A link between human papilloma virus vaccination and primary ovarian insufficiency: current analysis

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Purpose of review
The cause of primary ovarian insufficiency (POI) is multifactorial. Known causes include external factors such as chemotherapy, radiotherapy, exposure to endocrine-disrupting chemicals, infections that lead to a permanent insult to the ovary, autoimmune conditions, and genetic causes. An association between the quadrivalent antihuman papilloma vaccine (HPV4) and POI was recently suggested.

Recent findings
An increasing number of cases of POI post-HPV4 are being reported. Possible mechanisms for the suspected effect of HPV on female reproductive function are a toxic effect or an autoimmune response. The trigger could be the vaccine immunogen contents or the adjuvants, the latter are used to increase the immune reaction. The adjuvant in HPV4 contains aluminum. Animal models have shown aluminum exposure to inhibit expression of female reproductive hormones and to induce histologic changes in the ovaries. Specific genetic compositions may be more susceptible to developing an autoinflammatory syndrome after exposure to an environmental factor.

Summary
The mechanisms responsible for POI are not yet fully understood. Although case reports cannot establish causation, awareness of a possible link between HPV4 and POI will help to identify and manage future cases that may arise.

Keywords
adjuvant, aluminum, autoimmune/inflammatory syndrome induced by adjuvants, autoimmunity, human papilloma virus vaccine, primary ovarian insufficiency

INTRODUCTION

Primary ovarian insufficiency (POI), also termed premature ovarian failure or hypergonadotrophic hypogonadism, is characterized by the triad combination of amenorrhea for at least 4 months, sex steroid deficiency, and two measurements, at least 1 month apart, of serum concentrations of follicle-stimulating hormone (FSH) of more than 40 IU/l, in a woman aged less than 40 years (>2 SD under the mean menopausal age) [1–3]. POI is estimated to affect, approximately, 1% of women by age 40 years, 1 : 1000 women by age 30, and 1 : 10 000 women by age 20 [4]. However, current prevalence rates of POI are not known. This review will discuss the cause of POI and focus on the most recent findings regarding the possible association between the quadrivalent human papilloma virus vaccination (HPV4) and POI.

CAUSES OF PRIMARY OVARIAN INSUFFICIENCY

The causes of POI are multifactorial, and can classically be divided into three categories.

External causes

The most straightforward cause is an iatrogenic insult to the ovaries secondary to chemotherapy or radiotherapy [5]. Toxic effects caused by endocrine-disrupting chemicals (EDCs) can lead to POI via two mechanisms: altering the availability of ovarian hormones; and altering binding and activity of the hormone at the receptor level. Among possible EDCs are pesticides, plasticizers (e.g., bisphenol A and phthalates), dioxins, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons [6]. Cigarette smoking was found to be associated with premature

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KEY POINTS

- Elucidation of the mechanisms responsible for POI will improve diagnostic tools, treatment approaches, and prevention strategies of POI in adolescents and women.
- As case reports cannot establish causation, we cannot yet conclude whether POI that is present in adolescents following human papilloma virus vaccine 4 is related to this vaccination.
- Future studies of the effect of the aluminum-containing adjuvant in genetically susceptible patients may help to reveal the mechanisms involved in POI.

menopause and increased risk of idiopathic POI [7]. Viral infections such as HIV and mumps have been presumed to be causes of POI.

Autoimmune diseases

Approximately, 10–30% of women with POI have organ-specific autoimmune diseases, the most commonly reported is hypothyroidism, and the most clinically important is Addison's disease. POI is also associated with autoimmune polyglandular syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), and rheumatoid arthritis. Subsequent detection of autoantibodies supports the diagnosis of autoimmune POI. POI can be isolated with antiovarian autoantibodies, or a shared autoimmune response with the adrenal. POI patients who also have adrenal autoimmunity commonly present with autoantibodies that recognize several types of steroid-producing cells of the adrenal cortex, testis, placenta and ovary, called steroid cell antibodies. Autoimmune oophoritis is characterized by a mononuclear inflammatory cell infiltrate in the theca cells of growing follicles, with early-stage follicles without lymphocytic infiltration. This infiltrate includes plasma, B cells, and T cells. A novel classification criterion for autoimmune POI was recently proposed, comprising subdivision into three distinct categories (possible, probable, and confirmed) based on autoantibodies, autoimmune disease, and ovarian histology [8▪].

Genetic causes

A genetic basis for POI is gaining headway, as discoveries from the human genome project and next-generation sequencing promote our understanding of the factors involved in ovarian development. Many genes have been involved in the development of POI, among them fragile X mental retardation 1 (FMR1) premutation, BMP15, LHR, FSHR, INHA, FOXL2, FOXO3, ERa, SF1, ERb, and CYP19A1 genes, as well as X chromosome abnormalities including deletions, translocations, and numerical abnormalities such as Turner's syndrome [9]. Inconsistent results regarding the involvement of these genes in POI have been observed among studies, presumably the result of genetic variability among ethnic groups [10]. Importantly, the cause of POI remains unknown in, approximately, 75–90% of cases. We here review the possible role of HPV vaccine and POI.

THE ROLE OF VACCINATION AND PRIMARY OVARIAN INSUFFICIENCY

The role of vaccination and POI has recently been suggested and a number of case reports have been published [11▪,12,13] (Table 1). All patients had normal puberty, all but one initially presented with a change from regular cycle to irregular and scant periods. This concurs with the general presentation of POI, which tends to develop after normal puberty and established regular menses, with primary amenorrhea presenting in only about 10% of cases. Oligomenorrhea or polymenorrhea may appear early, yet sometimes menses stop abruptly [2]. Only one of the case studies (case 3, Table 1) was immunized prior to menarche. Time lapsed from the start of irregular menses until definite diagnosis, probably because irregular menses are common in this age group. Importantly, treatment with oral contraception could mask the diagnosis of POI, and the window for intervention and preservation of ovary reserve. In all the cases the teens/young women underwent thorough diagnostic work-ups, including differential diagnostic tests. Interestingly, antiovarian and/or antithyroperoxidase antibodies were detected in three of the six cases (cases 1,3,4, Table 1). POI developed in two sisters (cases 2,3), suggesting possible genetic susceptibility predisposing to postvaccination POI.

To define the association between POI and the HPV vaccine an analysis was carried out based on the major national surveillance databases for adverse events following the administration of the vaccine [14]. Four cases were retrieved from the Vaccine Adverse Event Reporting System, one case from the Australian database and two from the European database. A trial to identify more cases according to hospital discharges with the diagnosis of POI did not reveal any results [14]. However, most individuals with suspected POI are not hospitalized for such evaluation, thus this trial does not contribute much.

THE HUMAN PAPILLOMA VIRUS VACCINE

Recombinant synthesis of the HPV L1 protein, the major component of the HPV capsid, leads to

Table 1. Published cases of primary ovarian insufficiency in women who received human papilloma virus vaccination

Case number	Health status	Age (years)			Type of vaccine	Work-up diagnosis				Reference number
		At menarche	At HPV vaccination	At diagnosis		Presentation	Antibodies (Ab's)	Genetic studies	Ultrasound	
1	Healthy	13	14	16	HPV4	Irregular menses, scant menses	Positive antithyroid peroxidase and antithyroglobulin Ab's	46XX, Fragile – normal galactosemia – normal	Normal	[12]
2	Healthy, sister of case 3	13.5	14	15	HPV4	Irregular menses	Negative antiadrenal and antiovarian Ab's	46XX, Fragile X – normal, FSH receptor – normal		[13]
3	Healthy, sister of case 2	15	13	15.3	HPV4	Onormaly two menses	Positive antiovarian Ab's	46XX, Fragile X – normal FSH receptor – normal		[13]
4	Healthy	13	21	23	HPV4	Irregular menses	Positive antithyroid peroxidase Ab's	46XX, Fragile X – normal	Normal	[13]
5	Cerebral Palsy, Asperger, Epilepsy	11 (on contraceptive pills since age 12)	12.9	18	HPV4	After cessation of contraceptives, amenorrhea	Negative antiadrenal, antithyroid and antiovarian Ab's	46XX, Fragile X – normal galactosemia – normal	Left ovary not visualized	[11▪]
6	Healthy	10	14	17	HPV4	Irregular menses	Negative antiadrenal and antiovarian Ab's		Normal	[11▪]

FSH, follicle-stimulating hormone; HPV, human papilloma virus.

assemblage of virus-like particles (VLPs). When administered with an adjuvant, these VLPs induce a higher immune response than occurs after a natural infection. Two vaccines were developed to protect against the infection of HPV. The bivalent vaccine (Cervarix) contains 20 μg each of HPV 16 and HPV 18 L1 proteins, the two most common HPV oncogenic types causing cervical cancer, with an adjuvant containing aluminum hydroxide 3-O-desacyl-4-monophosphoryl lipid A. The quadrivalent vaccine (Gardasil, HPV4) contains 40 μg of HPV 16, 20 μg of HPV 18, 20 μg of HPV 6, and 40 μg of HPV 11, adding protection against genital warts (HPV types 6 and 11), and includes amorphous aluminum hydroxyphosphate sulfate as an adjuvant.

PRECLINICAL AND CLINICAL STUDIES PRIOR TO INTRODUCING THE HUMAN PAPILLOMA VIRUS VACCINE

According to Little and Ward [11▪] three major problems in the introduction of the HPV4 vaccine raise questions about its safety. First, in the preclinical studies for toxicity, rats were tested with only two vaccine doses rather than with the complete vaccination course. Moreover, long-term reproductive studies of vaccinated female rodents are still needed. Second, phase II and III clinical studies of the safety of HPV4 on female fertility are lacking. Studies assessing the safety of HPV4 on ovarian function are limited due to a number of reasons: about 50% of the girls studied were lost to follow-up at 12 months; contraception use may have posed a masking effect on ovarian function; adverse events were only recorded two weeks after vaccinations; and medical conditions occurring more than 7 months after vaccinations were not considered to be associated with the vaccine.

Finally, autoimmunity or toxic effects may be triggered or enhanced by adjuvants, as well as by the immunogen contents of the vaccine [15,16]. An adjuvant is defined as 'any substance that acts to accelerate, prolong, or enhance antigen-specific immune response' [17]. An adjuvant may stimulate the immune system and increase the response to a vaccine, without itself conferring any specific antigenic effect. The adjuvant in HPV4 contains aluminum. Yet, the placebo selected for the control in several of the phase III safety studies of HPV4 was the aluminum adjuvant present in the vaccine solution, amorphous aluminum hydroxyphosphate sulfate. Thus, the demonstration of similar safety profiles between HPV4 and a placebo could be due to the effect of the adjuvant [18].

HUMAN PAPILLOMA VIRUS AND OTHER AUTOIMMUNE RESPONSES

Interestingly, the HPV vaccine, specifically HPV4, has been shown capable of prompting an autoimmune response [16], such as to multiple sclerosis-like disease [19], acute disseminated encephalomyelitis [20], SLE [21,22], postural tachycardia orthostatic syndrome [23,24], and cerebral vasculitis [25]. On the contrary, a large population-based cohort study conducted in Denmark and Sweden, based on more than 696 000 doses of HPV4 among women, did not show consistent evidence to support causal associations between exposure to HPV4 and between autoimmune, neurologic conditions, or venous thromboembolism [26]. In a case-control study conducted in France, no increased risk was observed following HPV4, for idiopathic thrombocytopenic purpura, central demyelination/multiple sclerosis, Guillain–Barré syndrome, connective tissue disorders (including SLE, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus, and autoimmune thyroiditis, compared with a control group [27]. Furthermore, a study of almost 4 million women (ages 10–44) in two Scandinavian countries, with two years follow-up, reported that the HPV vaccination was not associated with the development of multiple sclerosis or other demyelinating diseases [28▪].

MECHANISMS FOR THE SUSPECTED EFFECT OF HUMAN PAPILLOMA VIRUS 4

Several mechanisms may be involved in an effect of HPV4 on the female reproductive function. One proposed mechanism is toxicity. Among the toxins investigated to cause POI is the aluminum metal that composes the adjuvant. Despite its abundance and ubiquitous distribution, aluminum is known to have hazardous effects on living organisms [29]. Aluminum can cause toxic effects in the brain, bone, immune, and hematopoietic systems, by interfering with cellular and metabolic processes [29,30]. Occupational exposure to aluminum caused, for example, decreases in levels of thyroid stimulating hormone and prolactin among mine workers [31]. Environmental exposure to aluminum, as well as to other toxic metals is considered to contribute to cognitive impairment in children living in rural areas [32]. Regarding neurodegenerative diseases, the removal of aluminum improved symptoms of multiple sclerosis [33]. In animal models aluminum has been shown to accumulate in the male and female reproductive systems and was shown to be an endocrine disruptor [34–36]. In addition, both hormonal and histological assays demonstrated inhibition of reproductive functions in female rats during subchronic aluminum exposure in drinking water [37,38]. In the latter experiment, aluminum hampered body and ovary weight and suppressed secretions of estradiol, progesterone, lutenizing hormone (LH), and FSH [38]. Another experiment reported that subchronic aluminum exposure in drinking water during a period of 120 days disrupted ovarian structure and function. Aluminum was found to disturb the metabolic balances of trace minerals, to inhibit the activities of enzymes involved in energy production, and to decrease the expressions of LH and FSH receptors [37]. Moreover, exposure of Nile tilapia fish to water containing aluminum decreased protein concentrations in their ovaries [39]. Aluminum was also shown to have a toxic effect on the ovarian structure and size of the Chinese hamster, to induce decreases in E2, FSH, LH, and their receptors, and to decrease proteins and enzymatic activities [40].

The second proposed mechanism is autoimmune. Over recent years, evidence has accumulated in support of what is now referred to as Autoimmune/inflammatory Syndrome Induced by Adjuvants syndrome (ASIA), a term recently coined by Shoenfeld and Agmon-Levin [41]. This term is used to describe an 'umbrella' of clinical conditions namely siliconosis, Gulf War Syndrome, Macrophage Myofasciitis Syndrome, sick building syndrome, and postvaccination phenomena, which share signs and symptoms [16]. The most frequently reported symptoms include myalgia, myositis, arthralgia, neurological manifestations, fever, dry mouth, and cognitive alterations. The shared presence of these symptoms suggests a common denominator, which has been identified in the adjuvant. Appearance of the immune-mediated conditions mentioned above follows chronic stimulation of the immune system by agents with adjuvant characteristics. The prevalence of immune-mediated conditions is rising in a number of geographical areas and these geoepidemiological changes may be explained by a complex of genetic and environmental factors.

Although specific genetic compositions (i.e., HLA DRB1, HLA DQB1) may predispose to the emergence of an autoimmune or an autoinflammatory syndrome, the presence of an external or endogenous environmental factor, which triggers the immune response, is a necessary condition. Aluminum, silicone pristane, and infectious components are some of the environmental factors that comprise an immune adjuvant effect [17,41]. See Table 2 for a summary of the significance versus the concerns in HPV4.

Table 2. Important issues in human papilloma virus vaccination and primary ovarian insufficiency

Significance of HPV vaccine	Concerns with the HPV vaccine
HPV causes cancers of the cervix, vagina, vulva, penis, anus, and oropharyngeal cancers. It also causes anogenital warts (condyloma acuminata).	HPV4 received a Fast Track approval by the FDA following a six-month priority review process.
The HPV vaccine has very high efficacy for prevention and decreases the burden of HPV infection and its sequealae.	Routine Pap smear provides early diagnosis and early management of cervical cancer.
Large cohort studies found no evidence supporting associations between exposure to HPV4 vaccine and autoimmune, neurological, and venous thromboembolic adverse events.	The number of case reports of autoimmune side-effects following the HPV administration has increased.
Only a very small proportion of individuals who receive vaccination will subsequently develop POI.	Information on the real established incidence of POI is lacking.
HPV4 is given to young girls, one of the peak periods prone to autoimmune diseases.	Temporal association is hard to assess.
	There is a genetic predisposition for who is susceptible to develop ASIA.

ASIA, Autoimmune/inflammatory Syndrome Induced by Adjuvants; FDA, Food and Drug Administration; HPV, human papilloma virus; POI, primary ovarian insufficiency.

HUMAN PAPILLOMA VIRUS INFECTION

Of the more than 150 types of HPV, approximately, 40 are transmitted through sexual contact and infect the anogenital region and other mucosal sites of the body [42,43]. Mucosal HPV types are classified as either high-risk HPV (oncogenic) (types 16 and 18) or low-risk HPV (types 6 and 11). High-risk HPV causes many cancers of the cervix, vagina, vulva, penis, and anus. HPV16 is linked to many oropharyngeal cancers. Low-risk HPV causes anogenital warts and recurrent respiratory papillomatosis. The prevalence of types HPV 6 and 11 among sexually active women aged 18–25 years was 2.2%, and of types 16 or 18 was 7.8%. Among the great breakthroughs in medicine, there is no doubt that vaccinations are on the top of the list. Vaccinations have made a tremendous change in disease care, and have completely abolished some of the most severe causes of morbidity and mortality. The HPV vaccine demonstrates very high efficacy for prevention and for reduction in the burden of HPV infection and its sequelae. Nonetheless, we must always question and test the safety profile of vaccinations. Although adjuvants augment vaccine potency, they can cause side-effects and may induce ASIA among individuals who are genetically prone [44▪,45].

CONCLUSION

The mechanisms responsible for ovarian dysfunction are not yet fully understood. Elucidation of these mechanisms will improve diagnostic tools, treatment approaches, and prevention strategies of POI in adolescents and women. As case reports cannot establish causation, we cannot yet conclude whether POI that is present in adolescents following HPV4 is related to this vaccination. We should be aware of the first signs of suggestive amenorrhea, such as irregular menses, and try not to mask it with oral contraceptives until a first work-up is completed. Future studies of the effect of the aluminum-containing adjuvant in genetically susceptible patients may help to reveal the mechanisms involved.

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Conflicts of interest

N.G. declares no conflict of interest. Y.S. has served as an expert witness in cases involving adverse vaccine reaction in the no-fault U.S. National Vaccine Injury Compensation Program.

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