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Meta-analysis of pregnancy outcomes in pooled randomized trials on a prophylactic adjuvanted glycoprotein D subunit herpes simplex virus vaccine☆

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ABSTRACT

The primary objective of this investigation was to assess whether the AS04-adjuvanted herpes simplex virus (HSV) glycoprotein D candidate prophylactic vaccine against genital herpes disease increases the risk of spontaneous abortion associated with pregnancy conceived within the vaccination exposure window (vaccine dose received within the period starting 60 days before and ending 20 weeks post-conception day). We performed a meta-analysis of studies designed as part of the clinical development program for this vaccine, to examine the relative risk of abortion (spontaneous or elective) associated with unintended vaccination exposure during pregnancy. Nineteen studies, completed before September 2010, were eligible; 5 matched the inclusion criteria for this analysis (presence of a control arm and at least one adverse pregnancy outcome reported). All vaccinated women ($N = 19{,}727$) were included, of whom 660 reported a pregnancy during the study period. Overall, 13.3% of pregnancies in the HSV vaccine group and 11.0% in the control group resulted in spontaneous abortion; 24.2% and 20.0% resulted in elective abortion. Among 180 women with a first pregnancy conceived in the vaccination exposure window, 16.7% (HSV vaccine) and 9.5% (control) had a spontaneous abortion and 38.5% and 33.3%, elective abortion. The relative risk for spontaneous abortion associated with vaccine exposure during the risk period for abortion in the course of pregnancy was 1.7 (95% CI: 0.7–4.6). For all women receiving HSV vaccine, this relative risk was 1.3 (95% CI: 0.8–2.1). The corresponding relative risks for elective abortion were 1.2 (95% CI: 0.7–2.0) and 1.3 (95% CI: 0.9–1.8). There was no apparent relationship to dosing and no difference between groups in gestational age at the time of spontaneous or elective abortion. In conclusion there is no statistical evidence that the investigational HSV vaccine increased the risk of spontaneous or elective abortion.

1. Introduction

In trials evaluating vaccination against sexually transmitted diseases, such as those related to herpes simplex virus (HSV) or human papilloma virus (HPV), the target population often includes women of childbearing age. Even with the stringent precautions that are always put in place to avoid pregnancies in clinical trials, there is nonetheless the potential for participants to become pregnant during the vaccination period, resulting in a potential risk of unintentional exposure to the study vaccine. Only limited data are available to assess this risk. Indeed, vaccination is generally discontinued for women who become pregnant during a study, and no additional immunizations are administered to these women. Furthermore, unless the vaccine is specifically designed for maternal immunization, clinical studies designed to evaluate pregnancy outcomes would not be included in the vaccine development program. Still, for any licensed vaccine, the magnitude of any increased risk of miscarriage and of the number of pregnancies at risk are important factors in personal and public health decisions regarding vaccination.

In this context, a meta-analysis was performed on studies from the GlaxoSmithKline Vaccines (GSK) HSV vaccine clinical development program, in order to evaluate the potential relative risk (RR) for abortion (spontaneous or elective) associated with HSV vaccination.

2. Material and methods

2.1. Eligibility criteria

All interventional GSK-sponsored studies in the HSV vaccine prophylactic clinical development program that were

Abbreviations: RR, relative risk; LMP, last menstrual period; EDC, estimated date of conception; EDD, estimated date of delivery; CI, confidence intervals.

☆ Available at: http://www.gsk-clinicalstudyregister.com/; ID: HSV meta-analysis.

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completed before September 2010 were eligible for inclusion in the meta-analysis. Data from all females who received either the investigational AS04-adjuvanted herpes simplex virus (HSV) glycoprotein D candidate prophylactic vaccine against genital herpes disease (HSV vaccine) or a control vaccine in eligible studies were included. GSK study numbers for the 19 eligible studies were the following: HPV-001 (208141/001 NCT00698893), HSV-002 (208141/002, NCT00697567), HSV-005 (208141/005), HSV-006 (208141/006), HSV-007 (208141/007), HSV-014 (208141/014), HSV-015 (208141/015, NCT00698490), HSV-016 (208141/016, NCT00698568), HSV-017 (208141/017, NCT00699764), HSV-019 (208141/019), HSV-023 (208141/023), HSV-024 (208141/024), HSV-026 (208141/026), HSV-037 (208141/037), HSV-038 (208141/038), HSV-039 (208141/039, NCT00057330), HSV-040 (208141/040, NCT00224484), HSV-041 (208141/041), HSV-042 (208141/042, NCT00224471). Protocol summaries can be obtained from http://www.gsk-clinicalstudyregister.com/. For the present meta-analysis, the study ID is 'HSV meta analyses'.

Studies had to meet the following criteria for inclusion in the meta-analysis of spontaneous or elective abortions: the presence of a control group in the study; the presence of at least one pregnancy outcome of interest, i.e. spontaneous or elective abortion with or without apparent congenital anomaly.

The data lock point for the analysis of pregnancy outcome from the HSV program was 27 October 2010. All women of childbearing potential enrolled in the HSV vaccine program were advised to use an effective birth control method during the entire study period and 2 months after the completion of the vaccination series. They were tested for pregnancy with urine kits, immediately prior to each vaccination. The observation period began immediately after vaccination.

2.2. Cohorts analyzed

All women who received at least one vaccine dose in the selected studies (total vaccinated cohort) were included. Men enrolled in 3 of the studies (HSV-007, -016 and -017) were not included. The vaccines received were either the investigational HSV vaccine or a control product (hepatitis A vaccine [HAV] (*Havrix*™, GSK Vaccines), placebo or AS04 adjuvant system alone used as a control, depending on the selected study).

2.3. Ethics

All studies were conducted in accordance with the 1996 version of the Declaration of Helsinki and with the International Conference on Harmonization (ICH) *Good Clinical Practice* guidelines.

Study protocols were approved by the Institutional Review Board of the institutions taking part and/or local ethics committees. Written informed consent was obtained from all subjects prior to the performance of any study-specific procedures.

2.4. Statistical analyses

The RR estimate and 95% confidence intervals (CIs) were computed using the exact conditional likelihood approach stratified for the study effect (Proc StatXact4 for SAS Users, 1999) [3].

2.5. Endpoints

The primary endpoint was to evaluate the risk of spontaneous abortion associated with pregnancy conceived within the vaccination exposure window.

Secondary endpoints were: to evaluate the risk of elective abortion associated with pregnancy conceived within the vaccination exposure window, or any spontaneous or elective abortion.

Only the first reported pregnancy was considered for subjects who became pregnant more than once during the follow-up period of the study (23 subjects).

According to international consensus, the gestational age is measured from the first day of the last menstrual period (LMP). The pregnancy onset date or estimated date of conception (EDC) is defined as the date of LMP +14 days. In case LMP was unknown, the EDC was calculated as the estimated date of delivery (EDD) by ultrasound minus 266 days. The vaccination exposure window was considered unknown if both the LMP and the EDD were unknown, or it could not be determined based on available parameters obtained from the pregnancy report (e.g. ultrasound examination or clinical assessment of the newborn).

Spontaneous abortion is defined as the termination of a pregnancy without human interference prior to 20 weeks post-conception day (or 22 weeks of gestation) [6]. Elective abortion is defined as the induced termination of a pregnancy due to personal choice or medical reasons prior to 20 weeks post-conception day (or 22 weeks of gestation).

A pregnancy was considered to be in the vaccination exposure window if a vaccine dose was received within a period starting 60 days before and ending 20 weeks post-conception day.

3. Results

3.1. Study selection for the meta-analysis

Nineteen GSK-sponsored interventional studies conducted as part of the HSV vaccine development program and completed before September 2010 were screened for inclusion in the meta-analysis. Five of these met the conditions required for evaluation of the RR of the adverse pregnancy outcomes of interest (Table 1). Study name abbreviations for the selected studies were as follows: HSV-007, HSV-016, HSV-017, HSV-039 and HSV-040. In line with the nature of this analysis, only data from female participants were included. Women who received the candidate HSV vaccine were included in the HSV vaccine group. The control group included women who received AS04 adjuvant alone (study HSV-007) or placebo control (studies HSV-016, HSV-017 and HSV-040), or who received the active comparator HAV (studies HSV-039 and HSV-040).

3.2. Study characteristics

In the 5 selected trials, 19,727 women (10,964 in the pooled HSV vaccine groups and 8763 in the control groups) were vaccinated and thus were included in the meta-analysis. Of the total subjects included in the meta-analysis, the largest single group, 8323 women, came from the HSV-039 efficacy study. The numbers of women vaccinated, reported pregnancies, and pregnancy outcomes for each study included in analysis are shown in Table 1. For the 19,727 women who received at least one vaccine dose during the studies, the mean age was 23.6 ± 10.3 years in the HSV vaccine group and 22.0 ± 9.3 years in the control group (age range: 10–80 years). The majority (86%) of women were of white/caucasian heritage in both groups. Six hundred and sixty women became pregnant during the study period (368 in the HSV vaccine group and 292 in the control group), of whom 370 (56%) came from the HSV-039 efficacy trial. For the 660 women with at least one pregnancy reported in these studies, the mean age was 22.9 ± 5.4 years in the HSV vaccine group and 23.1 ± 5.2 years in the control group (age range: 13–45 years). Demographic characteristics for women who reported at least one pregnancy, for each group, are reported in Supplementary Table 1.