IN THE NAME OF GOD

2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction

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2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction

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Introduction

- The prevalence of thyroid disorders in women aged 20–45 years is high, and that of subfertility is increasing worldwide in part due to improved public awareness and diagnosis. Therefore, the female partner in a subfertile couple carries a high risk of concomitant thyroid disorders.

The prevalence of thyroid disorders in this group of women

- has been estimated to be between
- 5 and 7% for subclinical hypothyroidism (SCH)
- 2–4.5% for overt hypothyroidism (OH)
- 0.5–1% for hyperthyroidism, and
- 5–10% for thyroid autoimmunity (TAI)

Subfertility

- Subfertility is estimated to affect between 8 and 12% of reproductive aged couples worldwide.
- **Males** are found to be solely responsible for **20–30%** of subfertility cases but contribute to 50% of cases overall . In 2005, 56% of assisted reproductive technology (***ART***) cycles were performed in *Europe*, 23% in *Asia*, and 15% in *North America*; furthermore, worldwide, the use of ART is increasing over the years.

Thyroid autoimmunity (TAI)

- **Directly** → menstrual disturbances and subfertility
- **Indirectly →GNRH & prolactin**

- Although restoring thyroid function can normalize the menstrual pattern and/or the reproductive hormonal profile, it is not always followed by pregnancy.

Assisted reproductive technology (ART)

- In case of:
- male subfertility
- endometriosis
- tubal obstruction
- surgery, and/or an ART procedure may be necessary

Thyroid autoimmunity (TAI)

- **TAI** is the major cause of (**subclinical) hypothyroidism** in Europe and is more prevalent in women with **idiopathic subfertility** and **PCOS** than in fertile women.
- The prevalence of TAI is also higher in women with diminished ovarian reserve (**DOR**) and premature ovarian insufficiency [**POF**].
- TSH levels are **inversely** correlated with AMH.

ART procedure

- **Before** the in vitro phase of the **ART** procedure, ovarian stimulation (**OS**) is performed, aiming to collect as many oocytes as possible. OS leads to an increase in **oestradiol** levels and consequently **TBG** levels, and that **increased demand** on the thyroid gland can lead to (subclinical) hypothyroidism in women with **TAI**.
- Women already treated with LT4 should adapt the dose of **LT4** at **least 4 weeks before OS**.
- Women with (subclinical) hypothyroidism should initiate LT4 to keep serum TSH levels < 2.5mIU/L.

ART procedure

The number of oocytes retrieved (NOR)	Fertilization rates and embryo quality	Live birth rate (LBR)
influenced by TAI Not	might be impaired Woman: **TSH> 4.0** mIU/L	thyroid dysfunction before ART **TSH levels >3.5**
thyroid function Not	may be improved with LT4 treatment	Euthyroid TAI on ART pregnancy outcomes, no decreased LBR
>30 years **strongest predict**		

In a meta-analysis mainly including women with TSH levels >4.0 mIU/L, LT4 treatment increased LBR to comparable rates to those in women without elevated TSH.

This discrepancy with previous meta-analysis concluding a detrimental impact of TAI could be due to the inclusion of women with lower TSH levels <3 & and the use of ICSI .

Women of **subfertile couples**

- For all the above-mentioned reasons, ***women*** of **subfertile couples** should be **screened** systematically for serum **TSH** and **TAI** before an **ART** procedure.
- Women with serum TSH >4.0 mIU/L and OH should be treated with LT4 **independently** of the presence of **TAI**.
- In women with TSH levels >2.5 mIU/L and TAI, treatment with LT4 ***could be*** initiated in a **case-by-case** manner taking into account among other causes of female subfertility and a history of **previous (failed) ART treatments**.

Methodology/Definitions

- The strength of the recommendations and the quality of evidence supporting each were rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system .
- The ETA task force for this guideline used the following coding system:
- (a) strong recommendation indicated by 1 and
- (b) weak recommendation or suggestion indicated by 2.
- Evidence grading:
- ØOOO denotes very low-quality evidence;
- ØØOO, low quality;
- ØØØO, moderate quality; and
- ØØØØ, high quality.

Definition of SCH

- SCH is the association of a normal free thyroxine level (**FT4**) and an increased serum **TSH** level above the upper limit of normality.
- Ideally, this **upper limit** is determined in an assay and population-specific cohort and in the scope of (sub)fertility in women in the age range 20– 45 years.

ULRR

- Most **centres do not have** these normative data, and therefore the upper limit of normality is most often synonym for the upper limit of the reference range (ULRR) of the assay used. The most commonly used commercial assays in Europe have an ULRR for serum TSH between **3.60 and 4.31** mIU/L.
- We propose to define SCH (and to initiate treatment with LT4) from a TSH cutoff >4.0 mIU/L or >ULRR if the latter is >4.0 mIU/L.

TAI

- The term “TAI” is used in many recommendations/ suggestions and throughout the document when at least one type of thyroid Ab was increased according to the manufacturer’s threshold. (TPO ab, Tg ab)
- In exceptional cases, sonographic features of autoimmunity were provided.

Discussion

Thyroid Disorders and Female Subfertility

Subfertility

- Subfertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy **after 12 months** or more of regular unprotected sexual intercourse .
- Female-related subfertility accounts for 35%, male factors for 30%, and combined male and female factors for 20% of the causes of subfertility. In 15% of the cases, the cause remains unknown .

Overt hypothyroidism (OH)

- In OH, a number of different hormonal changes can be noted.
- Altered **metabolic clearance**,
- ↑ peripheral **aromatisation**, and
- ↓**SHBG** result in ↓ total serum testosterone (**Te**) and oestradiol (**E2**) ↑unbound fraction of Te & E2
- In addition, **prolactin** levels tend to increase, which may impair pulsatile secretion of **GnRH**.

Overt hypothyroidism

- **ovulatory dysfunction**
- an **insufficient corpus luteum** with **low progesterone** production
- Indeed, **menstrual aberrations** are reported in **25–60%** of the cases compared to 10% in euthyroid women .
- ↑adverse effects on fertility as well as **early** and **late complications** of **pregnancy**
- If treated with **LT4**, hormonal changes are usually **reversed**, restoring **a normal menstrual pattern** and **potentially improving fertility**.

Prevalence of SCH

- Whether the **prevalence of SCH** is ***higher*** in subfertile women remains **uncertain**.
- Similarly, any detrimental impact of SCH on fertility is yet to be established.

TAI in Women with Subfertility

- **TAI** is the **most common autoimmune** disorder in **women** in the **reproductive age** range.
- The **prevalence** of TAI can vary by ***ethnic*** background but is typically estimated at around **10%.**
- Overall, TAI is **characterized** by increased levels of **TPOAb** and associated with high(er) **TSH** concentrations .
- Although a **higher prevalence** of elevated **TgAb** levels has been reported in women with subfertility, their **significance** remains **uncertain.**

TAI in Women with Subfertility

- **Research examining** TAI prevalence in **subfertile** women or any association between TAI and fertility outcomes is therefore largely based on the presence of increased **TPOAb levels alone**.

TAI in Women with Subfertility

- **A meta-analysis** pooling 4 studies found that thyroid antibodies are associated with unexplained subfertility in euthyroid patients (OR 1.5, 95% CI: 1.1– 2.0).
- Nonetheless, the mechanism connecting TAI and idiopathic subfertility remains speculative.

TAI in Women with Female Subfertility

- However, there seems to be **no benefit** of LT4 treatment before conception on pregnancy outcomes in euthyroid women with TAI facing **subfertility** or **recurrent miscarriage.**

TAI reflects a *general immune imbalance*

- the presence of TAI reflects a *general* ***immune imbalance*** that could lead to failure of implantation,
- it was shown that TPO is expressed at gene and protein levels in the endometrium and placenta and may explain the higher frequency of miscarriage and infertility in patients with TAI .
- Furthermore, another specific cause of subfertility, **PCOS**, has been associated with TAI .

PCOS

- **polymorphisms** of the PCOS-related gene for **fibrillin-3** alter the **activity of TGF-β**, a *regulator* of immune tolerance.
- In combination with a **high oestrogen-to-progesterone** *ratio*, this may contribute to autoimmunity .

Recommendations/Suggestions

- We recommend that all women seeking medical advice for subfertility should be screened for serum TSH and TPOAb.
- TgAb can be added systematically according to the local regulatory authority rules. (1, ØØØO).
- We suggest that subfertile women with **TSH levels >2.5** mIU/L and **without increased TPOAb** levels (according to the local reference range) should be screened for the presence of increased **TgAb** levels if not yet done at initial workup (2, ØØOO).

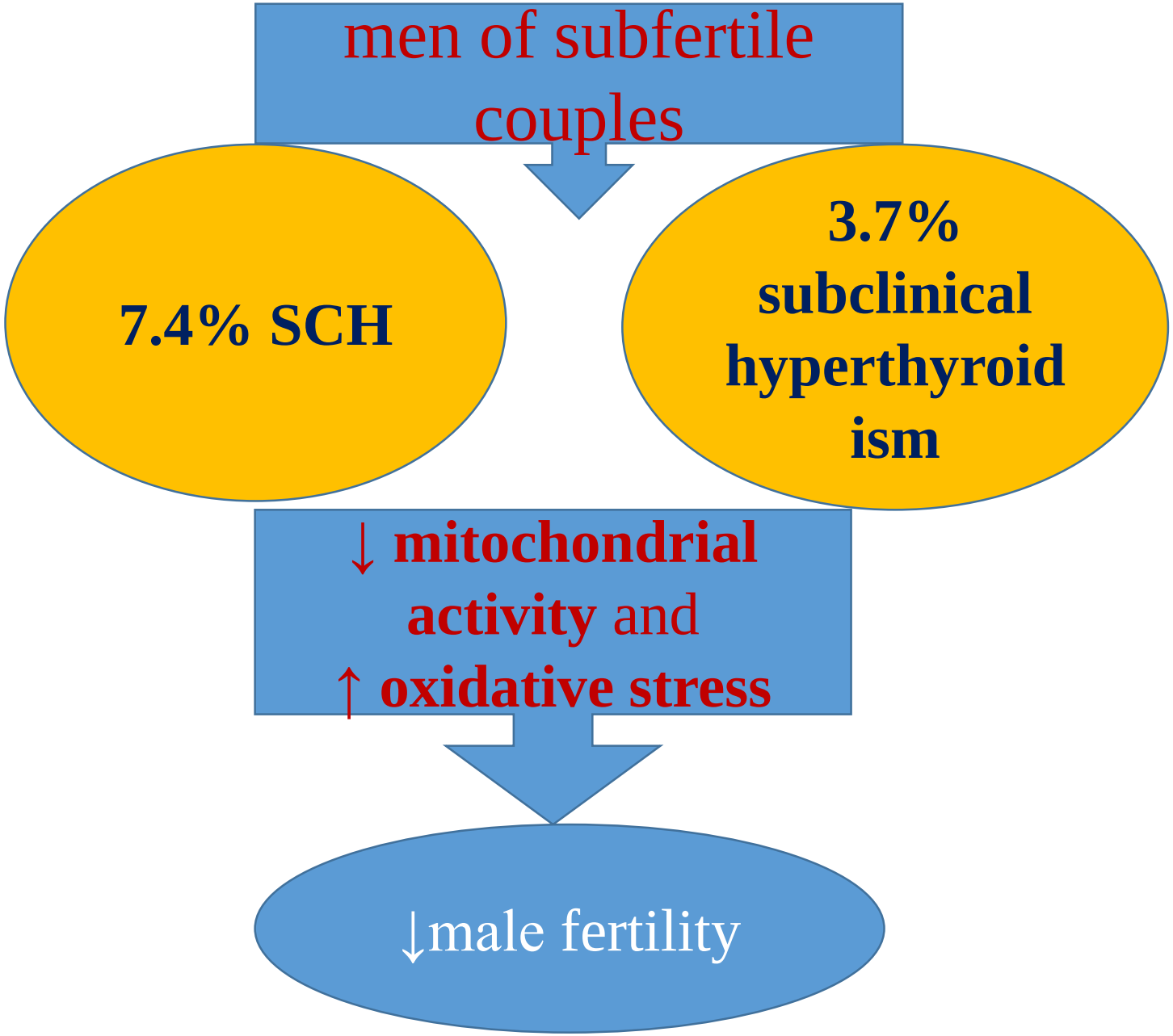
- We recommend **LT4 treatment** should be started promptly in case of **overt thyroid dysfunction** (1, ØØØO).
- We recommend **LT4 treatment** when TSH values are above **4.0** mIU/L or ULRR (1, ØØOO)

Thyroid Disorders and Male Subfertility

- Benign thyroid diseases (namely, hyperthyroidism, hypothyroidism, and TAI) have all been associated with adverse effects on male fertility.
- In case of thyroid malignancies, treatment with radioactive iodine (RAI) may have adverse effects on male fertility, and it has been suggested that **thyroid malignancies** per se might be more prevalent in men with **azoospermia**.
- However, unlike the evidence regarding female subfertility and thyroid diseases, the evidence regarding male subfertility and thyroid diseases is **limited**.

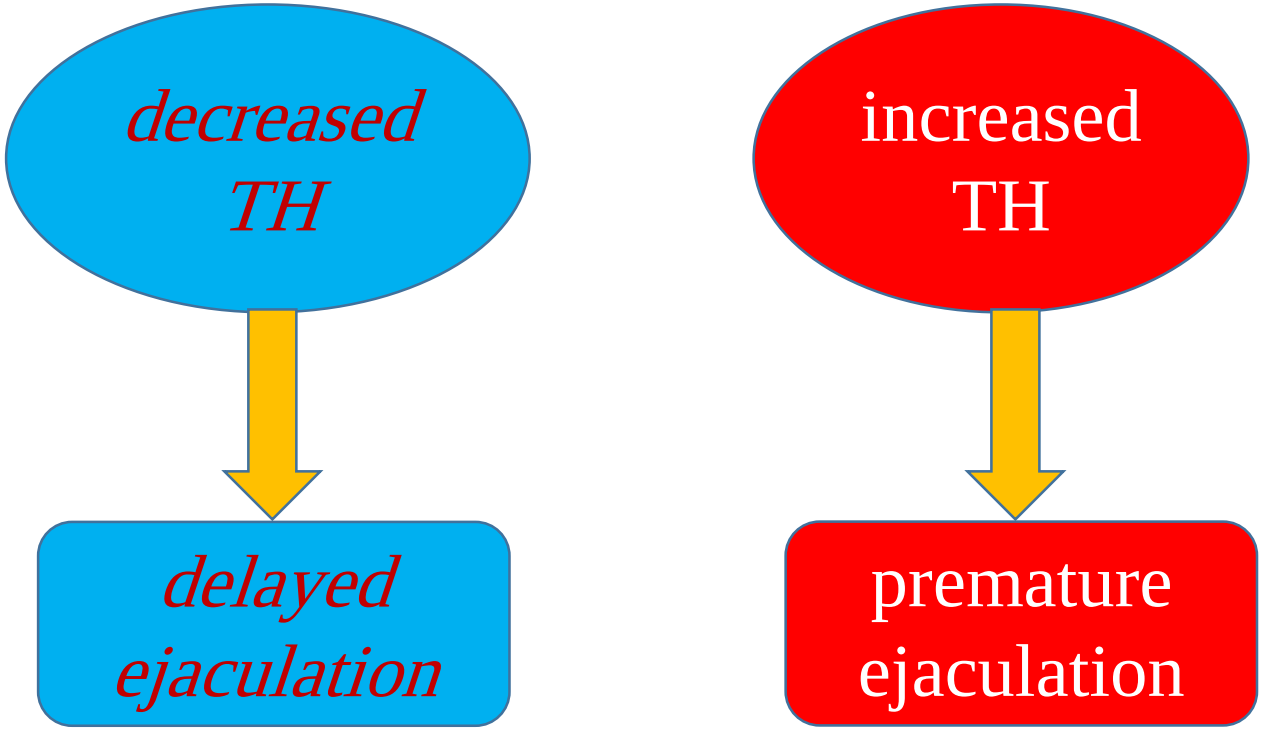
Thyroid Dysfunction and Male Subfertility

- **TH** may influence male fertility both **prenatally**, by intervening on **Sertoli cell maturing** , and
- ***postnatally***, having an effect on ***Leydig cell differentiation*** and ***steroidogenesis*** .


men of subfertile couples
7.4% SCH
3.7% subclinical hyperthyroid ism
↓ mitochondrial activity and ↑ oxidative stress
↓male fertility

Erectile function

- dependent on **TH** concentrations



Adverse effects of hypothyroidism on male fertility

- **Foetal**
- **Early neonatal**
- **Adult life**
- Increased abnormalities in **sperm morphology** and **motility** have been described in case of **prolonged OH** in adults.

Subfertile hyperthyroid men

- **Symptoms:**
- impaired libido
- ↑ oestrogens (gynaecomastia)
- erectile dysfunction, including premature ejaculation
- **abnormal sperm parameters:**
- ↓sperm motility
- abnormal morphology
- In any case, **treating** hyperthyroidism seems to **improve sperm** parameters, even if not restoring all sperm parameters to normal.

TAI in subfertile men

- in a longitudinal registry-based study with an 8-year follow-up, **subfertile men** (postvasectomy excluded) developed more **TAI** in comparison with age-matched controls (hazard ratio **[HR] 1.60**, 95% CI: 1.02–2.52)

TAI in subfertile men

- The underlying reasons for this association may be due to **lower androgen** levels in subfertile men, but **TAI** can also be a marker/reflection of a more generalized **underlying immune** disorder also causing the subfertility.
- Noteworthy concerning the latter hypothesis is the higher prevalence of other autoimmune disorders (**lupus, rheumatoid arthritis,** and others) too.
- However, in one study, the prevalence of TAI was **not different** between subfertile and fertile men .

- We recommend **against** the systematic screening for thyroid disorders (TSH and TPOAb) in males of subfertile couples (1, ØØØO).
- We suggest screening for thyroid dysfunction (TSH) in men with **ejaculation** and **erectile** dysfunction and/or altered **semen parameters** (2, ØØOO).
- We recommend **not postponing ART** treatment (IVF/ ICSI) in case of subclinical or overt hypo- or hyperthyroidism in the male as long as sperm parameters are not severely affected (1, ØØOO).

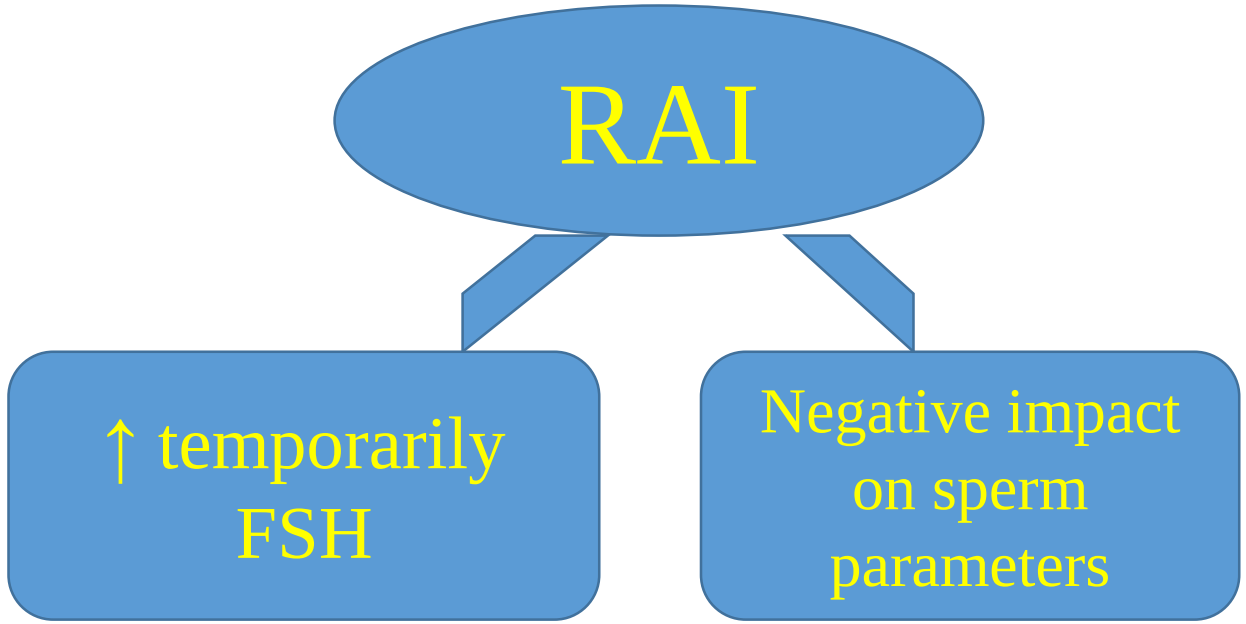
Thyroid Malignancies and Male Subfertility

Subfertile men & thyroid malignancies

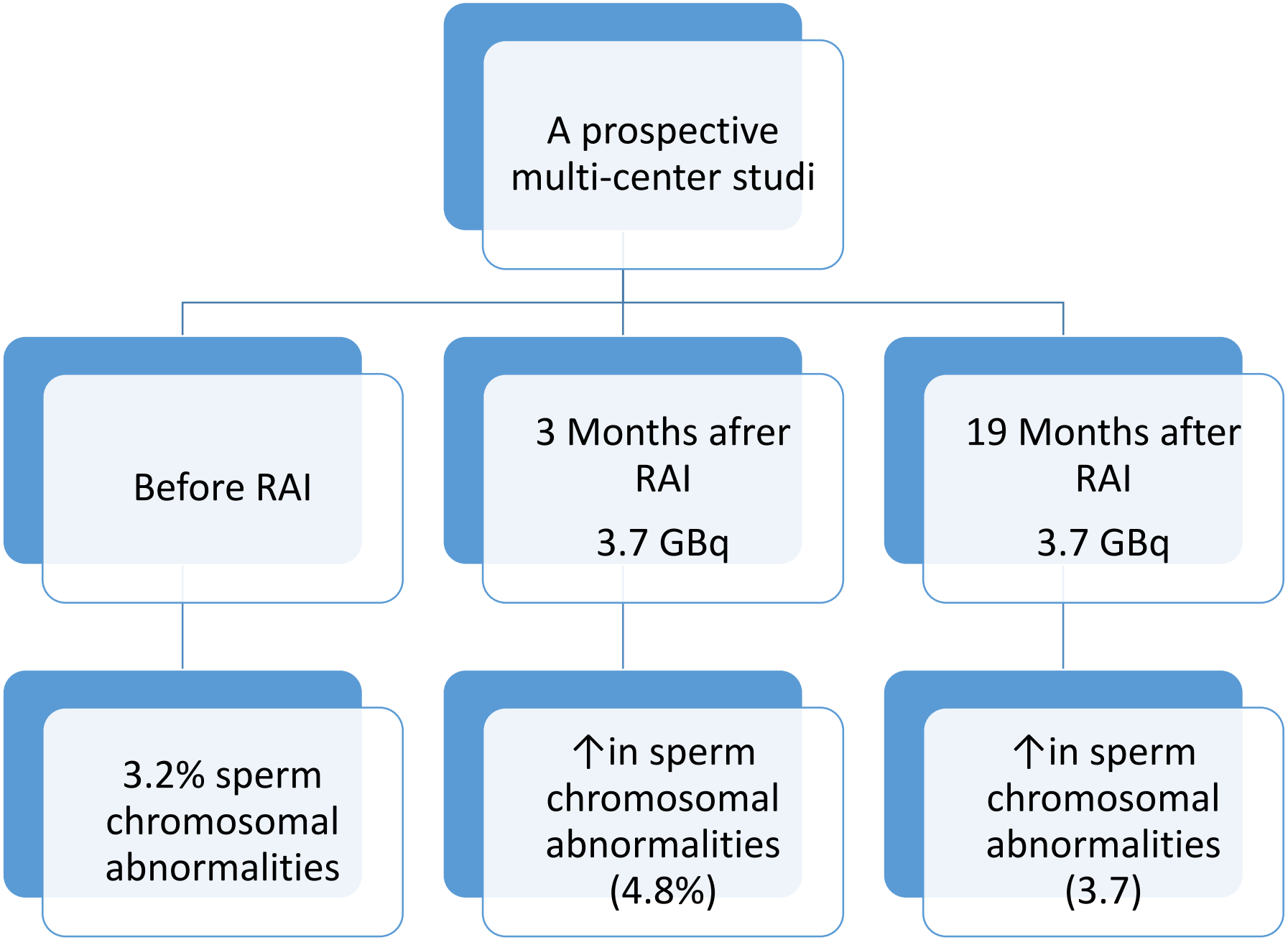
- In an analysis of the US Claims database, it was reported that **subfertile men** had an increased risk of thyroid malignancies, in comparison with controls (HR 1.52, 95% CI: 1.01–2.30) .
- In another large-scale epidemiological study, it was demonstrated that first- and second-degree relatives of men with azoospermia have **twice** the risk of developing thyroid cancer comparing to fertile population (HR 2.12, 95% CI: 1.26–3.57; HR 1.57, 95% CI: 1.03– 2.39, respectively), though no difference was detected among relatives of unselected subfertile men and fertile controls .
-

- We recommend **against** screening all **subfertile men** and their **relatives** for **thyroid cancer**

RAI and Fertility Considerations


RAI
↑ temporarily FSH
Negative impact on sperm parameters

- In a prospective multi-centre study where men with differentiated thyroid cancer were assessed before and 3 and 13 months after thyroid ablation (3.7 GBq), there was an increase in sperm chromosomal abnormalities (disomies or aneuploidies) at both time points (increasing from 3.2% before RAI to 4.8% 3 months and to 3.7% 13 months after RAI; $p < 0.01$) . This is important as, at the time, it is suggested that men who need to take RAI are advised to postpone their fertility attempts for 120 days


A prospective multi-center studi
Before RAI
3 Months afrer RAI
3.7 GBq
19 Months after RAI
3.7 GBq
3.2% sperm chromosomal abnormalities
↑in sperm chromosomal abnormalities (4.8%)
↑in sperm chromosomal abnormalities (3.7)

$p < 0.01$

long-term impact of RAI on male fertility

In general, evidence is **reassuring** that there is **no long-term impact** on male fertility after a **single RAI** ablation though adverse effects are reported after multiple RAI treatments and above 15 GBq (400 mCi) .

RAI

- We recommend that men who desire fertility and need to undergo an ablative dose of RAI to **wait at least 120 days** before attempting conception/giving sperm for **IVF/ICSI** (1, ØØOO).
- We do **not recommend** delaying **RAI treatment** for thyroid cancer for fertility reasons. However, it is advised that fertility issues/family planning are discussed before RAI treatment, and if multiple doses might be necessary (cumulative >15 GBq/400 mCi), **sperm banking** should be offered (1, ØØØO)

Primary ovarian insufficiency (POI)

- is defined as loss of ovarian function before age 40 and affects about
- 1:10,000 women by age 20,
- 1:1,000 by age 30, and
- 1:100 by age 40.
- Causative mechanisms for POI include
- genetic factors (20–25%),
- autoimmune conditions (4–30%), and
- iatrogenic factors (i.e., ovariectomy)
- though the majority of the cases remain idiopathic .
- Increased prevalence of **genetic alterations** and **autoimmune disease** in women with DOR suggests that POI and DOR may represent different degrees of the same spectrum .

POI & Hashimoto’s thyroiditis

- In a prospective study in women suffering from POI, conducted at the National Institutes of Health in the USA, **Hashimoto’s thyroiditis** was encountered in **37% of POI** women with **Turner syndrome** (**45XO**) and in 15% of POI patients with 46,XX karyotype, a prevalence that significantly exceeded that in the female US population (i.e., 5.8%, $p < 0.001$; RR 3.0, 95% CI: 2.3–3.7) .

- The European Society of Human Reproduction and Embryology recommends screening for **TAI** in all women diagnosed with **spontaneous POI** . Consequently, since women with POI/DOR have a higher prevalence of TAI, they might also have a higher prevalence of SCH .

- We recommend screening women with POI and DOR for thyroid dysfunction (serum TSH) and autoimmunity (1, ØØØO).

- diminished ovarian reserve (DOR)

- We recommend screening **subfertile women** with unexplained subfertility or in their later reproductive years (i.e., ≥35 years) for thyroid dysfunction (**serum TSH**) and autoimmunity (1, ØØØO).
- We suggest LT4 treatment in subfertile women with TAI and serum TSH >2.5 mIU/L on a case-by-case basis to allow for optimized ovarian reserve (2, ØØOO).

RAI and Fertility Considerations

RAI & AMH

- In a Dutch study that included **65 women** with a mean age of 32 years, AMH levels significantly declined during the first 12 months (i.e., −55%) and stabilized thereafter in the single RAI group, while a further decline was demonstrated (i.e., −85% after 48 months) after **multiple RAI treatments**.
- The steepest decrease was observed in women aged 35 years and above.

RAI treatment & live births

- Whether **RAI** treatment for well-differentiated thyroid cancers was related to **lower birth rates** was evaluated in a large US registry-based study of 18,850 women. While comparable birth rates were observed in the whole cohort, women aged 35–39 years experienced a **29% reduction in live births** after RAI treatment ($p < 0.01$).
- Time to live birth was prolonged in women aged 20–39 years ($p < 0.0001$) .
- Yaish et al. showed comparable results with a nadir at 3 months after treatment and a loss of about 30% from baseline after 12 months.

- We recommend that **RAI** treatment for thyroid cancer is **not delayed** for fertility reasons. However, women (**especially >35 years**) should be informed on the impact of RAI on the LBR (1, ØØØO).

Thyroid Disorders and Ovarian Retrieval Rate/ Fertilisation/Embryo Quality

- **FRs** were **63%** in women with **TAI** and *72% in negative controls* ($p < 0.05$).

- number of oocytes retrieved= NOR

ART outcomes & with and without TAI

- Poppe et al. recently performed a meta-analysis on ART outcomes in women with and without TAI who exclusively underwent **ICSI**. FRs of 1,196 oocytes from TAI-positive and 6,200 oocytes from TAI-negative women **were comparable** (OR 1.02, 95% CI: 0.89–1.16).
- Even more important, comparable miscarriage rates were observed, suggesting that **ICSI** may overcome the impeding effects of thyroid **antibodies** on oocytes and embryos.

- We suggest offering **ICSI** for women with evidence of TAI as the **preferred** fertilisation method in the course of assisted reproduction (2, ØØOO).

- Weghofer et al. demonstrated poorer **embryo quality** in women with **TAI and DOR** despite normal TSH.

- We recommend **LT4 treatment** in women with **TAI** and TSH levels **>4.0** mIU/L/ULRR to keep TSH levels 2.5 mIU/L on a case-by-case basis to allow for optimized **embryo development** (2, ØOOO

Thyroid Function and OS

OS

- Controlled OS is an integral part of ART, initiated with a **pituitary downregulation** with either GnRH analogues or antagonists, followed by OS with Gn, and terminated with a single injection of human chorionic gonadotropin (hCG) for ovulation induction. OS induces a rapid and supraphysiologic increase of **serum E2** (4,000–6,000 ng/L) that reaches levels similar to those observed in the second part of pregnancy.

↑TBG

- E2 rise results in an excess of TBG production and sialylation by the liver , leading to a reduced clearance rate of TBG and ultimately in a decrease in free TH.

- In addition, a direct effect of the high E2 levels on thyrotropin-releasing hormone has been described, and all these mechanisms together can explain an increase in TSH levels due to OS . In approximately **one out of 3 euthyroid patients**, serum TSH levels exceeded 2.5 mIU/L during ART cycles, and the TSH elevation can last 1–3 months after OS .

- Accordingly, during OS, patients with **positive TPOAb**, due to the **impaired thyroid function reserve**, show increased TSH values and **decreased FT4** levels with respect to TPOAb-negative women.

Hypothyroidism and/or TAI

- As a conclusion, OS negatively alters thyroid function in women with hypothyroidism and/or TAI. The effects seem to **last up to 3 months** after treatment, though studies with longer follow-up are required for definite conclusions.

The serial evaluation of thyroid function

- in women with treated hypothyroidism or euthyroid with TAI undergoing OS should be performed, starting from the second hCG measurement if the woman is pregnant (which is ~6 weeks after the start of OS or 3 weeks after the ovulation induction).
- Serial testing of thyroid function is likely not needed for euthyroid women without TAI, unless they are treated with LT4.

- LT4 treatment might be considered for TSH levels >2.5 mIU/L with TAI and should be started for TSH levels >4.0 mIU/L or >ULRR. Finally, more studies are required to investigate the impact of OS in women with increased **TgAb** levels and/or sonographic criteria of TAI and no TPOAb.

- We recommend checking TSH levels after OS (in case of pregnancy, the day of the **second/confirmatory hCG measurement**) in women with TAI during LT4 treatment or after the initiation of it (1, ØØØO).
- **(euthyroid with TAI)**
- We do not recommend serum TSH monitoring after OS for euthyroid women without TAI, unless treated with LT4 (1, ØØØO).
- (which is ~6 weeks after the start of OS or 3 weeks after the ovulation induction)

- We recommend adjusting **LT4 dosage** in women already treated for (subclinical) hypothyroidism be**fore OS** to keep serum **TSH levels 2.5** (1, ØØOO).
- We suggest treating TAI-positive women with TSH levels >2.5 and <4 mIU/L/ULRR with a low dose of LT4 (usually 25–50 μg daily) before OS on a case-by-case basis (2, ØØOO).

- We recommend treating TAI-positive women with TSH levels >4.0 mIU/L/ULRR before OS to keep serum TSH levels < 2.5mIU/L/ULRR before OS (1, ØØOO).
- We do not recommend treating euthyroid women without TAI before OS (1, ØOOO).

Thyroid Disorders and ART (IVF/ICSI) Outcomes

- One of the remaining questions in the field is whether LT4 administration in euthyroid women with TAI **improves ART outcomes.**
- Pooled data of women undergoing ART (both IVF and ICSI) have suggested that women with TAI (n = 299) are at increased risk of **miscarriage** and have **lower LBRs** compared to women without TAI (n = 1,931) [15].
- In contrast, a more **recent meta-analysis** focussing solely on women undergoing **ICSI did not show differences** in miscarriage and LBRs between women with (n = 114 for outcome miscarriage and n = 95 for outcome LBR) and without (n = 651 for outcome miscarriage and n = 531 for outcome LBR) TAI [17].
- ICSI only as the type of ART
- **Intracytoplasmic sperm injection (ICSI)**

- This question has been addressed in a Cochrane systemic review including studies up till April 2019 . Two studies could be included that randomized a total of 686 euthyroid women (TSH levels <4.2 and <4.8 mIU/L, respectively) to treatment with LT4 or placebo/no treatment . **LT4 treatment** had no effect **on live birth**, clinical pregnancy, or **miscarriage**. The quality of evidence for the outcome live birth was low.

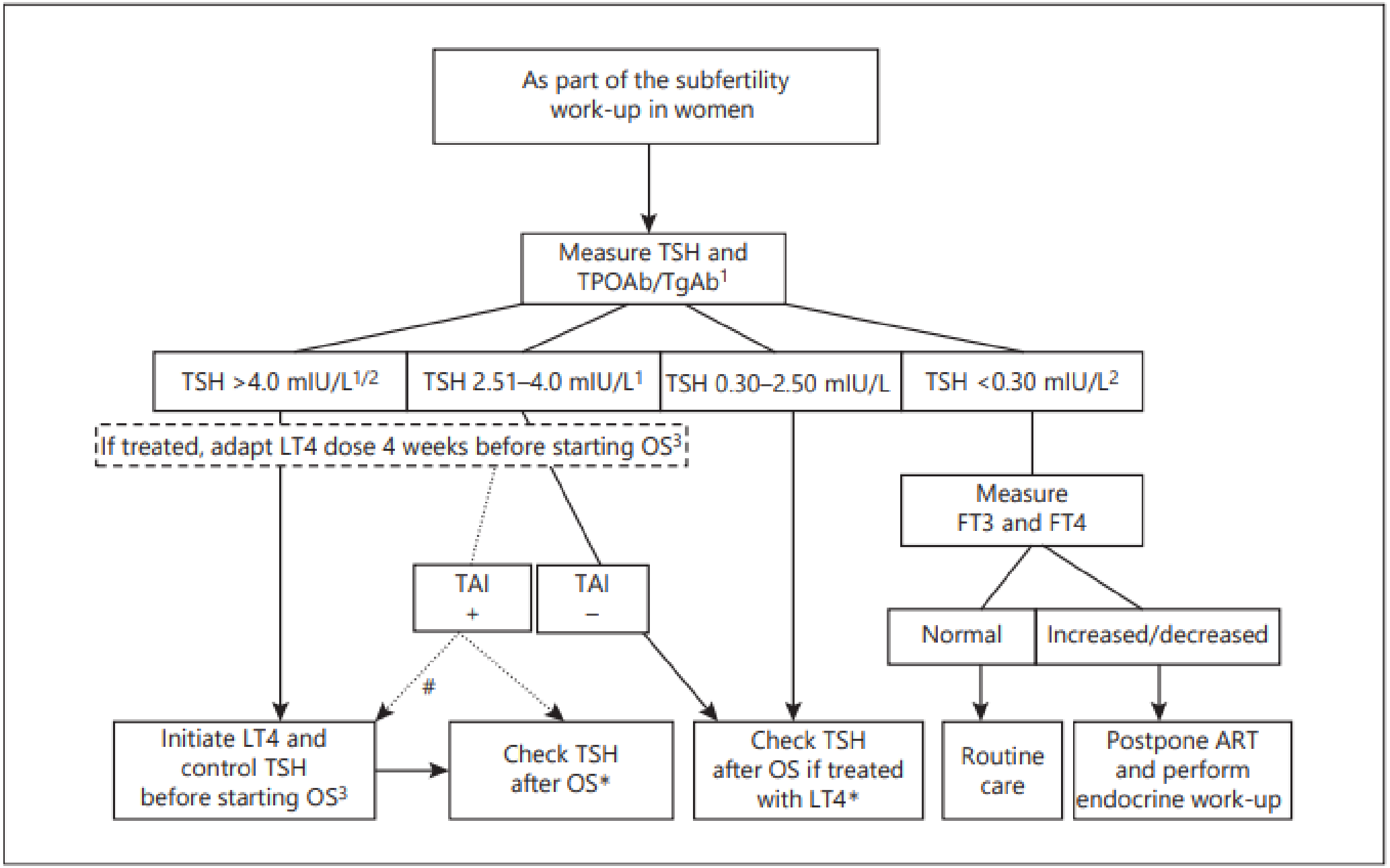
- We suggest that euthyroid women with TAI undergoing IVF/ICSI should not be treated systematically with LT4 (2, ØØOO).

- We suggest that LT4 treatment is initiated before OS in women with TSH levels >4.0 mIU/L/ULRR undergoing IVF/ICSI (2, ØOOO).

Screening/Management in Daily Practice

TSH >2.5 mIU/L & ↑ TPOAb

- Therefore, we cannot recommend systematic treatment of all euthyroid women (TSH >2.5 mIU/L) with increased TPOAb levels. In this particular group, a decision to treat can be made on a **case-by-case** basis, taking into account factors such as
- ovarian causes of subfertility (**DOR and POI**),
- **older age (>35 years),** a
- history of **recurrent miscarriage**, or
- **high levels of thyroid antibodies** even if the woman is already considered as TAI positive .
- Future studies should define these criteria more clearly.


As part of the subfertility work-up in women
Measure TSH and TPOAb/TgAb[1]
TSH >4.0 mIU/L[1/2]
TSH 2.51–4.0 mIU/L[1]
TSH 0.30–2.50 mIU/L
TSH <0.30 mIU/L[2]
If treated, adapt LT4 dose 4 weeks before starting OS[3]
TAI +
TAI –
Measure FT3 and FT4
Normal
Increased/decreased
#
Initiate LT4 and control TSH before starting OS[3]
Check TSH after OS*
Check TSH after OS if treated with LT4*
Routine care
Postpone ART and perform endocrine work-up

- Fig. 1. Algorithm for workup and management of thyroid disorders in women of subfertile couples starting an ART procedure.
- 1 If not possible for local terms, then measure TgAb in case TSH >2.5 mIU/L and negative TPOAb/look for sonographic criteria of TAI if available.
- 2 Or above/below the reference range of the assay for non-pregnant women or institutional population-specific values.
- 3 LT4 dose depending on baseline TSH level and body weight; start 25 μg when TSH 2.51–4.0 mIU/L → target TSH<2.5 mIU/L. # Decide to treat on a case-by-case basis (cf text for details). *In case of pregnancy, the day of the second/confirmatory hCG measurement. TAI, thyroid autoimmunity; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; LT4, levothyroxine; hCG, human chorionic gonadotropin; OS, ovarian stimulation; ART, assisted reproductive technology.


Thanks for your attention