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Kris Poppe,<sup>1,2</sup> Daniel Glinoeer,<sup>2</sup> Brigitte Velkeniers<sup>1</sup>

<sup>1</sup>Department of Endocrinology, Free University Brussels (VUB), Brussels, Belgium

<sup>2</sup>Department of Internal Medicine, Thyroid Investigation Clinic, Université Libre de Bruxelles, Centre Hospitalo-Universitaire Saint-Pierre, Brussels, Belgium

Corresponding author:

Kris Poppe

Department of Endocrinology

Universitair Ziekenhuis Brussel

Free University Brussels (VUB)

Laarbeeklaan 101, 1090 Brussels, Belgium

Tel.: +32 2 4776424

Fax: +32 2 4776428

E-mail: kris.poppe@uzbrussel.be

**Kris Poppe**

Department of Endocrinology, Free University Brussels (VUB),  
Brussels, Belgium.

**Daniel Glinoyer**

Department of Internal Medicine, Thyroid Investigation Clinic,  
Université Libre de Bruxelles, Centre Hospitalo-Universitaire  
Saint-Pierre, Brussels, Belgium.

**Brigitte Velkeniers**

Department of Endocrinology, Free University Brussels (VUB),  
Brussels, Belgium.

## Thyroid International

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## Summary

Infertility, or the inability to become pregnant after 1 year of unprotected intercourse, is both a medical and psychological problem for 10–15% of the couples. Although its prevalence seems to be stable over time, the impression is of an increasing problem associated with several environmental factors and/or other (auto-immune) diseases. Of all autoimmune diseases, thyroid autoimmunity (TAI) is the most common, affecting 5–20% of women in the childbearing period and can be associated with both hypo- and hyperthyroidism. In women of reproductive age, thyroid dysfunction can lead to a variety of gynaecological disorders ranging from menstrual irregularities to infertility arising from many different pathophysiological mechanisms. Treatment of thyroid dysfunction can normalize the menstrual abnormalities, but it has not been proven that it therefore improves fertility itself. The prevalence of isolated TAI (with normal thyroid function) is higher in some causes of infertility-related disorders such as endometriosis and the polycystic ovary syndrome com-

pared with that in fertile women, although this association does not mean that there is a causal relationship. The prevalence of (subclinical) hypothyroidism does not seem to be higher in infertile women, compared with that in fertile women, although it remains difficult to estimate the exact prevalence as many studies suffer from selection bias.

In contrast to the many studies that have been published on the association between thyroid disorders during and after pregnancy (miscarriage, neurointellectual outcome and post-partum thyroiditis), the association with infertility has not been studied that extensively.

The aim of this paper is to give an overview of literature on the association between thyroid disorders and female infertility and how to manage them in clinical practice.

## Introduction

Thyroid hormones interact with both oestrogens and progesterone to maintain a normally functioning uterus and are necessary for the normal maturation of the oocytes. The impact of thyroid hormones has been reported to be both direct through the presence of thyroid hormone receptors on the ovaries and indirect through an impact on the secretion of sex hormone-binding globulin (SHBG), prolactin and luteinizing hormone-releasing hormone (LH-RH). Hypothyroidism is also associated with menorrhagia because of decreased production of factors VII, VIII, IX and XI. Both a normal thyroid function and immune system are thus necessary to obtain normal fertility.<sup>1,2</sup>

Infertility is the absolute inability to conceive (premature menopause, complete tubal obstruction or absence of sperm) after 1 year of regular intercourse with-

out contraception. The overall prevalence of infertility ranges from 10% to 15% and seems to be stable over the past few decades.<sup>3,4</sup> Female causes of infertility account for 35% of all couples, male related factors for 30%, a combination of both for 20% and idiopathic infertility for 15%.<sup>5</sup> The principal causes of infertility in females are endometriosis, tubal occlusion and ovulatory dysfunction (OD). Endometriosis, defined as the presence of uterine tissue outside its cavity, is deemed a cause of infertility when the disease is severe according to the American Society for Reproductive Medicine.<sup>6</sup> Infertility associated with OD relates to a heterogeneous group of disorders (WHO I hypogonadotrophic; WHO II normogonadotrophic; WHO III hypergonadotrophic).<sup>7</sup> Finally, there is the syndrome of idiopathic infertility present when both the spermogram and female work-up are normal.

## Female infertility and thyroid autoimmunity (with a normal thyroid function)

The prevalence of thyroid autoimmunity (TAI) is 5–10-fold higher in women compared with that in men, probably because of a combination of genetic factors, oestrogen-related effects and chromosome X abnormalities.<sup>8–10</sup> The number of studies investigating the prevalence of TAI in women with infertility has increased over the years and the main results are listed in Tab. 1.<sup>11–20</sup> The interpretation of these data is rendered difficult because some studies included one cause of infertility while in others different causes were included. Some studies were retrospective while others were prospective and the controls were often different, as were the assays used for thyroid antibody measurement. A trend that could be observed was that the prevalence of TAI was higher when endometriosis or ovarian failure was the cause of infertility. In a prospective case–controlled study by our group in 438 women of infertile couples, the prevalence of TAI was significantly higher in women with endometriosis compared with that in 100 age-

matched fertile women (29% vs 8%).<sup>17</sup> Two other studies also reported the association between TAI and endometriosis; one by Abalovich et al.,<sup>19</sup> in which women with endometriosis had 25% TAI versus 14% among controls and one by Gerhard et al.<sup>21</sup> reporting 44% TAI versus 9%, respectively. However, in a recent Brazilian study aimed specifically at investigating the association between TAI and endometriosis, this association could not be confirmed (15% vs 22%). It should, however, be mentioned that the prevalence of TAI in the control group was much higher compared with that in most other studies.<sup>20</sup> Endometriosis has frequently been associated with the presence of autoantibodies to endometrial antigens, complement deposits, decline in the concentration of natural-killer cells and cytotoxic effects on autologous endometrium. The higher prevalence of TAI in this type of infertility could be due to an, as yet unidentified, common immune disorder associated with both pathologies.<sup>22–24</sup>

One other particular association has been observed between TAI and women with OD causes of infertility. In a study by Janssen et al.,<sup>18</sup> this relationship was demonstrated in the particular case of polycystic ovarian syndrome (PCOS), in which 27% of the women had TAI compared with only 8% in women without this syndrome ( $p < 0.0001$ ). According to these authors, the association could be explained by the increased oestrogen-to-progesterone ratio as it occurs typically in PCOS. In the study by Abalovich et al.,<sup>19</sup> an increased

prevalence of TAI was found in women with premature ovarian failure, which also might have been due to a shared autoimmune etiology. The underlying pathogenic mechanisms explaining the association between TAI and infertility remains largely speculative since neither animal models nor in vitro data are available. Several mechanisms probably coexist, as the various causes of female infertility encompass markedly heterogeneous diseases.

## Female infertility and subclinical hypothyroidism (SH)

The prevalence of hypothyroidism in women of reproductive age varies between 2% and 4% and, in most cases, is due to chronic autoimmune thyroiditis.<sup>8,25</sup> Hypothyroidism can be associated with menstrual irregularities and other types of reproductive disorders and, thus, may finally lead to infertility.<sup>26</sup> Krassas et al.<sup>27</sup> investigated the presence of abnormal menses in relation to hypothyroidism and showed that the prevalence of oligomenorrhoea was 23% compared with 8% among euthyroid controls and, furthermore, the menstrual abnormalities were positively correlated with serum thyroid-stimulating hormone (TSH) levels. Hypothyroidism can lead to menorrhagia due to a decreased production of coagulation factors, such as factor VII, VIII, IX and XI.<sup>28</sup> Severe hypothyroidism can also lead to OD through different types of interactions between thyroid hormones and the female reproductive system. Thyroid hormone receptors have been described in human oocytes, where they synergize with the LH/hCG receptor, mediated by follicle-stimulating hormone to exert direct stimulatory effects on granulosa cell function (i.e. progesterone production) and on trophoblastic differentiation.<sup>29,30</sup> In an in vitro fertilization setting, Cramer et al.<sup>31</sup> showed that serum TSH levels were significantly higher among women who produced oocytes that failed to be fertilized, and that among women who had a least one oocyte inseminated, the likelihood that they would have fewer than 50% of

their eggs fertilized was significantly related to higher TSH levels.

The concept of SH has been challenged as data have indicated that, physiologically, variations in T4 concentrations remain narrower within an individual than among that in a given reference population. These data might, however, reflect an abnormally low value for T4 concentrations in patients with SH and could thus be interpreted as overt hypothyroidism.<sup>32</sup> More recently, some authors proposed to restrict the upper limit of serum TSH to 2.5 mIU/l with the argument that the majority of women without TAI have a serum TSH  $< 2.5$  mIU/l.<sup>33</sup> Not all authors agreed with these arguments and proposed to add age as an independent factor to determine in who the cut-off could be lowered. Based on observational population studies, it has been shown that in patients  $> 70$  years of age, the upper serum TSH level is probably  $> 4.2$  mIU/l.<sup>34</sup> Since most women in the reproductive age group are  $< 45$  years of age, the upper limit of 2.5 mIU/l seems to be accepted in that particular group according to this age criterion. It should, furthermore, be mentioned that most infertile women will undergo a certain type of controlled ovarian hyperstimulation (COH) in preparation for assisted reproductive technology (ART) procedures. Several studies have indicated that COH leads to an important strain on thyroid function, especially in women with associated

TAI.<sup>35-38</sup> Thus, besides age, a history of treatment for infertility may be an additional argument toward lowering the upper limit of the serum TSH reference range.

The prevalence of SH in infertile women is not easy to determine due to a potential number of biases. When infertile women are diagnosed with (subclinical) hypothyroidism, it will probably be one of the first problems that will be treated by the general physician or the gynaecologist, before they are referred to a fertility clinic. In some studies, the definition of SH is based on a thyrotrophin-releasing hormone (TRH) test, while in others it depends on basal TSH. However, the controls are very heterogeneous in the different studies. In *Tab. 2*, the most relevant studies on the prevalence of SH in infertile women are summarized.<sup>17,19,21,39-43</sup> The most important tendency seems to be that SH is more frequent in infertile women with OD compared with that in fertile women and in women with other causes of infertility. In the study by Bohnet et al.,<sup>39</sup> SH was considered to be the cause of infertility itself and, therefore, 11/20 women were treated with 50 µg levothyroxine (LT4) daily. In those women, the levels of progesterone normalized and 20% became pregnant. Gerhard et al.<sup>21</sup> reported a positive correlation between basal TSH, LH and testosterone concentrations in the early follicular phase. Women with elevated serum TSH levels had a lower pregnancy rate than women with a normally stimulated serum TSH. In a study by Arojoki et al.,<sup>41</sup> the prevalence of SH was 4% and that of overt

hypothyroidism 3.3% in 299 infertile women. The highest percentage of women with SH was observed in the group with OD (6.3%). Grassi et al.<sup>42</sup> investigated 129 women from couples with infertility caused by OD, a male factor or idiopathic infertility. Six women (4.6%) had a basal serum TSH level greater than 4.5 mIU/l, and of these, five had TAI. Mean duration of infertility was significantly longer in women with thyroid disorders (abnormal TSH and/or TAI) than in those without (3.8 years vs 2.6 years;  $p < 0.005$ ). Raber et al.<sup>43</sup> investigated 283 women referred for infertility and women with SH (based on a TRH test) who were treated with LT4 and followed up over a 5-year period. Overall, the prevalence of SH was 34%, which is unusually high and is associated with the specific referral pattern. Among the women who became pregnant during follow up, in more than 25%, SH persisted at the time of conception. Women who never achieved a normal basal serum TSH level (or a TRH-stimulated TSH level  $< 20$  mIU/l) became pregnant with lesser frequency than those in whom thyroid function normalized.

The prevalence of SH is considerably higher in studies in which the TRH test was used than in those in which only the upper limit of basal serum TSH was used. This difference might once more indicate that, in older studies using less sensitive measurements of serum TSH, the actual TSH reference levels are perhaps slightly too high in the setting of infertility.

## Female infertility and (subclinical) hyperthyroidism

In the general population, the prevalence of subclinical hyperthyroidism is ~1.5%.<sup>44</sup> Studies on the association between subclinical hyperthyroidism and infertility are scarce and often surrogate endpoints such as the menstrual pattern are investigated rather than specific endpoints such as pregnancy rate and/or outcome. In a study by Joshi et al.,<sup>26</sup> 65% of hyperthyroid women with a history of reproductive problems had menstrual irregularities, compared with 12% in healthy controls ( $p < 0.001$ ). In another study by Krassas et al.,<sup>45</sup> irregular

cycles were present in only 46/214 (22%) of hyperthyroid women. Of these, 24 had hypomenorrhoea, 15 polymenorrhoea, 5 oligomenorrhoea and 2 menorrhagia; none had amenorrhoea. The prevalence of menstrual abnormalities was 2.5 times higher than in the control population (8%). Treatment of hyperthyroidism appeared to frequently correct these cycle changes.

Several aspects of the reproductive axis influenced by an excess of thyroid hormones are comparable with

the situation in hypothyroid women. In hyperthyroidism SHBG production, the conversion of androgens to oestrogens and the gonadotrophin response to GnRH are increased.<sup>46</sup> The decrease in menstrual flow may also be related to effects on haemostatic factors, including the synthesis of factor VIII.<sup>47</sup> Despite these metabolic changes, hyperthyroid women usually maintain ovulation, according to endometrial biopsies.<sup>48</sup>

## Management in clinical practice

Although systematic screening for thyroid disorders in pregnant women seems to be cost-effective, the decision to perform this in clinical practice remains a matter of debate. This discussion will not be repeated in the scope of this paper, since many original and reviews papers have recently been published on this matter.<sup>2,51-54</sup>

In our opinion, the systematic screening for thyroid disorders is warranted in the case of female infertility for several reasons. A proposition for screening and treatment is summarized in *Fig. 1* in an algorithmic form.<sup>55</sup> The major reasons for performing such screening are: the increased prevalence of TAI in infertile women (especially in women with endometriosis and ovarian dysfunction) and the beneficial effects of LT4 therapy when (subclinical) hypothyroidism is detected and confirmed. These beneficial effects have been shown to be present on the surrogate endpoints (menstrual cycle, LH pulsatility and hyperprolactinaemia), although data

Women with hyperthyroidism and fertility problems should be treated with antithyroid drugs and/or surgery according to the cause of hyperthyroidism. Treatment with radioiodine is not recommended, especially when women plan to start an ART procedure, with the possibility of an early pregnancy.<sup>49,50</sup>

on the impact on hard endpoints (pregnancy/live birth rate) are limited to one study and thus it remains difficult to draw conclusions.<sup>56</sup>

In women with a normal serum TSH (when still considering 2.5–4.0 mIU/l) and no associated TAI, we propose that thyroid function is checked after COH, since the latter is known to have an important impact on thyroid function. In the case of a normal TSH and associated TAI, COH may lead to SH, which is undesirable in the preliminary stages of pregnancy.<sup>36,38</sup> Therefore, we also propose that this group of women is treated with LT4. This attitude may change if the upper limit of the serum TSH reference range is lowered.

The opportunity to avoid a psychologically difficult and expensive ART procedure are thus additional and not negligible (human) arguments for screening and treating infertile women with certain thyroid disorders.

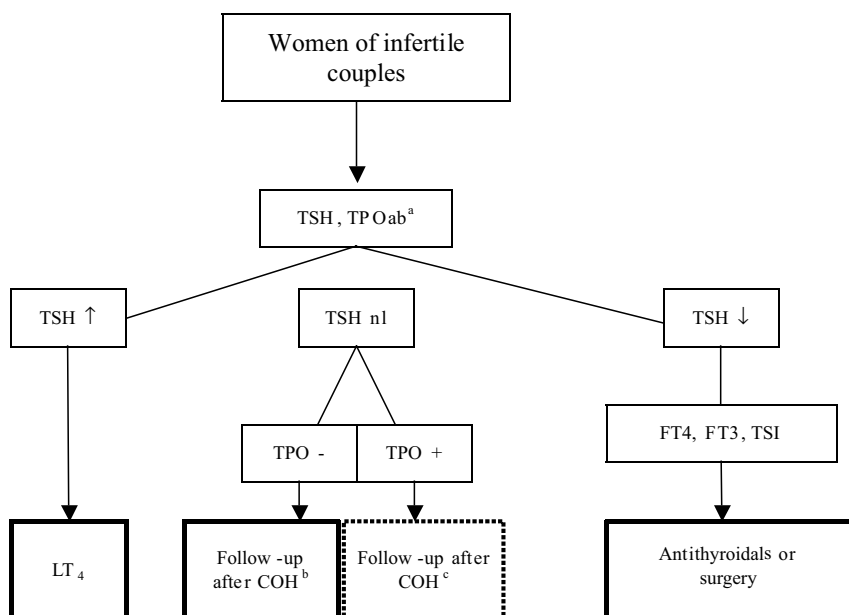
## Conclusions

Infertility is a complex disorder that in a quarter of the couples is due to a female cause. Thyroid hormones play an important role in normal reproductive function, both through direct effects on the ovaries and also indirectly by multiple interactions with other sex hormones. Therefore, thyroid dysfunction can lead to menstrual irregularities and, thus, finally to infertility. We propose the systematic screening of infertile women for thyroid dysfunction and autoimmunity, especially when endometriosis or ovarian dysfunction is the cause of infertility. When hypothyroidism is diagnosed, LT<sub>4</sub>

treatment should be initiated in order to restore normal menses and normalize other parameters necessary for a normal fertility. Similarly, the likelihood of performing a psychologically and economically difficult ART procedure can be reduced.

Further research is needed to answer crucial issues such as why thyroid autoimmunity is more linked to certain types of infertility.

**Figure 1.** Diagnostic and therapeutic approach of infertile women<sup>55</sup>



COH: controlled ovarian hyperstimulation; TPO, peroxidase; TSH, thyroid-stimulating hormone.

<sup>a</sup>Control thyroid function when altered within appropriate interval.

<sup>b</sup>Consider treatment with LT<sub>4</sub> when altered thyroid function after COH.

<sup>c</sup>Treat with LT<sub>4</sub> before COH when TSH is 2.5–4 mIU/l.

**Table 1.** Studies on the association between thyroid autoimmunity (TAI) and female infertility<sup>2</sup>

Author ref (country, year)	Type of thyroid antibody	Cause of infertility	Control description	TAI in patient vs control, %	RR (95% CI)	P
Wilson et al. <sup>11</sup> (UK, 1975)	Tm + Tg	OD	Age matched, post-partum	10 vs 14	0.7 (0.3–1.9)	NS
Roussev et al. <sup>12</sup> (USA, 1996)	Tm + Tg	I, OD, E	'Healthy', non-pregnant	8 vs 0	1.2 (0.1–11)	NS
Geva et al. <sup>13</sup> (Israel, 1997)	Tm + Tg	I, T	Age matched, 'healthy', nulligravidae	19 vs 5	3.8 (0.8–17.3)	NS
Kutteh et al. <sup>14</sup> (USA, 1999)	TPO + Tg	I, OD, T, E	Reproductive age, parous	19 vs 15	1.3 (0.9–2.1)	NS
Kaider et al. <sup>15</sup> (USA, 1999)	TPO + Tg	I, OD, E	Fertile	31 vs 15	2.1 (1.1–3.9)	0.02
Reimand et al. <sup>16</sup> (Estonia, 2001)	Tm	I, OD, E	Unselected population	2 vs 4	0.5 (0.1–2.2)	NS
Poppe et al. <sup>17</sup> (Belgium, 2002)	TPO	All causes	Age matched, fertile	14 vs 8	1.7 (0.9–3.5)	NS
Janssen et al. <sup>18</sup> (Germany, 2004)	TPO + Tg	OD (PCOS)	Age matched, no PCOS	27 vs 8	3.2 (1.9–5.6)	<0.0001
Abalovich et al. <sup>19</sup> (Argentina, 2007)	TPO	All causes	Age matched, fertile	25 vs 15	1.8 (1.0–3.2)	NS
Petta et al. <sup>20</sup> (Brazil, 2007)	TPO + Tg	E	Fertile/no E	9 vs 16	0.5 (0.3–1.0)	NS

CI, confidence interval; E, endometriosis; I, idiopathic; NS, non-significant; OD, ovulatory dysfunction; PCOS; polycystic ovarian syndrome; RR, relative risk; T, tubal disorders; Tg, thyroglobulin; Tm, microsomal; TPO, peroxidase.

**Table 2.** Prevalence of subclinical hypothyroidism (SH) in female infertility<sup>2</sup>

Author ref (year)	Definition of SH	SH in patients, %	SH in controls, %	Type of study
Bohnet et al. <sup>39</sup> (1981)	Basal TSH >3 mU/l or peak TSHa >15 mU/l	10.8 (20/185)	No controls	P
Gerhard et al. <sup>21</sup> (1991)	Peak TSHa >20 mU/l	43.2b (80/185)	No controls	P
Shalev et al. <sup>40</sup> (1994)	Basal TSH >4.5 mU/l	0.7 (3/444)	No controls	R
Arojoki et al. <sup>41</sup> (2000)	Basal TSH >5.5 mU/l	1.3 (4/299)	2–3 <sup>c</sup>	R
Grassi et al. <sup>42</sup> (2001)	Basal TSH >4.5 mU/l	4.6 (6/129)	No controls	P
Poppe et al. <sup>17</sup> (2002)	Basal TSH >4.2 mU/l	0.9 (4/438)	<1 <sup>d</sup>	P
Raber et al. <sup>43</sup> (2003)	Basal TSH >4 mU/l or peak TSHa >15 mU/l	33.9 (96/283)	No controls	P
Abalovich et al. <sup>19</sup> (2007)	Basal TSH >5 mU/l	10.2 (25/244)	1.9 <sup>d</sup>	R

P, prospective study; R, retrospective study; TSH, thyroid-stimulating hormone.

<sup>a</sup>After thyrotrophin-releasing hormone-stimulation test.

<sup>b</sup>1/185 patients had a basal serum TSH >6 mU/l (0.5%).

<sup>c</sup>Prevalence in the Finnish population.

<sup>d</sup>Fertile women.

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*Figure 1* was modified with permission from the authors of reference 55.

*Tables 1* and *2* were modified with permission from the authors of reference 2.

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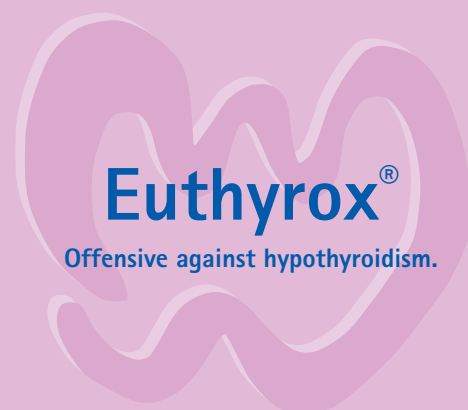


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