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Results on exposure during pregnancy from a pregnancy registry for AS04-HPV-16/18 vaccine

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ABSTRACT

Objective: To assess pregnancy outcomes after exposure to AS04-HPV-16/18 vaccine (*Cervarix*, GSK, Belgium) prior to, or during pregnancy, as reported to a pregnancy registry.
Methods: A pregnancy exposure registry was established to collect data in the United Kingdom and the United States. Exposure was defined as vaccination with AS04-HPV-16/18 within 60 days before the estimated conception date and delivery. Reporting was voluntary.
Results: Between September 2007 and November 2015, 306 pregnancy exposure reports were received of which 181 were prospective, evaluable reports. From these 181 reports, 154 (85.1%) pregnancies resulted in a live birth, 14 (7.7%) in spontaneous abortion, one (0.5%) in stillbirth, and 12 (6.6%) were electively terminated. There was no clustering of outcomes with respect to the timing of exposure. There were 18 infants born with a congenital anomaly of which nine were minor structural defects, seven were major structural defects, one was a hereditary disorder and one was likely the result of a congenital infection. In three cases of structural defect (two minor and one major), there was a temporal association to vaccination during the critical developmental period of gestation. There was no cluster or constellation of congenital anomalies suggestive of possible teratogenesis.
Conclusion: The pharmacovigilance plan to investigate the effects of inadvertent exposure to AS04-HPV-16/18 vaccine during pregnancy included assessment of pregnancy outcomes among women enrolled in clinical trials, evaluation of pregnancy exposure reports from all countries as part of routine passive safety surveillance, a large, well conducted post-authorization observational study, and the pregnancy registry. These registry data complement other data from clinical trials and post-marketing surveillance showing no evidence that vaccination with AS04-HPV-16/18 during the defined exposure period (within 60 days before conception until delivery) increases the risk of teratogenicity.

1. Introduction

The AS04-adjuvanted human papillomavirus HPV-16/18 vaccine (*Cervarix*, AS04-HPV-16/18, GSK, Belgium), was first authorized in 2007 and is now licensed in more than 130 countries. The vaccine is indicated from 9 years of age for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. The target population for AS04-HPV-16/18 includes young women of child-bearing age in whom pregnancy is frequent. Thus, determining pregnancy outcomes following inadvertent exposure to AS04-HPV-16/18 during pregnancy is important in this population.

As for most vaccines, pre-licensure clinical studies were not designed to evaluate the safety of AS04-HPV-16/18 in pregnant women, and data at the time of licensure were insufficient to recommend vaccination during pregnancy. In the clinical program, inadvertent exposures during pregnancy occurred despite precautionary measures to prevent pregnancy. In a pooled analysis of pre-licensure clinical trial data (in almost 30,000 women of whom 16,142 received AS04-HPV-16/18), there were 1737 pregnancies (870 in AS04-HPV-16/18 recipients) reported over the follow-up period (7 months to 5.5 years) [1]. Pregnancy outcomes were very similar between groups exposed to AS04-HPV-16/18 or to control

Abbreviations: EDD, estimated date of delivery; HPV, human papillomavirus; LMP, last menstrual period; PHE, Public Health England; SA, spontaneous abortion; UK, United Kingdom; US, United States; FDA, U.S. Food & Drug Administration.

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vaccines, except for an imbalance in the number of spontaneous abortions (SA) in women 15–25 years of age who became pregnant around the time of AS04-HPV-16/18 vaccination (SA rate of 11.0% in AS04-HPV-16/18 vaccinees, 5.8% in recipients of hepatitis A vaccine and 8.3% in recipients of aluminum-adjuvanted HPV-16/18 vaccine) [1]. The Center for Biologics Evaluation and Research (CBER) in the United States (US) requested to further investigate the pregnancy outcome of SA. To this end, the Pharmacovigilance plan was designed to explore initiatives to generate more data on outcomes of exposed pregnancies. This included close monitoring of exposed pregnancies in ongoing/active clinical trials, an observational epidemiological study, passive surveillance through spontaneous reporting and establishment of a pregnancy exposure registry.

The requested post-licensure epidemiological study investigated the rate of SA among women vaccinated with AS04-HPV-16/18 around pregnancy onset using the Clinical Practice Research Datalink in the United Kingdom (UK). The UK was selected because of high uptake of AS04-HPV-16/18 following a national school-based immunization campaign [2,3]. The study assessed the frequency of SA among 15-to-25-year-old women who had received AS04-HPV-16/18 between 30 days before and 45 days of gestation, compared to a non-exposed control group [3]. The study showed no evidence of an increased risk of SA (and other adverse pregnancy outcomes) in young women inadvertently vaccinated with AS04-HPV-16/18 during the defined exposure period. The frequency of SA was 11.6% among 207 exposed women, and 9.0% among 632 non-exposed women (hazard ratio 1.30, 95% confidence interval: 0.79–2.12) [3].

A second pooled analysis of clinical safety data evaluated more than 57,000 women of whom more than 33,000 received AS04-HPV-16/18 in clinical trials and follow-up studies [4]. Of the 10,476 reported pregnancies, 935 were exposed to vaccination within 60 days prior to pregnancy onset until delivery. Among the 935 exposed pregnancies, congenital anomalies were reported in 12 cases (2.5%) in AS04-HPV-16/18 recipients, and in 11 cases (2.5%) in women who had received control vaccines. No concerns were raised with regards to pregnancy outcomes including SA, stillbirth, elective termination and congenital anomalies, or other indicators such as weight and gestational age at delivery [4].

The pregnancy exposure registry was established in the UK and the US. The goal of the registry was to evaluate the risks of adverse pregnancy outcomes, including major teratogenic effects, in the offspring of women inadvertently exposed to AS04-HPV-16/18 during pregnancy. The registry was closed on 17 November 2015 and the results communicated to the European Medicines Agency. Here we report the findings from GSK's pregnancy registry, which completes the pharmacovigilance plan to assess outcomes in pregnancies exposed to AS04-HPV-16/18.

2. Methods

2.1. Definitions

Congenital anomaly: any morphological, functional and/or biochemical developmental disturbance in the embryo or fetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, fetopathies, genetic diseases with early onset, developmental delay and others [5]. Congenital anomalies were defined following the Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program [6,7]. Structural defects were classified as minor (no serious medical consequences) or major (serious medical, surgical and cosmetic consequences) [8,9].

Exposure (risk period): vaccination with AS04-HPV-16/18 within 60 days before the estimated conception date and delivery.

Prospective report: where the outcome of the pregnancy was not known at the time of reporting.

Retrospective report: where the outcome of pregnancy was known at the time of reporting.

Spontaneous abortions (SA): intrauterine death up to 22 weeks of gestation [5]. Includes miscarriage and missed abortion.

Elective termination: Elective/therapeutic termination or induced abortions.

Stillbirth: Intrauterine death occurring after week 22 of gestation.

First trimester: from last menstrual period (LMP) through week 13 of gestation.

Second trimester: weeks 14–27 of gestation.

Third trimester: week 28 through term.

2.2. Registration and follow-up

In September 2008, universal immunization using AS04-HPV-16/18-vaccine was initiated in the UK for 12-to-13-year-old girls, with a catch-up program among 14-to-18-year olds. Coverage of the 3-dose regimen was 81% in 2010 [10]. As part of an enhanced safety surveillance established by the Medicines and Healthcare products Regulatory Agency [11], GSK set up a Pregnancy Exposure registry for AS04-HPV-16/18 in the UK in collaboration with Public Health England (PHE, formerly the Health Protection Agency). A registry managed entirely by GSK was established after the registration of AS04-HPV-16/18 in the US in September 2009. Registration to either registry was always voluntary and could be prospective or retrospective.

In each country, reporting of adverse events and vaccine-exposed pregnancies to the registry was made by telephone through GSK's 'Call in' system. Members of the public had access to the registry through the GSK registry website [12].

Enrolment to the UK Registry: UK healthcare providers were informed through the Green Book (which has the latest information on vaccines and vaccination procedures in the UK), HPV vaccine campaign materials and the PHE website [13], to report all cases of pregnant women who received HPV vaccines to PHE. On receipt of initial reports made by telephone or via the website, PHE sent out a registry enrolment form (usually to the woman's general practitioner). Each case was followed up until approximately 10 weeks after the estimated date of delivery (EDD), at which time a second form was sent to the healthcare provider. At each step, two follow-up requests and one phone-call were made to encourage completion of the registry forms. A report was considered lost-to-follow-up when the phone-call did not result in collection of useful information, or in the return of a registry form indicating the case as lost-to-follow-up.

Enrolment to the US registry managed by GSK Vaccines: Members of the public had access to the registry through the local AS04-HPV-16/18 Prescribing Information and the FDA Pregnancy Registry website. Initial and follow-up data were collected using questionnaires. Case follow-up by telephone contact or a form mailed to the health professional was performed within 6 weeks of the EDD to ascertain outcome. At least three attempts were made to obtain outcome information before any case was considered lost-to-follow-up. The reporter was contacted if the reported information was insufficient or needed clarification.

For all live births in both countries, follow-up was also solicited from the healthcare provider one year after birth.

2.3. Inclusion and exclusion criteria

Pregnancy reports were considered eligible when the following data were available: (1) documentation that AS04-HPV-16/18 was administered within 60 days before pregnancy onset or at any time

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