Immunologic Treatment in Premature Ovarian Failure

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- Premature ovarian failure (POF) represents one of the most enigmatic and challenging conditions in reproductive medicine, that requires multidisciplinary approach and management.

- Unexplained
- Autoimmune
- Genetic

- Between 10 and 30% of women with POF have a concurrent autoimmune disease.
- The most commonly reported being hypothyroidism.
- The most clinically important hypoadrenalism.

- As well as association with:
  - myasthenia gravis
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - Crohn's disease

- For many women in whom the cause of ovarian failure is unknown, autoimmunity may be the pathogenic mechanism, as a primary, or secondary immune dysfunction process against the ovaries.

- Autoimmune attack might be general or in most instances, partial, reversible, and responsible for, in many cases, fluctuating course of the POF.

Autoimmune

- Autoimmune polyglandular syndromes
- Associated non-glandular autoimmune diseases

Autoimmune polyglandular syndromes

- APS-I
- APS-II
- APS-III

APS-I

- Also called APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy) is a
- rare autosomal recessive disease
- caused by mutation in the AIRE (autoimmune regulator) gene
- It mainly affects children, and is associated with mucocutaneous candidiasis, ectodermal defects, hypoparathyroidism, Addison's disease, and POF that occurs in 40–60% of cases.

APS-II

- Also called Schmidt–Carpenter syndrome
- an autosomal dominant disease, linked to chromosome 6, and associated with HLA-B8DR3DR4 haplotypes
- comprises Addison's disease, insulin-dependent-diabetes, and POF with the prevalence of which is 10-25%.

APS-III

- APS-III is quite similar to APS-II
  - except there is no adrenal deficiency
  - but other autoimmune diseases, such as anemia perniciosa or vitiligo are often associated.

- Cases of POF associated with antiadrenal autoimmunity represent a homogeneous and well-characterized subgroup of ovarian failure
- whereas in other forms of this disease, there is a large diversity in clinical, immunological and histological features.

Immunological features of autoimmune POF

- The detection of autoantibodies directed against various ovarian targets strongly supports an autoimmune aetiology of POF.
- Different autoantibodies were found in different clinical features of autoimmune POF.

- POF patients associated with adrenal autoimmunity commonly presented with autoantibodies that recognize several types of steroid-producing cells of the adrenal cortex, testis, placenta and ovary, therefore called steroid cell antibodies (SCA), with the prevalence of which is ~60% in APS-I patients; 25–40% in APS-II patients; and almost 78–100% in patients with both Addison's disease and POF.

- In POF patients not associated with adrenal autoimmunity, as well as in isolated, or idiopathic POF, the prevalence of SCA remains <10%.
- In those patients other autoantibodies could be found, divided into non-ovarian, and ovarian autoantibodies.

- Thyroid autoimmunity is the most prevalent (25–60%) associated endocrine autoimmune abnormality reported in POF patients without an adrenal autoimmune involvement, and with the presence of high levels of non-ovarian, thyroid peroxidase antibodies, leading to clinical/subclinical hypothyroidism development.

- Antiovarian autoantibodies (AOA) are usually considered to be a suitable, and independent marker of autoimmune ovarian disease, although their specificity and pathogenic role is questionable.

- There are several autoantibodies towards specific ovarian targets potentially mediated autoimmune damage in POF:
  - 3β-hydroxysteroid dehydrogenase autoantibodies, particularly found in isolated idiopathic POF
  - gonadotropin receptors autoantibodies
  - zona pellucida autoantibodies
  - anti-oocyte cytoplasm antibodies towards MATER ("Maternal Antigen That Embryos Require").

- Abnormalities of the cellular immunity, i.e. T lymphocytes (especially effector helper, CD4-positive T cells), macrophages and dendritic cells, also play an important role in autoimmune reactions, particularly in the development of autoimmune lesions, described also in POF.

- Sometimes autoantibodies to the ovary may have been present in the ovary without reaching detectable levels in the serum or inducing local inflammation.

Immunologic treatment strategies in POF

- Although in most of the cases POF is idiopathic, there is need for further tests looking for a specific aetiology, such as autoimmune, and genetic studies, the latter especially important in familial POF.

- The strong association of POF with APS makes screening for this condition essential.
- In idiopathic POF full attention must be given to the investigation of indirect autoimmune signs, such as association with possible autoimmune diseases (clinical aspects, hormone levels, and antibodies).
- The recovery of ovarian function may occur after regression of the autoimmune status and control of coexistent endocrine disease.

- Immunosuppressive therapy, using different dose and term of glucocorticoids should be considered in a selected population of well defined autoimmune POF patients, as well as in idioptahic POF patients.