Re: Specific Antibody Levels at the Cervix During the Menstrual Cycle of Women Vaccinated With Human Papillomavirus 16 Virus-Like Particles

We read with interest the article by Nardelli-Haefliger et al. (1) in which the authors reported an approximate nine-fold reduction in cervical anti-human papillomavirus 16 (HPV16) immunoglobulin (Ig; specific IgG and total IgG and IgA) levels at the time of ovulation in 11 women who received aluminum-free (i.e., adjuvant-free) HPV16 L1 virus-like particle (VLP) vaccine synthesized in a baculovirus system (1). The authors hypothesized that the efficacy of prophylactic HPV16 L1 VLP vaccines may be reduced during the peri-ovulatory phase in women who are not using hormonal contraception.

We recently reported (2) the primary efficacy results of a multicenter, placebo-controlled trial of a prophylactic HPV16 L1 VLP vaccine in 2392 women aged between 16 and 23 years. The HPV16 L1 VLPs were synthesized in yeast and formulated on aluminum adjuvant. In the primary efficacy cohort, the vaccine was found to be 100% ef-
ffective in preventing persistent cervico-vaginal HPV16 infection and related cervical intraepithelial neoplasia for a median of 17.4 months following the completion of vaccination.

In our study (2), information on contraceptive use was collected at each visit and contraceptive methods were divided into ovulation-suppressing contraceptives (i.e., oral or parenteral hormone contraceptives) or non-suppressing contraceptives (i.e., barrier, abstinence, rhythm). The extent of use of these categories of contraceptives was assessed in two ways: 1) the number of individuals who reported use of an ovulation-suppressing contraceptive on at least one study visit and 2) the overall duration of exposure to ovulation-suppressing contraceptives, measured in woman-years at risk. In the primary efficacy cohort, 77% of women reported use of an ovulation-suppressing contraceptive on at least one study visit. However, many women used these products for only short periods of time or intermittently. Thus, ovulation-suppressing contraceptives were used in only 54% of the woman-years at risk in this cohort. Hence, because vaccine efficacy was observed to be 100%, ovulation and potential fluctuations in cervical anti-HPV16 IgG levels did not appear to affect vaccine efficacy in our study.

In light of our study (2), the findings of Nardelli-Haefliger et al. (1) can lead to one of three alternate hypotheses. First, although vaccine-induced anti-HPV16 levels in cervicovaginal secretions may fluctuate during the ovulatory cycle, they remain sufficiently high to prevent HPV16 infection. Second, the efficacy of HPV16 L1 VLP vaccines is not affected by anti-HPV16 levels in cervical secretions—that is, because the HPV16 infectious cycle depends critically on infection of the basal cell layer of the cervical epithelium, the delivery of anti-HPV16 IgG by extravasated blood may be a more important determinant of vaccine efficacy. Third, the impact of ovulation-induced fluctuations in cervical anti-HPV16 IgG levels on HPV vaccine efficacy may be subtle; therefore, a larger study with longer follow-up would be required to detect such an effect.

Assuming that vaccine-induced anti-HPV16 in cervicovaginal secretions is an important mechanism for the vaccine’s protective effect, cervical IgG levels in the peri-ovulatory period would have to drop below the level required for maintenance of the vaccine’s protective efficacy to result in a clinical impact. Although such a level has not been defined, it stands to reason that vaccines that induce high levels of anti-HPV16 IgG are less likely than less immunogenic vaccines to be affected by peri-ovulatory fluctuations in cervical anti-HPV16 Ig levels. The vaccine formulation used in the study by Nardelli-Haefliger et al. (1) contained no adjuvant. In our experience, the use of aluminum adjuvant in the formulation of HPV16 L1 VLP vaccines increases serum anti-HPV16 IgG levels more than 10-fold compared with an adjuvant-free formulation. If our vaccine induced higher anti-HPV16 levels than those induced by the vaccine used by Nardelli-Haefliger et al., then our vaccine may be less prone to clinically meaningful decreases in cervical IgG levels than the formulation used by Nardelli-Haefliger et al. (1).

We have reported that vaccine-induced anti-HPV16 responses decline over time (2). Women in our study were followed for a median of 17.4 months after completing the vaccination. However, women remain at risk for HPV infection for several years. To fully address the impact in peri-ovulatory anti-HPV16 IgG levels on vaccine efficacy, it will be important to assess the duration of HPV16 L1 VLP vaccine efficacy over a longer period of follow-up.

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REFERENCES


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Editor’s note: E. Barr is an employee of Merck Research Laboratories, which is developing a quadrivalent human papillomavirus vaccine. L. A. Koutsky is currently conducting research that is sponsored by Merck Research Laboratories.

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RESPONSE

We thank Drs. Barr and Koutsky for their comments related to our recently published article, in which we reported that human papillomavirus 16 (HPV16) antibody levels at the cervix, following systemic immunization with an HPV16 virus-like particle (VLP) vaccine, vary substantially during the course of the menstrual cycle (1). We agree that long-term studies of vaccinees are needed to determine whether, and to what degree, these variations in HPV16 antibody levels may influence vaccine efficacy several years after vaccination. As noted by Drs. Barr and Koutsky and by ourselves (2), such efficacy results should help to clarify whether serum antibody or cervical antibody levels are the primary correlate of vaccine efficacy. In ongoing long-term efficacy studies, it may be useful to distinguish between the group of women who, after the vaccination period, do not use hormonal contraceptives at all and the group of women who use hormonal contraceptives intermittently, because it may be difficult to infer, with the latter group of women, whether their risk of HPV exposure will be similar during intervals on and off hormonal contraceptives.

In addition, we would also like to point out that the magnitude of the fluctuation we observed in HPV16 antibody levels at the cervix during the menstrual cycle was also seen for total immunoglobulin G levels at the cervix (1). Therefore, we believe that the observed menstrual cycle–dependent changes in HPV16 antibody levels at the cervix have nothing to do with our HPV16 VLP vaccine having been formulated without adjuvant, and we would expect that analogous fluctuations in antibody levels would be seen following systemic immunization with any VLP-based vaccine. We also note that, in apparent contrast to the observations of Drs. Barr and Koutsky, we did not find increased immunogenicity from the addition of aluminum adjuvant to the 50-μg dose of VLPs used in our study (1), although we have observed an adjuvant effect from...
aluminum when given with a 10-μg dose of VLPs (3).

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