The Antimullerian Hormone (AMH) and the Thyroid Autoimmunity

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Abstract

Infertility affects nowadays 10-15\% of the reproductive population which led to the rapid development of therapeutical methods such as ART (assisted reproduction techniques). Ovarian reserve plays a key role in evaluating these patients and their prognosis. The best tool that we have for appreciating ovarian reserve is AMH (antimullerian hormone). On the other hand, maintaining thyroid function in normal parameters is essential for reproduction. We review in our paper the liaison between these two factors: AMH and thyroid autoimmunity. It appears that thyroid autoimmunity may affect controlled ovarian stimulation in ART.

Keywords: ATPO; AMH; autoimmunity; thyroid hormones.

1. Introduction

The declining trend in fertility in the recent years has led to the rapid development of assisted reproductive techniques. Due to high procedure cost and ultimately the extensive impact on the patient’s health and well-being, there was a need of studying different factors involved in the outcome of fertility treatments.
2. Ovarian reserve

The primal factor needed for an appropriate reproductive function in females is represented by ovarian reserve. Environmental, genetic influences and age majorly influence this parameter [1]. Different terms are used to describe abnormalities of reproductive potential in women. Poor response to stimulation or reduced fecundity in menstruating women of reproductive age defines the term of “diminished ovarian reserve”, which is different from premature ovarian insufficiency and menopause [2]. Although evaluation of ovarian reserve cannot predict the remaining life span of reproductive years in these women, it can hasten their decision to become pregnant.

Several variables have been used to quantify the ovarian reserve among which day-3 FSH, antral follicle count and AMH (antimullerian hormone) are currently the most important [2]. Screening tests for ovarian reserve have allowed identification of infertile patients with poor response to gonadotropin stimulation, a lower chance of achieving pregnancy using ART (assisted reproduction techniques) or ovulation induction and patients at risk of developing ovarian hyperstimulation syndrome during ovulation induction [2].

3. AMH

AMH is a glycoprotein that belongs to the transforming growth factor-β superfamily and it is produced by the granulosa cells of preantral follicles and small antral follicles, and reflects functional ovarian reserve (FOR). It is a paracrine factor that inhibits the recruitment of the primary follicles, inhibits FSH (follicle stimulant hormone)-dependent follicle selection, and inhibits aromatase. By these means it counteracts early depletion of the follicular pool [2,3].

Because of the absence of intercycle and intracycle variability and the ability to detect a decrease in ovarian reserve earlier than other markers [2], AMH represents the most reliable marker for assessment of ovarian reserve and has the ability to predict response to stimulation with gonadotrophins and age of menopause [2,4]. Age has a pivotal effect on AMH levels, depletion of the pool of ovarian follicles translating in decreasing production with advancing age [5], but the rate of loss of primordial follicles is highly variable [2].

Age-specific AMH values are proposed with the lower limit being approximately: 0.5 ng/mL for 45 years, 1 ng/mL for 40 years, 1.5 ng/mL for 35 years, 2.5 ng/mL for 30 years, and 3.0 ng/mL for 25 years [2]. Also models for estimating ovarian reserve incorporating AMH have been implemented: the AAFA model uses four predictors (AMH, AFC-antral follicles count, circulating basal FSH and female age) [6], while the AFA model uses three predictors (AMH, FSH and age) [7].

4. Thyroid disorders

Both subfertility and thyroid disorders have an increased prevalence in women aged 20-45 years [8].

Thyroid disorders affect fertility of both males and females at various levels by disruption in the folliculogenesis, spermatogenesis and may lead to lower fertilization rate and lower embryo quality. The pathophysiology of these associations remains largely unknown [9]. Infertility in hypothyroid women is caused
by altered peripheral estrogen metabolism, hyperprolactinemia, and abnormal release of gonadotropin-releasing hormone [10].

5. Immunity

Women with premature ovarian failure have a high prevalence of autoimmune diseases, with Hashimoto’s thyroiditis (HT) being the most common [11,12,13]. Also, patients with autoimmune thyroiditis are at a higher risk for decreased ovarian reserve [14]. They also have a lower number of pregnancies and live births and lower AMH levels compared with controls [15]. Results outside the normal range may encourage them to expedite their reproductive plans if they desire a child.

Ovarian failure is presumed to be caused by the presence of anti-ovarian, anti-thyroid antibodies and abnormalities of cellular immunity in some patients with idiopathic POI (premature ovarian insufficiency) [12]. Imbalance between pro-inflammatory and anti-inflammatory cytokines exert a critical role in the induction of autoimmune thyroid diseases. Among these, IFNγ has a key role in thyroid immunopathogenesis leading to destruction of organs, humoral immune response, and increased cytokine production. It was demonstrated that serum levels of IFN-γ and its gene expression showed a significant positive correlation with TSH and thyroid antibodies and a negative correlation with AMH, FT3 and FT4 [16].

Also, levels of IL-6 and IL-21 negatively correlate with AMH. IL-6 is a glycoprotein mainly secreted by antigen-presenting cells that exerts an immunomodulatory role by promoting B and T cell proliferation and secretion of antibodies and IL-21 mainly regulated the severity of the autoimmune process [13].

6. Thyroid autoimmunity (TAI)

Thyroid antibodies may exert their effect on fertility potential by altering TSH and T4 levels but also in a TSH independent manner. Among the pathophysiological mechanisms underlying infertility in women with thyroid autoimmunity but euthyroid function are: T cell abnormality, hyperactivity and elevated mass of natural killer cells, polyclonal B cell activation and non-organ-specific autoantibodies, cross-reactivity, vitamin D deficiency, concurrent autoimmunity (i.e., endometriosis) [17].

The prevalence of TAI is increased in women with idiopathic subfertility, polycystic ovarian syndrome (PCOS), diminished ovarian reserve and premature ovarian insufficiency [8].

In the case of PCOS, environmental and hormonal factors may trigger abnormal autoimmune response in genetically predisposed individuals [18]. Polymorphisms of the PCOS-related gene for fibrillin-3 alter the activity of TGF-β, a regulator of immune tolerance and in association with a disequilibrium in estradiol (pro-inflammatory)-to-progesterone (immuno-suppressor) concentrations, may offer a plausible explanation for the increased prevalence of thyroid autoimmunity in females with PCOS [8]. It appears that ovarian reserve, measured with AMH levels is influenced in an inverse manner by the presence of ATPO (anti thyroid peroxidase antibodies) in PCOS women [18]. Nonetheless, ovarian depletion caused by autoimmune destruction seems to be a lengthy process, since serum AMH levels in adolescent girls appear not to be
influenced by the presence of HT [19]. Although it may seem discordant, high AMH levels in association with TAI in adolescents and low AMH levels in adult life may be explained by what is called “burn-out” theory. Autoimmunity leads to increased oxidative stress and destruction of follicles in a more advanced stage of development, which are more sensible to damage produced by free radicals. As a compensatory mechanism there is an extensive recruitment of primordial follicles and up-regulation of AMH-producing follicles followed by a more rapid depletion of follicles and decrease in the AMH levels. In conclusion, TAI may have a bi-phasic effect on AMH levels, with an increased levels in adolescent life by augmented production of growing follicles followed by a decline in adult life due to shrinkage of the follicular cohort [20].

In his longitudinal study, Bahri and his colleagues found that women with lower ovarian reserve had higher levels of ATPO at baseline followed by a positive trend of antibody overtime indicating that this category of patients may be at increased risk of developing hypothyroidism [21] but we could interpret his findings as this category being the one where the most detrimental effects of autoimmunity on the ovarian pool occurred.

Controversy arises when taking into account results of other studies who did not find any association between reduced ovarian reserve and thyroid autoimmunity in euthyroid women [22,23,24].

7. ATPO

Any association between TAI and fertility outcomes is largely based on the presence of increased ATPO alone [8].

The mechanism by which ATPO Abs alter fertility and pregnancy outcomes is not known. Even in the absence of decreased thyroid function, autoimmunity is associated with subfertility, recurrent embryo implantation failure, early pregnancy loss and adverse pregnancy outcomes. Many hypotheses have been proposed to explain the link between ATPO and subfertility or pregnancy loss. Thyroid autoimmunity may be reflective of a more generalized altered self-tolerance and subfertility and pregnancy loss may appear secondary to immune processes at the level of the reproductive tract [25]. Also, by altering its function, ATPO may interfere with the thyroid’s ability to adapt to the requirements of pregnancy. Although it was postulated that the relationship between autoimmunity and adverse reproductive outcome was biased by age, with ATPO being more frequent in older women, but this hypothesis was infirmed [9].

Serum ATPO can cross into the follicular fluid [20] and it was hypothesized that they can be responsible for a decrease in the quality and developmental capacity of the oocytes [9]. There are no experimental studies available exploring the pathophysiological mechanisms of thyroid antibodies in follicular fluid [20].

Zona pellucida, the extra-cellular matrix of the oocyte, important in sperm-egg interaction, fertilization, pre-implantation embryogenesis and folliculogenesis, is a probable target antigen in ovarian autoimmunity. Because of the similarity of antigens between zona pellucida and thyroid tissue, the zona-pellucida may also be involved in anti-thyroid antibodies immune attack [26].
ATG (antibodies antitiroglobulin)

If and to what extent ATG contribute to infertility and reduced ovarian reserve is currently unclear. In the study of Unuane and his colleagues 5% of women with infertility has isolated ATG and a significantly higher serum TSH compared to that in women without TAI [27].

TSH (Thyroid stimulating hormone)

TSH inversely correlates with AMH levels [29], and increased concentrations of TSH are associated with diminished ovarian reserve in infertile women [30]. Weghofer and his colleagues also reported that TSH levels ≥ 3 μUI/ml were associated with lower levels of AMH and decreased ovarian reserve after adjustment for thyroid autoimmunity [31]. As demonstrated in animal studies, increased levels of TSH may directly suppress follicle growth in a concentration-dependent manner and impair primordial follicle recruitment and dominant follicle selection through decreased production of thyroid hormones [32]. TSH was identified as a predictor of ovulation failure in women undergoing in vitro fertilization [33].

In a large Danish study on 11 254 women, impaired fertility was associated with TSH, ATPO level and the presence of subclinical hypothyroidism [34]. When TSH is in the normal range, thyroid antibodies are not likely to influence ovarian reserve but elevated TSH levels, by its conformational similarity with FSH may lead to increased folliculogenesis and may be involved in the decline of serum AMH levels [35]. Subclinical hypothyroidism appears negatively associated with AMH levels in women older than 35 years undergoing ART in a large retrospective trial [36].

However, in a study performed on more than 5000 women, Polyzos and his colleagues did not find any association between hypothyroidism or thyroid autoimmunity and diminished ovarian reserve [25]. Similarly, other studies did not find any significant correlation between ovarian reserve and thyroid function in infertile women [37,38].

8. Thyroid hormones (TH)

Both T3 and T4 are present in the follicular fluid and receptors for TH are expressed on the oocyte, so a direct action on the oocyte is possible. Also, by amplifying the effects of gonadotrophins, thyroid hormones play a positive role in folliculogenesis and ovulation [9].

Animal studies have revealed that ovarian reserve is affected by hypothyroidism directly through decreased thyroid hormone levels, and not by an elevation in TSH concentration, because granulosa cell express thyroid hormone transporters and receptors, and TH insufficiency leads to impaired folliculogenesis and a process of the follicles to undergo atresia, translating into lower AMH levels [20].

In his study, Koreevar and his colleagues found that lower fT3 and ATPO positivity were associated with a decreased ovarian reserved (measured using AFC) in women with DOR (diminished ovarian reserve) or
unexplained infertility. Thyroid hormone enhances the stimulatory effects of FSH on follicular growth and apoptosis suppression, potentially via regulating nitric oxide synthase [39].

9. T4 Treatment

Levothyroxine treatment has been proposed as a method to improve fertility. In their study, Kuroda and his colleagues reported that preconception LT4 treatment was salutary to increase AMH levels and improve follicular development in infertile Hashimoto’s thyroiditis patients with subclinical hypothyroidism [32]. The 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction suggested administering LT4 treatment in subfertile women with TAI and serum TSH > 2.5 mIU/L as a potential means to optimize ovarian reserve [8].

10. ART

To achieve a higher number of oocytes, ovarian stimulation (OS) is performed. OS leads to an increase in estradiol levels, and subsequently in thyroxine-binding globulin levels resulting in a smaller amount of free T4 available for utilization, and a subtle degree of hypothyroidism may occur. Therefore, women with subclinical hypothyroidism or those who are already on LT4 treatment require an adaptation of dosage to normalize thyroid parameters [8].

A study that evaluated the role of thyroid autoimmunity on outcomes of controlled ovarian stimulation (COS) demonstrated that although not a major influence in women with low ovarian reserve as predicted by AMH levels, thyroid antibodies impair the outcome of COS when the follicular pool is preserved [28].

11. Conclusion

The debate of whether the dominant mechanism affecting ovarian reserve is thyroid dysfunction or autoimmunity, or both, remains unsettled. Also, further understanding of pathophysiological mechanism involved will allow potential targeted interventions to be persuaded. Limitations of or study is that it is a review, it should be confirmed by further prospective studies.

References


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