# Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Serena Colafrancesco[1,2], Carlo Perricone[1,2], Lucija Tomljenovic[1,3], Yehuda Shoenfeld[1,4]

[1]Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel-Hashomer, Israel;
[2]Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy;
[3]Neural Dynamics Research Group, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada;
[4]Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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**Correspondence**
Yehuda Shoenfeld, Department of Medicine B, Chaim Sheba Medical Center, Tel Hashomer, 52621, Israel. E-mail: Shoenfel@post.tau.ac.il

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## Problem
Post-vaccination autoimmune phenomena are a major facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and different vaccines, including HPV, have been identified as possible causes.

## Method of study
The medical history of three young women who presented with secondary amenorrhea following HPV vaccination was collected. Data regarding type of vaccine, number of vaccination, personal, clinical and serological features, as well as response to treatments were analyzed.

## Results
All three patients developed secondary amenorrhea following HPV vaccinations, which did not resolve upon treatment with hormone replacement therapies. In all three cases sexual development was normal and genetic screen revealed no pertinent abnormalities (i.e., Turner's syndrome, Fragile X test were all negative). Serological evaluations showed low levels of estradiol and increased FSH and LH and in two cases, specific auto-antibodies were detected (antiovarian and anti thyroid), suggesting that the HPV vaccine triggered an autoimmune response. Pelvic ultrasound did not reveal any abnormalities in any of the three cases. All three patients experienced a range of common non-specific post-vaccine symptoms including nausea, headache, sleep disturbances, arthralgia and a range of cognitive and psychiatric disturbances. According to these clinical features, a diagnosis of primary ovarian failure (POF) was determined which also fulfilled the required criteria for the ASIA syndrome.

## Conclusion
We documented here the evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition. The increasing number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term clinical benefits of HPV vaccination are a matter of public health that warrants further rigorous inquiry.

## Introduction

Vaccines against human papilloma virus (HPV) are thought to represent a useful approach in the fight against cervical cancer. Although vaccines have proven to be a successful and cost-effective asset for preventive medicine, local or systemic adverse events, following vaccination, have been described. Specifically, there are increasing reports that autoimmune disorders can develop after vaccination.[1–4] At the same extent, the association between infectious agents exposure and the development of autoimmune diseases is well established.[5,6] Recently, a new syndrome, namely the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) or Shoenfeld's syndrome,[7–12] has been defined, alluding to the key role of adjuvants in inducing autoimmunity. The syndromes included in ASIA entail immune-mediated conditions that appear following a chronic stimulation of the immune system by agents with adjuvant characteristics.[7,10] Post-vaccination autoimmune phenomena represent a major issue of ASIA and different vaccines, including the HPV vaccine, have been found as possible causes.[3,9,13] Primary ovarian failure (POF) is a clinical condition with complex aetiology in which autoimmune mechanisms represent 20–30% of the cases.[14] This assertion is supported by different evidences: the presence of lymphocytic oophoritis, the detection of ovarian autoantibodies and the frequent association with other autoimmune diseases.[14] Herein, we describe three clinical cases, including two sisters, who developed POF following administration of the HPV vaccine. Genetic, metabolic and external environmental factors were excluded as POF causes, while the common denominator was the previous vaccination with HPV leading to the development of immune-mediated amenorrhoea.

## Case 1

A young previously healthy girl received three administrations of the quadrivalent HPV vaccine (T0, T1 after 4 months, T2 after 9 months) when she was 14 years old. Six months before the first injection, the patient had menarche. Her psycho-physical and sexual development were normal except that at the time she received the first HPV vaccine dose, she was complaining of irregular periods (every 2 months). After the first vaccination, the patient immediately started to complain of burning and heavy sensation in the injected arm, followed by skin rash and fever. Nausea and stomach aches lasted for 2 days after the injection, while in the subsequent 2 weeks, she further complained of cramping and headache. At the time of the second vaccine administration, she reported similar injection site related symptoms, accompanied by sleep disturbances, such as insomnia and night sweats. At the time of the third injection, the patient continued to experience the same symptoms: burning, pain and heavy sensation in the injected arm, headache and cramping. Insomnia associated with night sweats persisted and she started complaining of arthralgia, anxiety and depression. The patient reported that her last period occurred shortly after the last injection of the HPV vaccine. The hormonal screening showed the presence of increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) associated with very low levels of estradiol. Beta human chorionic gonadotropin (HCG) tested negative excluding pregnancy. The karyotype study was 46 XX, while molecular studies ruled out Fragile X syndrome and mutated follicle-stimulating hormone receptor (FSHR) gene. A pelvic ultrasound did not show any abnormality. According to these clinical and serological findings, POF diagnosis was determined. Even though the patient started therapy with medroxyprogesterone to stimulate bleeding, no improvement occurred and she continued to experience abnormal vaginal bleeding, night sweats, hot flashes and sleep disturbances.

## Case 2

This patient (the younger sister of the above-mentioned case) received three administrations of the quadrivalent HPV vaccine at the age of 13 under the same protocol as her sister. At that time, she had normal growth and sexual development. The patient complained, 10 days after the first injection, of general symptoms such as depression and sleep disturbances. She also experienced episodes of lightheadedness and tremulousness, anxiety, panic attacks and difficulties in focusing/concentrating in her school work. She had menarche at the age of 15 years, followed by another period 1 month later and none thereafter. Laboratory analysis showed high serum levels of FSH and LH with undetectable estradiol. The genetic test for Turner's syndrome,

Fragile X syndrome and FSHR gene was performed and resulted negative. Interestingly, the patient tested positive for antiovarian antibodies. She underwent a pelvic ultrasound without an evidence of abnormalities. In the light of these findings, a diagnosis of POF was determined and the patient was treated with several different hormonal replacement therapies with a poor therapeutic response.

### Case 3

The patient received the quadrivalent HPV vaccine in three administrations (T0, T1 after 2 months, T2 after 4 months) at the age of 21 years. Menarche occurred when she was 13 years old with normal monthly periods and a flow of 5–7 days, with mild cramps. A normal sexual development was reported. Few months after the last injection of HPV vaccine, she started complaining of irregular menses (off by 1–2 weeks) without an increase in bleeding or pain. The irregular periods worsened and the patient reported on menstruations every 3 months with bleeding only for 2 days. For this reason, she started drospirenone/ethinyl estradiol. Nonetheless, no improvement occurred and after discontinuation of therapy, at the age of 23 years, she complained of amenorrhoea. The laboratory tests showed the presence of very low levels of estradiol and increased FSH and LH. Testosterone, cortisol and prolactin serum level were found normal. Although the thyroid hormones were also in the normal range, the patients had positive antithyroid peroxidise (TPO) antibodies (134 IU/mL, n.v. 0–34). The karyotype evaluation and the search for Fragile X syndrome displayed no aberrations. A transvaginal and pelvic ultrasound did not reveal any abnormality. According to these findings and clinical features, a diagnosis of POF was determined. Thus, a therapy with medroxyprogesterone and estradiol was attempted, however, it did not improve her clinical condition.

## Discussion

Herein, we have described three cases of POF following HPV vaccination. To the best of our knowledge, an additional case of POF in a 16-year-old young woman who was vaccinated with the quadrivalent HPV recombinant vaccine has already been reported by Little and Ward.[15] In this case, as in our three cases, no other possible causes of POF were identified other than the HPV vaccine. Quoting the HPV vaccine manufacturer, the authors emphasized the fact that the post-marketing reporting of vaccine adverse events is voluntary and consequently, it is not always possible to reliably estimate the frequency of such reactions, let alone to establish a causal relationship to the vaccine. Further according to the authors, there may potentially be a group for whom the HPV vaccine is contraindicated and because the occurrence of POF carries major health implications, a long-term follow-up of ovarian function in a cohort of HPV vaccinated woman should be undertaken.[15]

POF is a syndrome consisting of primary or secondary amenorrhoea, hypergonadotropinemia and hypoestrogenemia. POF affects 1% of women under 40 years of age, 0.1% under 30 and 0.01% of women under 20 years and it is an important cause of infertility and psychological stress.[14] POF in young women can indeed have significant consequences for future health and prospects of motherhood. The aetiology includes specific genetic mutations (referred to oocyte, enzymes or hormones receptors), autoimmune or environmental causes (such as viral infections, chemotherapy, radiotherapy and pelvic surgery) or metabolic disturbances.[14] The possible autoimmune origin for POF has been speculated for a long time,[16] and one of the evidence which supports this origin is its frequent association with other autoimmune diseases (i.e. thyroiditis, Addison's disease, autoimmune polyglandular syndrome, systemic lupus erythematosus, Sjogren's syndrome, haemolytic anaemia and idiopathic thrombocytopenic purpura).[17] The presence of autoantibodies reactive to different parts of the ovary has been detected in many POF cases and the most commonly recognized autoantigens are on the ooplasm, theca, granulose, corpus luteum or zona pellucida.[18–20] More specific antigenic targets of autoantibodies have been identified in steroid cell enzymes including 3b-hydroxysteroid dehydrogenase (3b-HSD), cytochrome P450 side-chain cleavage enzyme (P450SCC) and 17$\alpha$-hydroxylase/17,20 lyase enzyme (CYP17A1).[14] Nonetheless, the detection of such antibodies has yielded conflicting results because of the different stages of disease in which the tests were conducted, methodological differences and the multiplicity of potential immune targets. In our cases, only one of the three patients had positive antiovarian antibodies. Given the difficulties in detecting these antibodies, an autoimmune origin of POF may be speculated for the other two cases. Indeed, the pres-

**Table I** The Suggested Criteria of Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)[7] in the Current Three Cases of Post-Human Papilloma Virus Vaccine Manifested Primary Ovarian Failure (POF). Note That for Positive Diagnosis of ASIA, Fulfilment of Either Two Major or One Major and Two Minor Criteria is Required

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Major criteria | | | |
| 1. Exposure to an external stimuli (infection, vaccine and/or immune adjuvants) prior to clinical manifestations | + | + | + |
| 2. The appearance of 'typical' clinical manifestations; | | | |
| Myalgia, muscle weakness | – | – | Not reported |
| Arthralgia and/joint pain | + | – | – |
| Chronic fatigue, un-refreshing sleep or sleep disturbances | + | + | Not reported |
| Neurological manifestations | + | + | Not reported |
| Cognitive disturbances | – | + | Not reported |
| Pyrexia | – | – | – |
| 3. Removal of inciting agent induces improvement | NA | NA | NA |
| 4. Typical biopsy of involved organs | Not assessed | Not assessed | Not assessed |
| Minor criteria | | | |
| 1. The appearance of autoantibodies (antiovarian, anti-TPO) | – | + | + |
| 2. Other clinical manifestations (e.g. amenorrhoea) | + | + | + |
| 3. Specific HLA (e.g. HLA DRB1, HLA DQB1) | Not assessed | Not assessed | Not assessed |
| 4. Evolvement of an autoimmune disease (POF) | + | + | + |

ence of antiovarian antibodies in the second case, in addition to the finding of the anti-TPO antibodies in the third case, lends support to the idea that autoimmune responses underlying POF can develop following HPV vaccination. Moreover, as POF developed in two sisters, a genetic susceptibility predisposing to post-vaccination POF is probable. The very unusual early age of disease onset may reinforce this suggestion as it was already observed in other immune-mediated diseases.[21,22] Furthermore, the patients experienced not only POF but also a constellation of other symptoms, including arthralgia, sleep disturbances and cognitive dysfunction, consistent with the diagnosis of the ASIA syndrome (Table I).[7, 9]

## POF as a Part of the ASIA Syndrome

The three cases of POF described herein clearly fulfilled the criteria for the ASIA syndrome (Table I). ASIA comprises a group of diseases including post-vaccination phenomena,[9,11,13] silicone implant–induced autoimmunity,[23] Gulf War syndrome,[24] macrophagic myofasciitis with chronic fatigue syndrome[25,26] and the sick-building syndrome[27] which share a common set of signs and symptoms. Shoenfeld and Agmon-Levin[7] proposed four major and four minor criteria for ASIA (Table I), and to diagnose ASIA, fulfilment of either two major or one major and two minor criteria is required. The criteria for ASIA enable the inclusion of patients with well-defined autoimmune diseases (i.e. multiple sclerosis, lupus) as well as those with ill-defined and non-specific yet clinically relevant conditions (i.e. myalgia, chronic fatigue and cognitive disturbances) under the spectrum of vaccine adjuvant-associated conditions.[9] The inclusion of the latter category of manifestations under ASIA is of special importance as these non-specific manifestations are all too easily ignored or disregarded as irrelevant and non-vaccine related not only by patients and physicians, but also by scientists involved in design of vaccine trials.[28,29] Nonetheless, many ill-defined medical conditions that fall under the ASIA spectrum are frequently disabling and thus of significant clinical relevance.[9,25]

Apart from a shared set of clinical manifestations, the other main common feature in ASIA is the presence of an immune adjuvant. An adjuvant is defined as 'any substance that acts to accelerate, prolong or enhance antigen-specific immune response'.[24] The adjuvant is able to stimulate the immune system and to increase the response to a vaccine, without having any specific antigenic effect in itself.[24] Vaccines, which contain infectious antigens either attenuated or recombinant, may induce autoimmunity by means of similar 'infectious' mechanisms such as molecular

mimicry, epitope spreading, bystander activation and polyclonal activation.[30,31] When this occurs, it can be subacute or sometimes a long time after the vaccination (i.e. months to years),[32–37] which leads to difficulties in identifying a definite causality between vaccination and autoimmune phenomena. The latter will most commonly occur in genetically predisposed individuals. Indeed, personal or familial susceptibility to autoimmunity and adverse response to a prior dose of the vaccine both appear to be associated with a higher risk of post-vaccination autoimmunity.[3,9]

## HPV Vaccines and Autoimmunity

In the current literature, there are numerous cases substantiating the link between adverse immune reactions and HPV vaccines, including fatal reactions. For example, Lee[38] recently reported a case of a teenage girl who underwent sudden unexpected death approximately 6 months after her third Gardasil HPV vaccine booster. The patient experienced adverse manifestations shortly after the first dose of Gardasil injection (i.e. dizziness spells, paraesthesia and memory lapses) which were further exacerbated after the 2nd vaccine booster after which she also developed excessive tiredness (indicative of chronic fatigue), night sweats, loss of ability to use common objects, intermittent chest pain and sudden unexpected 'racing heart'. Although the autopsy examination failed to identify any toxicological, microbiological or anatomical cause of death, further investigations carried by Dr. Lee[39] showed that the post-mortem blood and splenic tissues tested positive for HPV-16 L1 gene DNA fragments corresponding to those previously found in 16 separate Gardasil vials from different vaccine lots (suspected to represent contaminants from the vaccine manufacturing process). These findings suggested that the quadrivalent HPV vaccine was indeed the most probable causal factor in this particular case. Specifically, the HPV DNA fragments detected in Gardasil vials appeared to be firmly bound to the aluminium adjuvant used in the vaccine formulation and thus likely protected against enzymatic degradation by endogenous nucleases.[40]

Additionally, thus far HPV vaccination has been linked to several autoimmune diseases, including Guillain-Barré syndrome,[41] other demyelinating neuropathies,[42–44] systemic lupus erythematosus,[3] pancreatitis,[45] vasculitis,[46] thrombocytopenic purpura[47] and autoimmune hepatitis.[48] Of note, the most prevalent adverse events associated with HPV vaccines appear to be autoimmune neurological diseases.[49,50] For instance, Sutton et al.[42] reported five cases of female patients who developed a multifocal or atypical demyelinating syndrome within 21 days of immunization with the quadrivalent HPV vaccine. As hypothesized by the authors, the temporal association with demyelinating events in these cases may be explained by the potent immune-stimulatory properties of HPV virus-like particles which comprise the vaccine. Similarly, Chang et al.[51] reported two cases who developed CNS demyelination closely following the administration of the HPV vaccine. Acute disseminated encephalomyelitis in young women (15 and 17 years old) within 3–8 weeks after HPV vaccination has also been described.[52,53] Altogether, these observations led to the hypothesis that the HPV vaccine may have been released too quickly into the market, in the absence of rigorous safety evaluations.[49,54,55] Indeed, Gardasil appears to have failed to meet a single one of the four criteria required by the FDA for Fast Track approval.[54]

## Adjuvants in HPV Vaccines and Assessment of HPV Vaccine Safety in Clinical Trials

One of the most commonly used adjuvant in vaccines is aluminium[24] which is also present in HPV vaccines. There are two different brands of the HPV vaccine: the quadrivalent Gardasil (MSD) and the bivalent Cervarix (GSK). Both are composed of HPV L1 proteins that self-assemble to form virus-like particles but differ in the use of adjuvants.[56] While the first contains only aluminium hydroxyphosphate sulphate, the second contains a combination of an oil-based adjuvant monophosphoryl lipid A (MPL) and aluminium hydroxide (a proprietary brand of the vaccine manufacturer otherwise known as ASO4), thus leading to diverse boosts in immune responses between the two vaccines.[57] Another difference is the medium in which the vaccines are produced, *Trichoplusiani* cells for the Cervarix and *Saccharomyces cerevisiae* for the Gardasil. This distinction is even more intriguing because we know the potential of yeast to trigger autoimmune responses.[58] Nonetheless, a recent large observational study on the safety of the quadrivalent HPV vaccine allegedly identified no autoimmune safety concerns.[59] However, several important biases might have contributed to the negative findings of the study. Firstly, the study included all women who received at least one dose of the vaccine, thus making this particular population less sensitive for the detec-

tion of serious adverse reactions (given that such events occur with much lesser frequency when fewer doses of the vaccine are administered). Secondly, the research team failed to recruit appropriate expertise for diagnosis of autoimmune disorders. Namely, no immunologist/autoimmunologist, neurologist and ophthalmologist were present during the initial screening of the study participants which is particularly surprising in view of the fact that autoimmune conditions of interest that were examined included rheumatological, autoimmune disorders and neurological/ophthalmic conditions.[29,59] Finally, the Safety Review Committee failed to take into account the fact that autoimmune manifestations may be non-specific and not fitting a well-defined autoimmune condition[9,25,28] yet severely disabling.[26,35,60] Of note, the study was entirely funded by the quadrivalent HPV vaccine manufacturer Merck and all authors received previous founding from Merck and/or were consultants for the HPV vaccine manufacturer.[59]

Finally, a further major bias in evaluating HPV vaccine safety comes from the fact that in all clinical trials for both Gardasil and Cervarix, safety outcomes were compared between vaccine recipients and those who received an aluminium adjuvant containing 'placebo'.[49,50] This practice is common in vaccine trials,[61] despite much evidence showing that aluminium in vaccine relevant exposures can be toxic to humans,[34,35,60] and therefore, its use as a 'placebo control' in vaccine trials can no longer be justified.[61]

## Conclusions

We documented here the evidence indicating the potential of the HPV vaccine to trigger a life-disabling autoimmune-mediated condition such as POF. Given that persistently infected women with HPV seem not to develop cancer if they are regularly screened and that the long-term clinical benefits of HPV vaccination are still a matter of speculation, a more rigorous assessment of vaccine risks and benefits is recommend.[49,50,62] Thus, physicians should remain within the rigorous rules of evidence-based medicine, to adequately assess the risks versus the benefits of HPV vaccination.[63,64]

## Disclosure

An informed consent has been received from the patients present their cases. Y Shoenfeld has served as an expert witness in cases involving adverse vaccine reaction in the no-fault U.S. National Vaccine Injury Compensation Program. LT, SC and CP declare no conflict of interests. The authors thank the Dwoskin Family Foundation for support.

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