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EDITORIAL

Thyroid and assisted reproduction

Tiroides y reproducción asistida

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Assisted reproductive techniques (ART) have revolutionized reproductive medicine, representing a significant advancement for infertile couples and other parental situations increasingly seen in modern society.[1,2] According to the latest report from the Spanish Society of Fertility, ART rates are on the rise, and 11% of newborns in the country in 2021—22 were conceived via ART. Thyroid dysfunction, particularly autoimmune thyroiditis (AIT), affects both female and male fertility, although evidence in male fertility is more limited.[3,4]

The prevalence of autoimmune thyroid disease is higher in women undergoing ART.[5] In fertile Spanish women aged 20–45, estimates show 5% up to 7% have subclinical hypothyroidism; 2% up to 4.5%, overt hypothyroidism; 0.5% up to 1%, hyperthyroidism; and 5% up to 10%, thyroid autoimmunity (AIT).[6] AIT is more common in patients with idiopathic infertility, polycystic ovary syndrome, endometriosis, and premature ovarian failure.[5,7]

The relationship between AIT and ART outcomes remains controversial. A meta-analysis found that patients with AIT had lower implantation rates (OR, 0.72; n = 7118), higher miscarriage rates (OR, 1.52; n = 7606), and lower live birth rates (OR, 0.73; n = 11,417).[8] However, no such associations were observed in patients undergoing intracytoplasmic sperm injection (ICSI). In the same study, AIT was not associated with any markers of ovarian reserve: anti-Müllerian hormone (AMH), baseline FSH in the early follicular phase, antral follicle count, and the number of oocytes retrieved after ovarian stimulation, although it was noted that scientific evidence is of low quality. However, a recent large-scale retrospective study (15,728 patients) from a single center in China found no differences in in vitro fertilization (IVF) outcomes, with or without ICSI, between patients with or without anti-thyroid peroxidase antibodies (TPOAb) or between those with TSH above or below 2.5, leaving the issue open to discussion.[9]

Overt thyroid dysfunction has been associated with infertility through both direct and indirect mechanisms involving the ovary and oocyte, which contain TSH and thyroid hormone receptors,[3,10] and indirectly through effects on the hypothalamic-pituitary-gonadal axis, influencing both folliculogenesis and the luteal body response to LH.[3,11] It is hypothesized that AIT impacts fertility through 3 mechanisms: 1) association with generalized autoimmunity and increased cytotoxicity, 2) direct effects of anti-thyroid antibodies on the ovary-oocyte or at the endometrium-placenta level, 3) a decrease in T3 (relative hypothyroidism).[3,12] Monteleone et al. detected anti-TPO and anti-thyroglobulin antibodies in both serum and follicular fluid of infertile women, leading to the ''ovarian follicle hypothesis,'' suggesting a direct action of antibodies on the oocyte.[12] Rahnama et al. identified TPO expression in the endometrium and placenta.[13] Kelkar et al. discovered autoantibodies against the zona pellucida in women with premature ovarian failure, with these antibodies showing cross-reactivity with the thyroid.[14] It is hypothesized that this cross-reactivity may explain why ICSI—which does not require an intact zona pellucida—achieves better outcomes in cases of AIT.[8]

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The TABLET study (a prospective, double-blind, placebo-controlled clinical trial) randomized a total of 952 euthyroid women with AIT—with a history of prior miscarriage or infertility and a desire for pregnancy—to treatment with levothyroxine 50 μg/day or placebo (covering both natural and assisted conception). Treatment started preconception and continued throughout pregnancy, showing no differences in pregnancy rates, live birth rates, or gestational complications.[15] However, a meta-analysis and systematic review that included 3 randomized clinical studies (limited to patients undergoing ART) concluded that patients on LT4 had higher rates of fertilized oocytes, implantation, and live births.[16] Studies showing better outcomes included 2 where patients had TSH > 4 mIU/L. Another open-label clinical trial conducted in China with 600 patients randomized to receive LT4 treatment during in IVF processes vs no treatment found no differences in pregnancy, miscarriage, or live birth rates.[17] A Cochrane systematic review concluded that no definitive conclusions could be drawn due to the low and very low quality of included studies (3 studies, n = 820).[18] A more recent retrospective study of 706 AIT patients undergoing ART found that LT4 treatment improved obstetric outcomes only in the group with TSH between 2.5 and 4.[19]

While the optimal TSH threshold for preparing for pregnancy is still under discussion, adjusting LT4 treatment for women with hypothyroidism (and AIT) undergoing ART is essential. ART treatments involve significant changes in estrogen levels. Each type of ART (insemination, IVF with fresh transfer, or transfer following cryopreservation-thawing—cryotransfer) has different protocols and hormonal characteristics. Ovulation induction, required in many ART processes, involves treatment with GnRH agonists or antagonists or with estro-progestogens and gonadotropins, which affect estrogen and thyroxin-binding globulin (TBG) levels, altering LT4 requirements.[20] The estradiol levels achieved during ovulation stimulation cycles may approach those seen in pregnancy.[21] In recent years, there has been a shift from fresh embryo transfer (in the same stimulation cycle) to cryopreservation and subsequent thawed embryo transfer (cryotransfer).[22] Cryotransfer can occur in a natural cycle (without estrogen treatment) or in a substituted cycle (with oral or transdermal estrogen therapy). Pre-treatment with oral contraceptives is also common before stimulation cycles. These factors significantly influence LT4 dose adjustments. In my experience, ovulation stimulation requires the most variability in thyroid dose titration, while cryotransfer is more predictable. Although specific studies on this subgroup are lacking, dose adjustments during stimulation cycles should mimic those during pregnancy.

What about the thyroid function in patients undergoing ART? Gracia et al. studied 57 patients before, during, and after ovulation stimulation; only 9 had their hypothyroidism under control. Among patients with TSH < 2.5 mIU/L before the procedure, 44% showed an increase in TSH > 2.5 mIU/L during the procedure, with higher peaks being reported in patients with treated hypothyroidism.[21] Pregnancy rates were similar regardless of TSH levels > or <2.5 mIU/L during the procedure. Busnelli et al. reviewed a total of 72 patients with treated hypothyroidism undergoing IVF, finding 64% with TSH > 2.5 mIU/L on the day of peak hCG administration and 68% at 16 days.[23] These studies suggest that, in real-life settings, many LT4-treated patients experience TSH > 2.5 mIU/L during ART. Two meta-analyses reported TSH elevation during ART cycles, more pronounced in hypothyroid patients.[24,25] Given this, designing an LT4 dose adjustment plan (based on thyroid disease characteristics and the each ART cycle treatment and anticipated estrogenic increase) is crucial to prevent hypothyroidism and potential consequences. Although there are no specific studies on LT4 dose titration in ART patients, some groups have extensive clinical experience and established protocols.

What do clinical practice guidelines say? The European Thyroid Association (ETA) issued specific guidelines in 2021 for managing thyroid disorders in ART patients.[4] It recommends systematic screening for TSH and TPOAb (TGAb per local protocols) in subfertile women and treating patients with or without AIT with TSH > 4 mIU/L undergoing ART. For TSH between 2.5 and 4 mIU/L, individualization is recommended in cases of ovarian-related subfertility, age > 35 years, and recurrent miscarriage when AIT is present, to maintain TSH < 2.5 mIU/L. Treatment is not recommended for euthyroid women without AIT. The American Thyroid Association (ATA) 2017 guidelines[26] recommended maintaining TSH < 2.5 mIU/L in all ART patients. The SEEN-SEGO consensus document[27] suggests that women with positive AIT may consider LT4 treatment for infertility, ART, and recurrent miscarriage even with TSH < 2.5. Without AIT, treatment may be considered for TSH 2.5–4, implicitly recognizing 2.5 as the upper limit in ART patients, thus aligning more with ATA guidance (Table 1).

The ETA guidelines recommend measuring TSH after ovarian stimulation and on the day of the second confirmatory pregnancy test in women with AIT. They do not recommend monitoring TSH in euthyroid women without AIT unless on LT4 treatment. For women on LT4, the dose should be adjusted before ovarian stimulation to keep TSH < 2.5 mIU/L. In practice, many private ART centers require TSH < 2.5 mIU/L to initiate a process, leading to many referrals to endocrinology. The ETA guidelines also recommend ICSI as the preferred ART method in the presence of AIT.

In men, thyroid hormones affect fertility via effects on Sertoli cells, Leydig cells, and the hypothalamic-pituitary-gonadal axis[3]. Overt thyroid dysfunction is associated with abnormalities in semen parameters and erectile dysfunction. The ETA recommends checking TSH only in men with ejaculation issues, erectile dysfunction, or abnormal semen parameters.[4] ART treatment should not be delayed for overt thyroid dysfunction if semen parameters are not severely affected.

Despite the debate, guidelines, and the negative results of the TABLET study, patients undergoing ART—especially those with implantation failures and/or recurrent miscarriages—and their gynecologists often demand strict TSH control < 2.5 mIU/L. ART processes are highly sensitive, with significant emotional and financial impacts. Given the theoretical possibility that AIT may lead to hypothyroidism during ART and affect procedural success, it is essential to ensure euthyroidism, usually targeting TSH < 2.5 mIU/L, with treatment and monitoring for cases with AIT. It would be ideal to have parameters indicating the

Table 1 Recommendations for LT4 treatment in patients with infertility or undergoing ART. Clinical Guidelines.

	ATA 2017	ETA 2021	SEEN-SEGO Consensus
AIT +			
TSH > 4	Treat	Treat	Treat
TSH 2.5–4	Treat	Individualize: age > 35 years, recurrent miscarriage, ovarian-related subfertility	Treat (individualize for infertility, recurrent miscarriage, or preterm birth)
TSH < 2.5	Consider treatment due to potential benefits with minimal risk (25–50 mcg/day LT4)	Do not treat	Treat (individualize for infertility, recurrent miscarriage, or ART)
AIT −			
TSH > 4	Treat	Treat	Treat
TSH 2.5–4	Treat	Do not treat	Low doses can be used in IVF or ICSI to target TSH < 2.5 mIU/L
TSH < 2.5	Do not treat	Do not treat	Do not treat

LT4: levothyroxine; ART: assisted reproductive technology; ATA: American Thyroid Association; ETA: European Thyroid Association; SEEN: Spanish Society of Endocrinology and Nutrition; SEGO: Spanish Society of Gynecology and Obstetrics; AIT: autoimmune thyroiditis; TSH: thyrotropin; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection.

''thyroid reserve'' of AIT patients—the extent of glandular damage and their capacity to respond to increased demand. More studies are needed to predict thyroid response to estrogenic changes and test dose-adjustment protocols for different ART clinical scenarios. Meanwhile, it is reasonable to anticipate dose adjustments similar to pregnancy, increasing by 2 or 3 daily doses per week, depending on the patient's clinical data.

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