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Insights into the autoimmune aspect of premature ovarian insufficiency

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Premature ovarian insufficiency (POI) refers to a continuum of decreasing ovarian function in women before the age of 40. To date, the cause of POI in the majority of cases remain unresolved. Many cases has been linked to genetic, toxic, infections, enzymatic and iatrogenic causes.

A key function of the immune system is to identify and differentiate "self" and "non self" i.e. tolerance. Loss of self-tolerance results in an immune response against self-tissues and thus autoimmunity. Various investigations have highlighted the role of autoimmunity and its pertinence to POI. Several potential immune antigenic targets in the ovary have been reported to be involved in autoantibody induced autoimmune attack. The presence of lymphocytic oöphorits in ovarian samples of patients with POI provides histopathological evidence of autoimmune ovarian involvement. Finally, POI is strongly associated with other autoimmune conditions including for instance Addison disease, autoimmune polyglandular syndrome (APS) −1, APS-4, hypothyroidism, and diabetes mellitus

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among other autoimmune diseases. Taken together, these lines of evidence provide strong basis that support the role of autoimmunity as a potential cause of disease etiopathogenesis. Continuing research is increasingly providing more insight into the complex disease process. The aim of this review is to summarize the current literature related to the autoimmune nature of POI.

Introduction

Premature ovarian insufficiency (POI), sometimes referred to as primary ovarian failure is a common cause of female infertility, and is defined as amenorrhea for at least 4 months in women before the age of 40 with two one-month apart serum FSH levels in the menopausal range [1]. The prevalence of POI is estimated to be 0.9–3% in the general female population [2]. Two major mechanisms have been proposed to explain POI: follicle dysfunction and follicle depletion. In the former, follicles exist in the ovary, however a pathogenic process prevents their normal function, in contrast primordial follicle depletion is characterized by the failure of initial pool establishment in the uterus or accelerated expenditure and atresia of follicles during growth [1,3]. Semantically, the term primary ovarian insufficiency better captures the nature of the disease. Ovarian dysfunction is variable and refers to a continuum rather than a dichotomous state. Ovarian function remains variable and unpredictable in 50% of patients, spontaneous ovulation occurs in 20% of patients and about 5–10% of women conceive and deliver a child after receiving this diagnosis [1,4].

Patients typically presents with symptoms of estrogen deficiency including oligomenorrhea, or amenorrhea. The sequel of chronic hypoestrogenism can be dire for patients causing osteoporosis, cardiovascular disease progression, urogenital atrophy and increased all-cause mortality [5,6].

In the majority of POI cases (90%), the cause remains unestablished, thus idiopathic. Potential etiologies have been proposed including genetic abnormalities, metabolic/enzymatic dysfunction, infections, environmental factors, iatrogenic (following radiotherapy or chemotherapy) and autoimmune causes [7].

Several lines of evidence currently points toward a link to autoimmunity including the demonstration of ovarian autoantibodies, the presence of lymphocytic oöphorits on histological analysis and the strong association of POI with other autoimmune disorders [8,9]. The current review focuses on the role of autoimmunity in the pathophysiology of POI.

Immunological aspects of ovarian function

Antibodies in premature ovarian insufficiency

The antigens against which the immune system mounts the autoimmune response in POI are unknown, theoretically the immune response can target the ovarian follicle (granulosa and the thecal layer), the germinal component, or the zona pellucida [10].

Early investigations reported varied prevalence of antiovarian antibodies with results ranging from 24% to 73.3% [11,12]. Vallotton and Forbes [13] were the first to describe the presence of antibodies to ova cytoplasm and nuclear factor in POI patients. In their communication, 28 out of 187 patients had fluorescence of the oocyte cytoplasm pointing towards the presence of anti-oocyte antibodies. Among those 28 positive patients, nine had premature menopause. Other studies showed high prevalence of anti-oocyte cytoplasm antibodies in cases of fertilization failure or oocyte retrieval failure [14]. The antigen recognized by these antibodies remains unknown, however in an experimental mouse model of autoimmune ovarian disease, these antibodies targeted a 125 kDA protein called OP1. OP1 is

expressed in the oocyte and persists until the blastocyst stage, Knock out mouse model shows this gene inactivation results in sterility of female mice [15]. OP1 was later termed MATER (maternal antigen that embryos require) and was isolated in humans sharing approximately 67% sequence homology with the mice [16].

Zona pellucida represents the extracellular material surrounding the oocyte which is composed of glycoproteins with potential antigenic potency. ZP plays an integral role in sperm attachment, fertilization and supports communication between oocyte and follicle [17]. Microdot assay using human ZP antigens facilitated the detection of anti ZP antibodies from the sera of idiopathic POI patients. It is postulated that anti -ZP causes a significant blockage effect on sperm binding and penetration of human ZP [18,19]; the contribution of anti-ZP antibodies in low fertilization has been consistently reported in patients responding poorly to IVF therapy [20,21].

Given the nature of the disease and the findings pointing towards autoantibodies on the surface of granulosa cells, antibodies against gonadotropin receptors were investigated as potential targets. A small percentage of POI patients had detectable FSH receptor antagonist [22]. Anasti et al. [23], tested the role of antiovarian antibodies on the biological activities of FSH and LH by using transgenic cell line expression with human FSH receptor or human LH receptor. In a sample of 38 patients with POI, no inhibition was detected. Taken together there is currently poor evidence to support the role anti-gonadotrophin antibodies in disease etiopathogenesis [23].

Pasoto et al. [24], identified a potential 67 kDa antigen in bovine and human corpus luteum that interacted with antibodies in female patients with systemic lupus erythematous under the age of 40 and was associated with high serum FSH levels. This finding is presumed to represent the early stage of ovarian dysfunction in SLE patients, and provide potential explanation of POI.

With the advent of more specific assays, true histological and molecular targets have been identified. Several immunodominant autoantigens have been reported including heat shock protein 90-beta, alpha-actinin 4, heat shock 70 protein 5 (HSPA5), and beta-actin [11,25]. The previously mentioned antigens are known to play an important role in the process of fertilization. Actin plays an integral role of cell motility and maintenance of the integrity of the cell and the cytoskeleton. Depletion of actin results in abnormalities of chromosomal segregation, aberrant coalescence of telophase chromosomes and egg production [26]. Heat shock protein 70 has an integral role in protein processing in the endoplasmic reticulum and has anti-apoptotic functions [27]. Other studies demonstrated that embryos devoid of HSPA5 exhibited an increase in cellular apoptosis with high preimplantation lethality [26].

Research into other ovarian targets continues, Sundblad et al. [28] identified a new anti-ovarian antibody against an alpha-enolase in 19.1% of a group of 110 patients with POI. Anti-enolase antibody is not specific for POI and has been isolated in a variety of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, liver autoimmune disease, as well as other diseases [29–31]. Enolase is a metalloenzyme that plays an integral role in the glycolytic pathway, however its role in disease pathogenesis has yet to be determined [32].

Another major target in POI is the steroid hormone producing cells that are mainly isolated in patients with Addison's disease, further details will be discussed in a later section (see below).

Zhen et al. [9] investigated a panel of serologic autoimmunologic parameters in POI and attempted to elucidate the potential role in disease etiopathogenesis. In their analysis, POI subjects had significantly higher levels of anti-Jo-1 (10 among 96 POI patients, $p = 0.01$) and anti-PR3 (14 among 96 POI patients, $p = 0.001$). The increased levels of both antibodies suggest the contribution of an autoimmunologic process in disease pathogenesis, however their role remains elusive.

It is worth noting that antibody detection in POI can be challenging and may be hampered by the fact that the disease is diagnosed at an end stage (i.e. infertility and amenorrhea due to depletion of oocytes). At this stage, the exhaustion of oocytes' reserves parallels the loss of the antigenic target [33].

Relationship with other autoimmune diseases

The rationale of an autoimmune origin of POI stems, at least partly, from its association with other autoimmune diseases. Addison's disease (AD), also known as primary adrenal insufficiency, is an uncommon insidious disease resulting from the autoimmune loss of glucocorticoids and mineral

corticosteroids [34]. Early observational reports highlighted the association of ovarian failure to Addison disease with some cases preceding the disease by 8–14 years [35,36]. Moreover, autoimmune lymphocytic oöphorits which is characterized by the infiltration of mononuclear plasma B and T cells into the theca cell of growing follicles was described in cases diagnosed with primary adrenal insufficiency [37].

Close to one-fifth of POF cases have been diagnosed with other autoimmune diseases, one of the more pronounced associations is probably with the autoimmune polyglandular syndrome type one (APS-1) also known as autoimmune polyendocrinopathy-candidiasis-ectodeermal dystrophy/dysplasia (APECED). A mutation in the autoimmune regulator gene (AIRE) results in subsequent dysregulation in central tolerance process by which T-cells with potential reactivity to self-antigens are eliminated during differentiation process in the thymus [38]. It is estimated that 40% APS-1 female subjects develop POI [33,39].

Similarly APS-II also known as Schmidt-Carpenter syndrome an autosomal dominant disease comprising AD, insulin dependent diabetes, has been associated with POI with an estimated prevalence of 10–25% [40]. The association between POI and AD points towards the presence of cross reactive autoantibodies that target common antigens in steroid hormone producing cells. Indeed, antibodies to steroid-producing cells (StCA), a group of polyclonal immunoglobulins of the IgG class have been detected by immunofluorescence. Several antigenic targets for those antibodies have been identified including P450-17alpha hydroxylase, P450 side chain cleavage and 21 hydroxylase (21-OH). StCA are present in APS-I, APS- II, Addison's disease and POF [41,42].

StCA is found in the majority of coexisting AD and POF cases, however in patients with isolated POI or POI coexisting with other autoimmune diseases, StCA is almost always undetected [43]. In the study conducted by Reaeto et al. [39]on a large cohort of Italian women with AD, the prevalence of POI with AD was 20.2%, the prevalence varied with different types of APS, the highest was detected in patients with APS-1 (>40%), lower in APS-4 (30%), and lowest in APS-2 (16%). In patients with concurrent AD and POI, AD tends to develop before POI. A similar pattern is detected with APS-1, and APS-4. Such findings raise the possible need of StCA antibody testing in patients diagnosed with APS-1,APS-4 and AD aiming to stratify the risk for POI development. Contrary to the previous finding, POI tends to precede the diagnosis of AD in women with APS-4. StCA antibodies were detected in the majority of APS-1 patients presenting with POI (11 of 13; 84.6%), similarly patients with isolated AD and coexistent POI had a 70% positivity for StCA. Taken together, these observations indicate that StCA are good markers for POI in patients presenting with AD [39].

Other autoimmune diseases have been shown to coexist with POI including both endocrine and non-endocrine diseases such as hypothyroidism, diabetes mellitus, hypophysitis, thrombocytopenia purpura, vitiligo, autoimmune hemolytic anemia, rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis and hepatitis [42,44]. It is estimated that 10–40% of women with POI have another autoimmune disease, most commonly hypothyroidism (27%), followed by diabetes mellites (2.5%) [45].

Animal models in POI

Experimental animal models provide essential tools in exploring disease pathogenesis and guides research for the development of novel therapeutic options. Animal models can be broadly divided to spontaneous or artificially induced [46,47].

Experimental autoimmune oöphorits (EAO) can be induced in BALB/c mouse by immunization with bovine or rat ovarian extract in complete Freud's adjuvant. Allergic oöphorits has been detected as early as day 14, with lymphocytic infiltration into the ovaries. Germinal centers appear in thymus and spleen indicating the involvement of both B and T cells in the immune response. The passive transfer of T and B cells from spleen to naïve recipients resulted in disease induction, thus highlighting their pathogenic role [48]. Anti-ovarian antibodies were detectable after day 28, with titers correlating with the reproductive abilities of the recipients. Moreover, passive immunization with those antibodies resulted in a transient reduction in the reproductive capacities in the recipients [49,50]. Histological assessment revealed the characteristic recruitment of lymphocytes and macrophages, however major differences exist in follicular involvement; primordial follicles were involved in animal models in contrast to human oöphorits [49,50].

In another animal model, immunization with ZP was shown to cause a rapid atretic appearance and reduction in the number of growing follicles however, lacking the inflammatory oöphorits witnessed in the first model. Growing follicles disappeared by 30 weeks post immunization [51]. The main target appears to be ZP3, which is involved in sperm reception [52]. The adoptive transfer of ZP3 specific CD4+ cells was sufficient for induction of oöphorits, ZP3-specific CD4+ T cells mainly produced IL-2, and TNF indicating a Th1 response. Due to the lack of characteristic inflammatory oöphorits, this model is relevant in POI cases without coexisting AD.

Spontaneous EAO in neonatally thymectomized mice is another animal model of POI. Animals develop the disease at day 3 after birth among other organ specific autoimmune manifestation, with a mixed population of T cells and organ specific antibodies in the serum [53]. Thymectomy has to occur between the second and fifth day after birth to prevent the development of CD4+ T cells with regulatory or suppressor activity. Transfer experiment of CD4+ T cells of theymectomied donors caused the characteristic oöphorits in these patients [54,55]. In this model, histological features occur in an orderly sequence, starting with patchy infiltration of lymphocytes, then growing follicles are infiltrated with monocytes, macrophages, neutrophils and plasma cells. Autoantibodies are detected by day 28, and oöphorits is most severe between 4 and 14 weeks after thymectomy with follicular atresia. Ovarian atrophy then ensues after the resolution of active inflammation in week 14 [53,56,57].

Immunization of the SWZJ female model with p215-245 peptide from inhibin-alpha has been shown to activate CD4+T cells and induce EAO with unique biphasic phenotype, an early enhanced fertility followed by delated stage of POI. This autoantibody prevents inhibin mediated down regulation of FSH release thus increasing follicular maturation and ultimately results in accelerated depletion of the primordial pool and thus premature infertility [58].

When all of the above is considered together, it becomes clear that POI pathogenesis has both cellular and humoral components with anti-ovarian autoantibodies targeted at various antigens some of which remain undetermined.

Histological evidence of autoimmune nature of POI

Autoimmune lymphocytic oöphorits is an entity that was first described in subjects with concurrent AD. It is characterized with the presence of intense lymphocytic infiltration in the theca of growing follicles with a characteristic sparing of primordial follicles [59]. Potentially, these findings raise the possibility of developing immunosuppressive treatment modalities that can restore fertility. In an extensive review by Hoek et al. [37], it is demonstrated that in patients with coexisting POI and AD, the majority of cases had lymphocytic oöphorits and of all lymphocytic oöphorits cases, 78% had steroid cell antibody detected. Macroscopically, ovaries were either cystic or normal. It is postulated that cyst formation is partly secondary to high gonadotropin levels. Microscopically, primordial follicles and ovarian cortex was consistently spared. Developing follicles are predominantly infiltrated with mononuclear inflammatory cells, with a clear pattern of increased infiltration density during the various maturity phases. Preantral follicles have a thin rim of infiltrating lymphocytes whereas larger follicles have a more dense and extensive infiltration affecting both the external and internal theca. Moreover, the granulosa layer remains spared until luteinization. Similarly, atretic follicles, corpora lutea and corpora albicantia are also infiltrated. Such an infiltration pattern mirrors the presence of steroid producing cells thus highlighting their role as potential targets [59].

Immunohistochemistry reveals a predominant T cells (CD4+, and CD8+) with plethora of plasma cells in the ovarian infiltrate. It is postulated that the T cell population is the major player in driving cellular destruction, with plasma cells being responsible in antibody secretion (mainly IgG, but also IgA and IgM) [60,61].

Differences exist in the histological pattern of idiopathic POI in the absence of adrenal autoimmunity. Lymphocytic oöphorits is less likely encountered in the absences of AD. Notwithstanding, direct immunofluorescence provided evidence to the presence of immunoglobulins in the vascular wall of at least 50% of cases, and the stroma and follicular cells in 30% of the cases [62]. It is postulated that antibodies are present but in a low titree not high enough to induce local inflammation and thus oöphorits. Histological analysis in patients with isolated POI showed that 60% had fibrotic ovaries and lacked ovarian follicles, whereas in 40% of the cases, the number of follicles was variable from few to

numerous [63]. Due to the fact that the majority of the histological samples showed atrophic changes, it might be that this stage represents the end stage of the autoimmune process directed against ovarian structures, thus histological investigations could have been hampered by the end stage disease [37].

The prevalence of autoimmune oöphorits in POI remains unknown. Until recently, no reliable well-validated serum marker existed, and thus lymphocytic oöphorits can only be confirmed histologically [64]. Bakalov et al. [65] investigated the association between adrenal antibodies and lymphocytic oöphorits in women who presented with 46 XX spontaneous premature ovarian failure. By controlled evaluation including women who tested negative for adrenal antibodies, a significant association was detected between adrenal cortex autoantibodies and the presence of histologically confirmed autoimmune oöphorits [65]. Therefore, these antibodies could be a surrogate marker and potentially can be used instead of invasive techniques to detect lymphocytic oöphorits.

Premature ovarian insufficiency and vaccination

Human papillomavirus (HPV) is one of the common sexually transmitted disease in the general population. Since 2006, HPV vaccination has been introduced globally including Europe and the United states [66]. The introduction of population scale vaccination raises apprehension especially in light of reported adverse effects.

Endocrinopathies and HPV have been often addressed in the literature. Colafrancesco et al. [67] reported three cases of POI following the first dose of HPV vaccination. Two of the patients seroconverged with positive autoantibodies including (anti-TPO, and anti-ovarian). On hormonal screening and serological evaluations, all patients demonstrated hormonal profiles suggestive of ovarian failure including increased follicle stimulating hormone and luteinizing hormones and low levels of estradiol. Furthermore, 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. This report was substantiated by Little et al. [68,69] who presented four additional cases who developed POI following HPV vaccination. The girls were aged 16 and 18 years at diagnosis with a clinical history and hormonal profiles suggestive of POI. The diagnosis was established after exclusion of other causes including pregnancy, genetic, endocrinal and other causes. In their report, the authors additionally questioned the safety of the vaccine pertinent to the female reproductive system. For instance, in the HPV safety study on animal model, the influence of HPV on the reproductive system was not recorded, measured or analyzed on the long term period. Furthermore, adverse clinical trials (Phase II and III) were flawed by the loss to follow up cases, and an abundance of patients who started taking contraceptive pills thus masking ovarian insufficiency, among other concerns.

Several mechanisms by which an infectious antigen may induce autoimmunity have been defined [70] including for instance *Molecular mimicry* between infectious antigens and self-antigens, which is the most common mechanism, *Epitope spreading*, whereby invading antigens accelerate an ongoing autoimmune process by local activation of antigen presenting cells and over processing of antigens is another mechanism and infectious organisms may induce autoimmunity via *polyclonal activation* of B lymphocytes or *bystander activation* which enhances cytokine production and further induce the expansion of auto reactive T-cells.

A proof of concept for the existence of molecular mimicry can be extrapolated from the various studies on HPV and the human proteome can be found in the extensive publications of Kanduc, who has delineated the cross-reactivity between the HPV 16 proteins as a model with the human proteins [71]. In two reports, the analysis of the antigen inoculated within the vaccine was done in order to identify peptide sharing between human proteins that, when altered, are associated with SLE. Several human peptides were shown to share heptapeptides with HPV peptides providing a possible involvement of HPV infection in the induction of SLE via a mechanism of immune cross reaction due to molecular homology [72,73].

Table 1 documents that a massive peptide sharing exists between Gardasil HPV L1s peptides and human proteins that – when altered, modified, deleted, mutated or improperly functioning – associate with ovarian failure, amenorrhea, infertility, follicle loss, altered growth of the fetus, etc.

Table 1
Peptides shared between Gardasil HPV L1s and human proteins related to ovarian dysfunctions, infertility, low weight at the birth and disorders in the newborn.

Human protein[a]	L1 Peptides[b] from:			
	HPV 6	HPV 11	HPV 16	HPV 18
ATM	SSRLL	SSRLL	–	SSRLL
ATS1	–	–	DPLKK	–
BRCA2	VSGHP, SGHPF, TVVDT	VSGHP, TVVDT,EEFDL	TVVDT, STILE	SGHPF, GHPFY, TVVDT
CCNB1	–	–	PVPVS	RPLPL, PLPLH, GCAPA
CE152	LLQSG	IKKVN, LLQSG		LELKN
CENPJ	–	–	KAKPK	
CTNB1	–	SGGYG	–	–
DAZL	–	–	–	ASTQS
EGFR	–	–	–	SSILE
FAK2	TPEKE	TPEKE	–	LELKN
FMN2	–	–	–	VPPPP
IF4G1	–	–	WGKGS	APSAT
IPSP	ASAAP	–	–	–
KASH5	–	–	LQPPP	–
KMT2B	GEPVP	GEPVP	LQPPP, CQKHT, TPPAP	LPPPS, APSAT
KMT2D	GEPVP, VSSEA, LSPPP*	GEPVP, VSSEA, LSPPP*	AGAVG, GLQPP,	PPPSV, HKAQG, LSQGD, TTPST
MEIOC	DSSLF	DSSLF	–	STNLT
NALP5	–	–	–	VSEDV, SEDVR
PCNT	SRLLA	EKEKQ, SRLLA	SRLLA, EKFSA, TAKRK	
PLK4	TGLEV, LSPPP	TGLEV, LSPPP	PDYIK	PPPSV
TRAIP	EVNLK, SELDQ	EVNLK, SELDQ	EVNLK	–
ZP3	–	–	–	LGVGL

554–558, 572–576, 608–612, 617–621, 626–630, 662–, 671–675, 689–693, 2273–2277. **Important note: that is, potential cross-reactions against viral LSPPP have 14 possible cross-reactive targets available in KMT2D**.

[a] Proteins described in detail at UniProt, PubMed and OMIM databases.

[b] Asterisk: LSPPP pentapeptide is repeated 14 times in the KMT2D sequence (amino acid pos: 449–453, 467–471, 494–498, 503–507, 536–540.

The numerical dimension of the sharing is enormous: forty-nine Gardasil HPV L1 peptides recur among 22 human proteins related to ovarian functions and fertility. It is a mathematical impressive datum when considering that the chance for two proteins to share a pentapeptide equals to 20^{-5} (ie, 0.0000003125).

Pathologically, Table 1 is even more impressive in light of the crucial functions exerted by the human proteins involved in the sharing. Indeed:

- ATM or serine-protein kinase ATM is involved in oocytes degeneration, infertility [74].
- ATS1 or A disintegrin metalloproteinase with thrombospondin motifs 1 is an ovulatory protein that correlates with oocyte fertilization capacity [75].
- CCNB1 or G2/mitotic-specific cyclin-B1 prevents aneuploidy in oocytes [76].
- BRCA2 or breast cancer type 2 susceptibility protein is implicated in diminished ovarian reserve; accelerated primordial follicle loss and oocyte DNA damage as well as susceptibility to breast cancer [77].
- CTNB1 or catenin beta-1, when altered, can lead to infertile polycystic ovary syndrome [78].
- DAZL or deleted in azoospermia-like has a critical role at the oocyte-to-zygote transition [79].
- EGFR or epidermal growth factor receptor is essential for the production of matured and developmentally competent oocytes [80].
- IF4G1 or eukaryotic translation initiation factor 4 γ1 is critical for oocyte maturation [81].
- IPSP or plasma serine protease inhibitor is involved in infertility [82].
- FAK2 or protein-tyrosine kinase 2-beta, lack of which in oocytes blocks sperm incorporation and egg activation [83].
- FMN2 or formin-2, lack of which results in polyploid embryo formation, recurrent pregnancy loss, and subfertility [84].

- KASH5 or protein KASH5 has a role in meiotic chromosome movement and homolog pairing, and infertility [85].
- KMT2B or histone-lysine N-methyltransferase 2B has a role during oogenesis and early development. Can cause anovulation/male infertility [86–90].
- KMT2D or histone-lysine N-methyltransferase 2D has a role during oogenesis and early development. Can cause anovulation/male infertility [86–90].
- MEIOC or meiosis-specific coiled-coil domain-containing protein MEIOC is required for meiosis and fertility in both sexes [91].
- NALP5 or NACHT, LRR and PYD domains-containing protein 5 is an Oocyte-specific protein that has an essential role for zygotes to progress beyond the first embryonic cell divisions and serves as an autoantigen in a mouse model of autoimmune premature ovarian failure [90].

Then, it is of utmost relevance the Gardasil HPV L1 peptide sharing with a group of 5 proteins, ie, **CE152, CENPJ, PCNT, PLK4. and TRAIP** (given bold in Table 1). Indeed, when improperly functioning because of modifications, mutations or alterations, these proteins specifically associate with low birth weight, intrauterine growth retardation, microcephaly with a bird-headed like appearance, and mental retardation (OMIM #210600) [92].

Finally, the most crucial experimental proof is the fact that the peptide sharing described in Table 1 has a high immunologic potential since almost all of the shared peptides occur and recur in hundreds of epitopes that have been experimentally validated as immunopositive. Table 2 reports a synopsis of the hundreds of such immunoreactive epitopes described, validated and cataloged at the IEDB database of Bethesda.

An additional significant factor in the induction of autoimmunity by vaccines is the presence of adjuvants, and specifically aluminum. Alum (aluminum oxyhydroxide) is widely used as an immunological adjuvants in vaccine, and concerns emerged following its role in macrophagic myofasciitis (MMF) in patients with chronic fatigue syndrome [93]. It is established that aluminum has specific characteristics including its long biopersistence in susceptible subjects which can lead to lysosome destabilizing effect and crystal induced rupture [94].

However, these reports and case series should be interpreted with extreme caution due to small sample size, reliance on self-reports, and most importantly the lack of controls. In 2017, DeLong published a study by analyzing information gathered in national health and nutrition examination survey. Sixty percent of women who did not receive the HPV vaccine had been pregnant at least once, whereas only 35% of women exposed to the vaccine had conceived. For the entire sample the odds ratio for women who received the vaccination to have been pregnant versus women not receiving the shot was 0.35 (95% CI 0.211–0.573). The methodology of was criticized for not controlling for confounding variables including the use of contraception and other variables that affect fertility rate including smoking, obesity and other diseases.

Aluminum used in HPV vaccine acts as an adjuvant by increasing the immune response to the antigen. Trif et al. [95] demonstrated high levels aluminum accumulation in the ovarian and uterine tubes of adult female mice fed high aluminum diet. Sub chronic aluminum chloride exposure has also been shown to result in damage of the structure and function of the rat's ovary. Moreover, aluminum exposure results in the decrease of the density of FSH and LH receptors and weakens the ligation of the ligand to their respective receptors [96]. It is postulated that the disruption of ovarian function results from a decrease in energy production secondary to damage to cell nucleus, mitochondria, rough endoplasmic reticulum and Golgi apparatus. Taken together these factors results in infertility of murine models [96].

In 2018 Naleway et al. [97] published retrospective study from a cohort of 199,078 female patients. Forty-six idiopathic POI cases were noted. The adjusted hazard ratio was 0.30 (95% CI 0.07–1.36) after HPV, 0.88 (95% CI 0.37–2.10) after Tdap, and 1.42 (95% CI 0.27–3.23) after MenACWY. Thus concluding that no statistical significant increased risk exists of POI after these vaccinations.

Conclusion

Primary ovarian insufficiency resulting in amenorrhea in women aged less than 40 remains an elusive entity. The etiopathogenic factors in the majority of cases remain to date unclear. Several lines

Table 2
Epitopes containing peptides shared between Gardasil HPV L1s and human proteins related to ovarian failure, infertility, follicle loss, altered pregnancy, newborn low weight and intrauterine growth retardation, *inter alia*. Column 1: Epitope IEDB ID number. Details and references at www.iedb.org. Column 2: Peptides shared between Gardasil HPV L1s and human proteins related to ovarian failure, and so on (see Table 1) in capital red letters.

1	2	1	2	1	2
20906	gliAGAVGgsllaal	436707	avnsyypTPPAPmpgpt	527928	TPPAPapaappstp
41601	mgliAGAVGgsllaalv	440137	rpVPPPPsl	528829	vhavAGAVGsvt
44978	nmgliAGAVG	443385	eglaRPLPL	530875	aptaeaPPPSV
64992	tlnVPPPPdpgr	446849	neVPPPPnl	538311	VPPPPmepdhpfysn
64993	tlnVPPPPdpgrastsgtpikk	447409	rlidLGVGL	538416	wrrsydVPPPPmepd
103482	pldTPPAPapppfrl	448327	sliSTILEv	542281	ggetvmvnaaAGAVGsvvgqiak
103664	TPPAPapppfrlpll	448936	SSRLLvasw	544507	pVPPPPppp
109716	pPVPVSkvvstdeyvartniyyha	449774	VPPPPhrpl	544726	riniPPPSV
110651	lcligckppigehWGKGSp	450351	yrLPPPSdpqy	554685	nrAPSATapspv
110652	lcligckppigehWGKGSpc	450403	aCQKHTPPAPkeDPLKKyt	555219	qktgtaemSSILEeri
110825	edtyrfvtsqaiaCQKHTppa	451610	aaPPPSVtv	556106	sigglaypPLPLHegppraps
111088	aCQKHTPPAPkedDPLKKyt	452240	alapASTQSpa	569400	VPPPPhrpl
111113	apkeDPLKKytfwev	452577	apaAPSATal	576831	RPLPLtsv
111351	GLQPPPggtledtyr	452958	avLELKNel	577388	rVPPPPpiar
111418	igehWGKGSpctnva	452965	aVPPPPssv	581703	ahgVPPPPil
111510	lpseatvylpPVPVS	455837	kpTPPAPal	585130	kprSSRLLtf
111581	ngicwgnqlfvTVVDTtrst	457829	qmptLPPPSV	586165	lpRPLPLlka
111653	PVPVSkvvstdgyva	457988	reLELKNtw	587145	pPPPSVlll
111811	STILEdwnfGLQPPPggtle	463417	apLGVGLgl	588250	repPVPVSi
111946	wgnqlfvTVVDTtrs	463566	APSATmssf	590873	VPPPPhrlp
112064	ckppigehWGKGSpct	468818	mptLPPPSV	591238	yenVPPPPty
112443	aCQKHTPPAP	471221	sPVPVSdtqkl	597311	ivgicLGVGL
112510	fnkpywlHKAQGhnn	472820	VPPPPgisl	600272	ppVPPPPpp
112526	glevgrgqplgvgvSGHPFl	472821	VPPPPlmpm	600425	qktgtaemSSILEerilgad
112526	glevgrgqplgvgvSGHPFl	472822	VPPPPpval	605727	rrppVPPPPr
112532	gvgvSGHPFlnkyddvensg	472823	VPPPPsleni	695446	mdfGLQPPeitsgem
112532	gvgvSGHPFlnkyddvensg	472824	VPPPPvpvl	707551	gftaTPPAPd
112553	itltadvmtyihsmnSTILE	473905	yparVPPPPpia	742160	vsdslvdAGAVGpqgfveed
112625	pseatvylpPVPVSkvvstd	474121	ysyparVPPPPpia	758472	avnsyypTPPAPmpg
112676	tnifyhasSSRLLav	474786	aeaPPPSVv	758473	avnsyypTPPAPmpgptt
112681	tnvyyhggSSRLLtv	477040	DPLKKhtl	765734	tvavnsyypTPPAPmp
112685	tsifyhagSSRLLtv	478595	ghLPPPSVay	765735	tvavnsyypTPPAPmpg
128096	rVPPPPpia	482020	LPPPSdpqy	766200	vnsyypTPPAPmpgp
146487	paVPPPPvp	484957	rVPPPPhga	766201	vnsyypTPPAPmpgpt
165360	tssisrAPSATtsk	485235	saLGVGLal	773402	hgnrgetgpsgpvgpAGAVGpr
179892	rPVPVStar	487428	tgtaemSSILEer	789215	eGLQPPtiwl
179919	vrPVPVSta	488769	yeaDPLKKell	789846	epPVPVSvlhrfpfssa
194072	kllePVPVSv	488958	yPVPVSpgv	792319	ggalkisAGAVG
194312	rVPPPPqsv	492322	hrVSEDVRsdf	792573	ggvrpahPVPVS
194463	vlaPLPLHgv	506675	lgmVPPPPp	810320	qivpGLQPPrvt
196887	VPPPPpppp	506884	LPPPSirv	810321	qivpGLQPPsvt
224101	teaPVPVSv	507216	mLPPPStpal	828059	vlAGAVGsflkg
423836	afdhdSSRLLy	510282	VPPPPptev	831834	yrfglgsvAGAVGata
425739	kafdhdSSRLLy	511664	APSATqpataetqhia	833581	khTPPAPkeDPLKKytfwevnlkekfsadldq
427526	stsSSILEy	511665	APSATqpataetqhiad	833653	kppigehWGKGSpctngdcpplelintviq
430882	lldalRPLPLdwmy	511666	APSATqpataetqhiadq	834005	mslwlpseatvylpPVPVSkvvstde
435571	rrlidLGVGL	512270	avnsyypTPPAPmpgp	861766	tSTILEnyf

of evidence point towards the role of autoimmunity as a primary cause of POI. Multiple potential immune antigens have been proposed as possible targets for antibody mediated autoimmune disease. The association with other autoimmune diseases and histopathological analysis of POI patients' ovaries support the autoimmune theory. Moving forward, the major drive in future research is to elucidate the underlying mechanism of ovarian damage, to devise specific noninvasive diagnostic tools, and potentially uncover novel approaches to treatment in this cohort of patients.

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Conflicts of interest

Y.S. appears as a medical consultant in vaccine compensation court, USA.

Practice points

- POI is defined as amenorrhea for at least 4 months in women before the age of 40.
- Etiopathogenesis remains uncertain, however genetic, toxic, infections, enzymatic and iatrogenic causes have been implicated.
- Autoimmunity as a cause is suggested by the presence of ovarian autoantibodies, lymphocytic oöphorits on histological analysis and the association with other autoimmune disorders.

Research agenda

- The development of non-invasive diagnostic tools for diagnosing lymphatic oophoritis.
- Elucidation of the underlying mechanism driving the disease process and thus potentially uncover novel approaches to treatment.
- The development of more specific assays for the detection of autoantibodies associated with POI.
- The association between vaccination and POI requires further evaluation with controlled prospective studies.

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