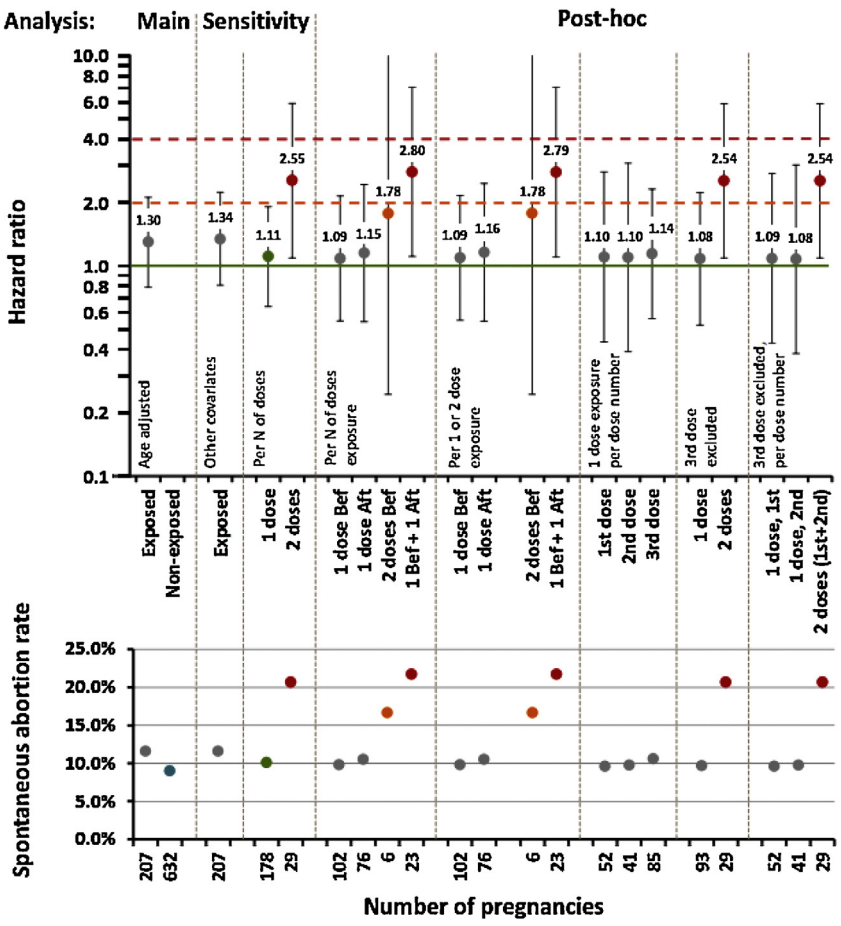

Fig. 2. Hazard ratios (HR) and spontaneous abortion (SA) rates for main, sensitivity and post-hoc analyses (-30/+45-day risk period) and interpreted using safety thresholds proposed by the Vaccines and Medications in Pregnancy Surveillance System [11].
The safety of any exposure cannot be considered absolute; estimates of safety reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. Grey circle: no evidence of increased risk of SA in the exposed cohort (HR not statistically significant and 95% confidence interval [CI] upper limit of HR ≤4); Olive circle: evidence of relative safety in terms of the risk of SA in the exposed cohort (HR not statistically significant and 95% CI upper limit of HR ≤2); Red circle: statistically significant increased risk of SA in the exposed cohort (for subjects receiving 2 doses during the risk period a positive association was defined, but this finding was based on 29 subjects included in the sensitivity analysis); Orange circle: no statistically significant increased risk, but the 95% upper limit of the HR ≥4; Green circle: non-exposed cohort; N = number; Bef = vaccine dose administered before last menstrual period; Aft = vaccine dose administered after FGD; error bars represent 95% Wald CI.

There were 557 babies born during the study period (51.4% male and 48.6% female). One minute Apgar scores were ≥8 in 89.7% and 91.3% of babies in each respective cohort.

Birth defects were confirmed in seven babies (5.9%, 7/136) from the exposed and 21 babies (6.0%, 21/421) from the non-exposed cohorts (Table 4). There were three neonatal deaths of which two were within 7 days of birth: one with an unspecified congenital abnormality and one with a thromboembolic disorder. The third death was due to sudden infant death syndrome 73 days after birth.

There was no evidence of a difference in the risk of other pregnancy outcomes between the exposed and unexposed populations for both risk periods (Supplementary Tables 5 and 6).

Table 4
Birth defects in the exposed and non-exposed cohorts (cohort for the analysis of other pregnancy outcomes −30 to +45 day and −30 to +90 day risk periods).

Characteristics	Categories	Exposed (−30 to +45), *N* = 136 *n* (%)	Exposed (−30 to +90), *N* = 210 *n* (%)	Non-exposed, *N* = 421 *n* (%)	Total, *N* = 557 *n* (%)
Birth defect	No	112 (94.1)	167 (94.9)	327 (93.4)	439 (93.6)
	Yes – confirmed	7 (5.9)	9 (5.1)	21 (6.0)	28 (6.0)
	Yes – unconfirmed[a]	0	0	2 (0.6)	2 (0.4)
	Missing	17	34	71	88
Classification[b]	At least one major birth defect	4 (57.1)	5 (55.6)	11 (52.4)	15 (53.6)
	At least one minor birth defect	3 (42.9)	4 (44.4)	10 (47.6)	13 (46.4)
	NA	0	0	2	2
	Missing	129	201	398	527

N = total number of babies. *n*/% = number/percentage of babies in a given category.
[a] The two unconfirmed birth defects were not classified (one congenital abnormality-not further specified and one undescended testicle).
[b] Major birth defects included: in the −30 to +45 day exposed cohort – positional talipes, diaphragmatic hernia, Trisomy 21, tetralogy of Fallot. Additionally in the −30 to +90 day exposed cohort – hypospadias. In the non-exposed cohort – microcephaly, developmental hip dysplasia, bilateral positional talipes, diaphragmatic hernia, oesophageal atresia, dislocation and subluxation of the hip, cystic kidney disease, cleft palate, cataract and lens abnormalities, peri-membranous ventricular septal defect, renal agenesis and dysgenesis, horseshoe kidney.

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4. Discussion

We observed an SA rate during weeks 1–23 of gestation in UK women 15–25 years of age of 11.6% in the exposed cohort (first day of gestation within −30 to +45 days of HPV-16/18-vaccine administration) and 9.0% in the non-exposed cohort. We found no evidence of an increased risk of SA in women whose first day of gestation was within −30 to +45 (or −30 to +90) days of HPV-16/18-vaccine administration, and there was no evidence of increased risk of any other adverse pregnancy outcome in exposed women. In a sensitivity analysis, we observed an increased risk of SA ($n = 6$) in the 29 women who received two HPV-16/18-vaccine doses in the risk period. Post hoc investigations suggested that the risk of SA increased in six women receiving two doses within a 4–5 weeks interval, where one dose was administered before and one dose after first day of gestation. The post hoc analyses confirmed no risk increase in subjects exposed to a single dose (HR close to 1) regardless of dose number or timing in relation to the first day of gestation.

The SA rates we observed are in range with the SA rate estimate from the feasibility assessment performed in CPRD GOLD on women aged between 11 and 50 years (11.6%), and with published rates for this and wider age ranges from the UK and developed countries [12–15]. The results are also consistent with an independent analysis on SA made by the National Cancer Institute in the United States [3], and with a later pooled analysis of HPV-16/18-vaccine clinical trial data from 40 countries and including data from 10,476 pregnancies, in which the SA rate within the −30 to +45 day risk period was 12.9% in HPV-16/18 vaccinees and 10.1% in women who received control vaccines [16].

An additional analysis was conducted on a previously reported pooled clinical trial database [16], that included women aged 15–25 years ($N = 9359$ pregnancies) vaccinated with HPV-16/18-vaccine or a control vaccine. In women with a single dose of HPV-16/18 administered during the −30 to +45-day risk period ($N = 326$) the risk ratio (RR) was 1.54 (95% CI 0.95–2.54); compared to women exposed to a control vaccine during the same period ($N = 338$); the RR for two-dose exposure ($N = 71$) was 1.21 (95% CI 0.27–7.33) versus controls ($N = 38$) (GSK unpublished data).

This targeted safety study to assess the risk of SA has been conducted in a large population-based database that is likely to be representative of the general population of young women in the UK. The CPRD GOLD database has been used to undertake other research on pregnancy [17–19]. The assessment of SA rates in our study was feasible using a combination of data coded in the CPRD GOLD, including the mother–baby link [20], and information from free text. We were able to confirm study endpoints and pregnancy outcomes in the majority of women and made attempts to minimise case ascertainment bias by blinding experts during case review. By defining the non-exposed cohort as vaccinated women with a distant history of confirmed HPV-16/18 vaccination, we overcame the potential limitation related to incomplete vaccination records, increasing the specificity of the control group since it is unlikely that women would be vaccinated again after completing the three-dose HPV-16/18-vaccine schedule. Nevertheless, 13.1% and 20.6% of women had one or two recorded doses only (Table 1). So the risk that they were exposed to an unrecorded dose could not be totally excluded. This approach also decreased the risk of differing healthcare behaviours between exposed and unvaccinated subjects, but led, as anticipated, to differences in terms of age at first day of gestation and exposure to the H1N1 pandemic (1st June 2009–28th February 2010 [21]). However, adjustment for these covariates and others corroborated the results of the main analysis. Sensitivity analyses adjusted for other possible risk factors, including missing data, yielded virtually the same results as the main analysis, suggesting that missing demographic data had no impact on the study results. Finally, early SA (before 9 weeks GA) may go unrecognised. These pregnancies were probably not documented in CRPD GOLD because women were not aware of their pregnancy. As they were not included in the denominator, the risk of underestimation of SA rate should be therefore limited. In conclusion, this study indicates that the rate of SA in HPV-16/18-vaccinated young women is consistent with rates reported in the literature. The results show that in young women who are inadvertently vaccinated around gestation, there is no overall increase in SA or in other adverse pregnancy outcomes compared to women with similar characteristics from the same population who were not exposed. Nevertheless, women who are pregnant or trying to become pregnant, are advised to postpone vaccination until completion of pregnancy.

Trademarks

Cervarix is a registered trademark of the GSK group of companies. Gardasil is a trademark of Merck & Co. Inc.

Sources of support

GlaxoSmithKline Biologicals SA was the funding source and was involved in all study activities including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Pallas was involved in the design of the study, review of patient profiles, data entry of additional information from free text, and review and approval of manuscript.

GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. The corresponding author had full access to the data and was responsible for submission of the publication.

Author contributorship

Laurence Baril had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Laurence Baril, Rachael Boggon, Sonia Hernandez-Diaz, Christina Chambers, Tjeerd Van Staa, Judith van den Bosch, Eveline Bunge, Dominique Rosillon.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: Laurence Baril.

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: Dominique Rosillon, Corinne Willame.

Obtained funding: Laurence Baril.

Administrative, technical, or material support: Eveline Bunge, Corinne Willame, Rachael Boggon.

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Laurence Baril, Dominique Rosillon, Maria Genalin Angelo and Julia Zima are employed by, and own stock options in, the GlaxoSmithKline Group of Companies.

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Tjeerd Van Staa declares no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.07.024.

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