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New Concerns about the Human Papillomavirus Vaccine



American College of Pediatricians – January 2016

The American College of Pediatricians (The College) is committed to the health and well-being of children, including prevention of disease by vaccines. It has recently come to the attention of the College that one of the recommended vaccines could possibly be associated with the very rare but serious condition of premature ovarian failure (POF), also known as premature menopause. There have been two case report series (3 cases each) published since 2013 in which post-menarcheal adolescent girls developed laboratory documented POF within weeks to several years of receiving Gardasil, a four-strain human papillomavirus vaccine (HPV4).^{1,2} Adverse events that occur after vaccines are frequently not caused by the vaccine and there has not been a noticeable rise in POF cases in the last 9 years since HPV4 vaccine has been widely used.

Nevertheless there are legitimate concerns that should be addressed: (1) long-term ovarian function was not assessed in either the original rat safety studies^{3,4} or in the human vaccine trials, (2) most primary care physicians are probably unaware of a possible association between HPV4 and POF and may not consider reporting POF cases or prolonged amenorrhea (missing menstrual periods) to the Vaccine Adverse Event Reporting System (VAERS), (3) potential mechanisms of action have been postulated based on autoimmune associations with the aluminum adjuvant used¹ and previously documented ovarian toxicity in rats from another component, polysorbate 80,² and (4) since licensure of Gardasil® in 2006, there have been about 213 VAERS reports (per the publicly available CDC WONDER VAERS database) involving amenorrhea, POF or premature menopause, 88% of which have been associated with Gardasil®.⁵ The two-strain HPV2, *Cervarix*TM, was licensed late in 2009 and accounts for 4.7 % of VAERS amenorrhea reports since 2006, and 8.5% of those reports from February 2010 through May 2015. This compares to the pre-HPV vaccine period from 1990 to 2006 during which no cases of POF or premature menopause and 32 cases of amenorrhea were reported to VAERS.

Many adolescent females are vaccinated with influenza, meningococcal, and tetanus vaccines without getting Gardasil®, and yet only 5.6% of reports related to ovarian dysfunction since 2006 are associated with such vaccines in the absence of simultaneous Gardasil® administration. The overwhelming majority (76%) of VAERS reports since 2006 with ovarian failure, premature menopause, and/or amenorrhea are associated solely with Gardasil®. When VAERS reports since 2006 are restricted to cases in which amenorrhea occurred for at least 4 months and is not associated with other known causes like polycystic ovary syndrome or pregnancy, 86/89 cases are associated with Gardasil®, 3/89 with *Cervarix*TM, and 0/89 with other vaccines administered independently of an HPV vaccine.⁵ Using the same criteria, there are only 7 reports of amenorrhea from 1990 through 2005 and no more than 2 of those associated with any one vaccine type.

Few other vaccines besides Gardasil® that are administered in adolescence contain polysorbate 80.⁶ Pre-licensure safety trials for Gardasil® used placebo that contained polysorbate 80 as well as aluminum adjuvant.^{2,7} Therefore, if such ingredients could cause ovarian dysfunction, an increase in amenorrhea probably would not have been detected in the placebo controlled trials. Furthermore, a large number of girls in the original trials were taking hormonal contraceptives which can mask ovarian dysfunction including amenorrhea and ovarian failure.² Thus a causal relationship between human papillomavirus vaccines (if not Gardasil® specifically) and ovarian dysfunction cannot be ruled out at this time.

Numerous Gardasil safety studies, including one released recently,⁸ have looked at demyelinating and autoimmune diseases and have not found any significant problems. Unfortunately, none of them except clinical safety pre-licensure studies totaling 11,778 vaccinees⁹ specifically addressed post-vaccination ovarian dysfunction. While data from those studies do not indicate an increased rate of amenorrhea after vaccination, the essential lack of saline placebos and the majority of participants taking hormonal contraceptives in those studies preclude meaningful data to rule out an effect on ovarian function.

A Vaccine Safety Datalink POF study is planned to address an association between these vaccines and POF, but it may be years before results will be determined. Plus, POF within a few years of vaccination could be the tip of the iceberg since ovarian dysfunction manifested by months of amenorrhea may later progress to POF. Meanwhile, the author of this statement has contacted the maker of Gardasil, the Advisory Committee on Immunization Practices (ACIP), and the Food and Drug Administration (FDA) to make known the above concerns and request that (1) more rat studies be done to look at long-term ovarian function after HPV4 injections, (2) the 89 VAERS reports identified with at least 4

months amenorrhea be reviewed by the CDC for further clarification since the publicly available WONDER VAERS database only contains initial reports, and (3) primary care providers be notified of a possible association between HPV and amenorrhea. A U.S. Government Representative responded that they “will continue to conduct studies and monitor the safety of HPV vaccines. Should the weight of the evidence from VAERS or VSD and other sources indicate a likely causal association between POF and HPV vaccines, appropriate action will be taken in terms of communication and public health response.”

The College is posting this statement so that individuals considering the use of human papillomavirus vaccines could be made aware of these concerns pending further action by the regulatory agencies and manufacturers. While there is no strong evidence of a causal relationship between HPV4 and ovarian dysfunction, this information should be public knowledge for physicians and patients considering these vaccines.

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The American College of Pediatricians is a national medical association of licensed physicians and healthcare professionals who specialize in the care of infants, children, and adolescents. The mission of the College is to enable all children to reach their optimal, physical and emotional health and well-being.

A printable Adobe Acrobat (pdf) copy of this position is available by clicking here: [New Concerns about the Human Papillomavirus Vaccine](#).

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